NCT #NCT03448939

CLINICAL STUDY PROTOCOL

Title: A Phase 3 Multi-Center, Double-Blind, Randomized, Vehicle-Controlled Study of S5G4T-1 in the Treatment of Papulopustular Rosacea

Protocol No: SGT-54-01: October 24, 2018

Protocol Version: 4

Original Version: 3.0

Sponsor: Sol-Gel Technologies Ltd.
7 Golda Meir St.
Weizmann Science Park
Ness Ziona 7403650, Israel

2. PROTOCOL APPROVAL – SPONSOR SIGNATURE PAGE

Protocol Title: A Phase 3 Multi-Center, Double-Blind, Randomized, Vehicle-Controlled Study of S5G4T-1 in the Treatment of Papulopustular Rosacea

Study Products: S5G4T-1 compared to Vehicle

Sol-Gel Technologies Ltd. commits to conduct the study as described herein in accordance with the current International Conference on Harmonization (ICH) – Good Clinical Practices (cGCPs) and the World Medical Association Declaration of Helsinki and in compliance with the obligations and requirements of the Sponsor as listed in 21 CFR Part 312. The following individuals approve the October 24, 2018 version of the SGT-54-01 protocol. All changes to this version of the protocol must have prior written approval and require an amendment or administrative letter.

Sponsor Representative:

[redacted]
Sol-Gel Technologies Ltd.
7 Golda Meir St.
Weizmann Science Park
Ness Ziona 7403650, Israel

Signature: [redacted]

Date: November 8, 2018

Medical Monitor:

[redacted]
Symbio, LLC
21 Perry St.
Port Jefferson, NY 11777

Signature: [redacted]

Date: [redacted]

Biostatistics and Data Management:

[redacted]
QST Consultations, Ltd.
11275 Edgewater Dr.
Allendale, MI 49401

Signature: [redacted]

Date: 7 Nov 2018

3. INVESTIGATOR PROTOCOL ACKNOWLEDGMENT

Protocol Title: A Phase 3 Multi-Center, Double-Blind, Randomized, Vehicle-Controlled Study of S5G4T-1 in the Treatment of Papulopustular Rosacea

Study Products: S5G4T-1 compared to Vehicle

I have read this protocol and commit to conduct the study as outlined herein, in accordance with the current International Conference on Harmonization (ICH) current Good Clinical Practices (cGCPs) and the World Medical Association Declaration of Helsinki and complying with the obligations and requirements of clinical investigator(s) and all other requirements as listed in 21 CFR Part 312 and all other applicable regulations. Any deviations will be agreed to by prior discussion between the Sponsor/Contract Research Organization (CRO) and me.

I am thoroughly familiar with the appropriate use of the investigational products(s), as described in this protocol, and any other information provided by the sponsor or designee, including, but not limited to, the current Investigator Brochure (or equivalent document). I agree to provide sufficient time, and adequate numbers of qualified staff and facilities for the foreseen duration of the clinical study to conduct the study properly, ethically and safely.

I agree to completely inform all Patients in this study concerning the pertinent details and purpose of the study prior to their agreement to participate in the study in accordance with cGCPs and regulatory authority requirements. I will be responsible for maintaining each Patient's consent form in the study file and providing each Patient with a copy of the signed consent form.

Investigator's Signature	Date
Investigator's Printed Name	

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5. PROTOCOL SYNOPSIS

5.1. Synopsis

Title:	A Phase 3 Multi-Center, Double-Blind, Randomized, Vehicle-Controlled Study of S5G4T-1 in the Treatment of Papulopustular Rosacea
Study Number:	SGT-54-01
Study Phase:	3
Indication:	Papulopustular rosacea
Study Period:	12 weeks (84 Days)
Study Products:	1. S5G4T-1: Encapsulated Benzoyl Peroxide (E-BPO) Cream, 5%, developed by Sol-Gel Technologies and manufactured by [redacted], Montreal, Canada. 2. S5G4T-2: Vehicle Cream, developed by Sol-Gel Technologies and manufactured by [redacted], Montreal, Canada.
Study Objectives:	To assess the efficacy and safety of S5G4T-1 compared to S5G4T-1 Vehicle when applied once daily for 12 weeks in patients with papulopustular rosacea
Study Design:	In this Phase 3, double-blind, vehicle-controlled study, patients will be admitted into this multi-center, double-blind, randomized, vehicle-controlled, parallel-group pivotal study only after a written informed consent has been obtained and after all inclusion/exclusion criteria have been met. Male and female patients at least 18 years of age with moderate or severe papulopustular rosacea [Investigator Global Assessment (IGA) grade 3 or 4] will be eligible for enrollment for daily treatment with S5G4T-1 or its vehicle for 12 weeks.
Study Population:	Approximately 350 male and female patients, at least 18 years of age, who meet the inclusion/exclusion criteria will be enrolled in the study.
Investigational Sites	It is estimated that up to 28 study centers in US will participate in this study.
Dosing:	Patients will be randomized in a 2:1 ratio to the study product or vehicle treatment group, respectively. Patients will apply the study product once daily for 12 weeks. Patients will use a “pea-size” amount for each area of the face (chin, left cheek, right cheek, nose, left forehead and right forehead). The study product will be spread as a thin layer in such a way as to provide an even distribution, avoiding the eyes, lips, inside the nose, mouth and all mucous membranes. Patients will receive detailed instructions on the method of application and quantity to use in order to assure that treatment is harmonized among all patients to best extent possible.

5.1. Synopsis

Methodology:	Clinical and Safety Evaluations will be performed at: 1. Visit 1/Screening 2. Visit 2/Baseline, Day 1 3. Visit 3/Week 2, Day 15 (± 3 Days) 4. Visit 4/Week 4, Day 29 (± 3 Days) 5. Visit 5/Week 8, Day 57 (± 3 Days) 6. Visit 6/Week 12, Day 85 (± 4 Days)/End of Treatment/End of Study) Patients will be admitted into the study after all inclusion/exclusion criteria have been met, including a clinical diagnosis of rosacea and after written informed consent has been obtained. Subjects with severe rosacea who are appropriate for systemic treatment need to be counseled regarding their treatment options by the Principal Investigator. At each visit, a 5-point IGA scale of rosacea; rosacea erythema, and telangiectasia; and inflammatory (papules, pustules) lesion counts will be performed and recorded. Safety will be assessed at all visits, and will include monitoring of local adverse experiences, Investigator Cutaneous Safety Assessment rating of dryness and scaling and Local Tolerability Assessment rating of itching and burning/stinging on a scale ranging from 0 (None) to 3 (Severe); patients will complete a Patient Reported Outcomes (PRO) questionnaire at Visit 2, 3, 4, 5 and 6 and Rosacea Quality of Life Questionnaire (RosaQoL) at Baseline and Visit 6 or at early termination.. Standardized photography of facial rosacea at Visit 2, 3, 4, 5 and 6 will be performed at select site(s). In addition to IGA, at each visit, the following safety measures will be recorded: monitoring for any AE including local and systemic; investigator Cutaneous Safety Assessment rating of erythema, dryness and scaling and Local Tolerability Assessments rating of itching and burning/stinging on a scale ranging from 0 (None) to 3 (Severe). Urine pregnancy tests will be performed on females of child-bearing potential at Screening, Baseline and every 4 weeks during study or at early termination. Regardless of the duration of the study, patients that exhibit serious adverse event (SAE), will be followed up until the SAE resolves, based on investigator's medical judgment.
Clinical Trial Duration	Screening: -35 to 0 days prior to Baseline Duration of treatment: 12 weeks/84 days Patients have the right to stop the study for any reason at any given time.

5.1. Synopsis

Study product dosage and Reference therapy	Encapsulated Benzoyl Peroxide Cream, 5% or vehicle will be dispensed every 4 weeks (Baseline, Week 4 and Week 8) to patients and used daily during the study. The study product and vehicle will be supplied in 55-gram pumps (total weight including pump is 85 grams).
Patient Inclusion Criteria:	Patients may participate in the study if they meet all of the following criteria: 1. Patient must sign an Institutional Review Board (IRB) approved written informed consent for this study. 2. Male and female 18 years of age and older. 3. Patients must have clinical diagnosis of moderate to severe rosacea with a Baseline Investigator's Global Assessment (IGA) Score of 3 (moderate severity) or 4 (severe) on a severity scale of 0 to 4. 4. Have a minimum total of 15 and a maximum total of 70 inflammatory lesions (papules and/or pustules) including those present on the nose. 5. Have two nodules or less (nodule defined as a papule or pustule greater than 5 mm in diameter) at Baseline. 6. Patients must be willing and able to understand and comply with the requirements of the study, apply the medication as instructed, refrain from use of the following medications (during the study, return for the required treatment period visits, comply with therapy prohibitions, and are able to complete the study): – topical rosacea medication including: Metronizadole 0.75% to 1%, Azelaic acid, Brimonidine, Oxymetazoline, Sodium Sulfacetamide 10%, Sulfur 5%, Benzoyl Peroxide, Clindamycin, Erythromycin, Benzoyl Peroxide and Clindamycin, Sulfur lotions, retinoids, Ivermectin Cream 1%, Ivermectin lotion 0.5%; or – topical and systemic (oral and injectable) antibiotics known to impact rosacea e.g., tetracycline and its derivatives, erythromycin and its derivatives, doxycycline and its derivatives, minocycline and its derivatives, azithromycin and its derivatives, clarithromycin and its derivatives, metronidazole and its derivatives, sulfamethoxazole, or trimethoprim and retinoids (e.g., isotretinoin)

5.1. Synopsis

Patient Inclusion Criteria (continued):	7. Patients must be willing to minimize or not significantly alter controllable external factors that might trigger rosacea flare-ups (such as spicy food, thermally hot foods, soups and drinks, hot environments, prolonged sun exposure, strong winds, alcoholic beverages, etc.) throughout their participation in the study. 8. Patients must be generally healthy and free from any clinically significant disease, other than rosacea, that might interfere with the study evaluations. 9. Sexually active females of child-bearing potential, excluding women who are sterilized (including Essure procedure, tubal ligation, bilateral oophorectomy or hysterectomy) or post- menopausal for at least 2 years, must use one of the following birth control options*: – Intrauterine device (IUD) – Hormonal (injections, implants, transdermal patch, vaginal ring) – Abstinence – Oral contraceptives – Female condom – Diaphragm with spermicides – Cervical cap with spermicides – Contraceptive sponge * In addition, patients entering the trial that are on hormonal contraceptives must have been on this method for at least 3 months (90 days) prior to the trial and continue the method for the duration of the trial. Patients who had used hormonal contraception and stopped must have stopped no less than 3 months prior to Baseline. Patients entering the study who had an Essure procedure must have had this procedure at least 3 months prior to the study and have undergone an Essure confirmation test to ensure its efficacy. A sterile sexual partner is not considered an adequate form of birth control.

5.1. Synopsis

Patient Exclusion Criteria:	The presence of any of the following will exclude the potential patients from entry into the study: 1. Females, who are pregnant, breastfeeding, or planning a pregnancy within the period of their study participation or were found to have positive pregnancy test at baseline or screening visits. 2. Presence of more than 2 facial nodules or any nodule greater than 1 cm. 3. Current or past ocular rosacea (e.g., conjunctivitis, blepharitis, or keratitis) of sufficient severity to require topical or systemic antibiotics. 4. Presence of any other facial skin condition that might interfere with rosacea diagnosis and/or assessment including but not limited to (e.g., on the face: rosacea conglobata, rosacea fulminans, acne vulgaris, acne conglobata, acne fulminans, or secondary acne (chloracne, drug-induced acne, etc.), facial pustulosis of the chin, dermatitis (including peri-orbital and seborrheic dermatitis), demodicidosis, facial keratosis pilaris, acute lupus erythematous, psoriasis, eczema, acneiform eruptions caused by medications, steroid acne, steroid folliculitis, sunburn, rhinophyma, or bacterial folliculitis). 5. Any uncontrolled, chronic or serious disease or medical condition that would prevent participation in a clinical trial or, in judgment of the Investigator, would put the patient at undue risk or might confound the study assessments. 6. Excessive facial hair (e.g., beards, sideburns, moustaches, etc.) that would interfere with diagnosis or assessment of rosacea. 7. History of unresponsiveness to topical benzoyl peroxide. 8. Concurrent use of drugs causing acneiform eruptions (e.g., azathioprine, haloperidol, halogens, lithium, systemic corticosteroids, phenytoin, phenobarbital, testosterone, anabolic steroids, isoniazid). 9. Known sensitivities to the study product ingredients. Allergy to benzoyl peroxide, parabens and glycerin or other ingredients listed in the investigator brochure.

5.1. Synopsis

Patient Exclusion Criteria (continued):	10. Use: – within 180 days prior to Baseline or during the study of oral retinoids (e.g., Accutane®) or therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed). – within 90 days prior to Baseline or during the study radiation therapy and/or anti-neoplastic agents. – start or change of dose within 90 days prior to Baseline or during the study of vasodilators, vasoconstrictors, anticoagulation or beta-blockers therapy and use throughout the study. Use of such therapy must remain constant throughout the study. – start or change of dose within 90 days prior to Baseline of hormonal treatment (oral, implanted, topical contraceptives and androgens). Use of such therapy must remain constant during the study. – within 30 days prior to Baseline or during the study of therapeutic Vitamin D supplements of greater than 2,000 units/day (daily multivitamins with Vitamin D not exceeding more than 2000 IU/day are allowed). If a patient on a constant stable prescribed weekly dose, they should remain on this dose during the study. – within 30 days prior to Baseline or during the study of (1) systemic steroids, (2) topical retinoids to the face (e.g., tretinoin) (3) systemic (e.g., oral or injectable) antibiotics known to impact rosacea (e.g., tetracycline and its derivatives, erythromycin and its derivatives, doxycycline and its derivatives, minocycline and its derivatives, macrolides and its derivatives, azithromycin and its derivatives, clarithromycin and its derivatives, metronidazole and its derivatives, sulfamethoxazole, bactrim or trimethoprim); short term treatment of all other antibiotics (not affecting rosacea for) ≤ 14 days for non-rosacea related conditions is acceptable, (4) immunosuppressive agents, or immunomodulators (e.g. cyclosporine, tacrolimus, pimecrolimus). – of medicated make-up (including anti-aging make-up) throughout the study and significant change in the use of consumer products within 14 days of study entry and throughout the study.

5.1. Synopsis

Patient Exclusion Criteria (continued):	– of niacin and niacinamide (Vitamin B3) within 24 hours of study entry and throughout the study. – of intranasal and inhaled corticosteroids do not require a washout and may be used throughout the study if at a stable and standard dose. 11. Facial use within 14 days prior to Baseline or during the study of (1) topical steroids, (2) topical anti-inflammatory agents or topical non-steroidal anti-inflammatory drugs (NSAID), (3) topical antimycotics, (4) any topical rosacea treatments (e.g., Metronizadole 0.75% to 1%, Azelaic acid, Brimonidine, Oxymetazoline, Sodium Sulfacetamide 10%, Sulfur 5%, Benzoyl Peroxide, Clindamycin, Erythromycin, Benzoyl Peroxide and Clindamycin, Sulfur lotions, Retinoids, Ivermectin) or (5) topical antibiotics. 12. Use on the face within 30 days prior to Baseline or during the study of (1) cryodestruction or chemodestruction, (2) dermabrasion, (3) photodynamic therapy, (4) acne surgery, (5) intralesional steroids, (6) laser resurfacing or electrodessication, (7) x-ray therapy, (8) pulse dye laser, (9) long-pulsed Nd-YAG laser, (10) Intense pulse light or pulse light laser, (11) electrocautery or electrocoagulation, (12) CO_2 laser, Fractioned lasers, or loop electrosurgery, (13) facial peels or other facial cosmetic surgery (e.g., Thermage®, etc.). 13. Use of medicated cleansers on the face (e.g., benzoyl peroxide, salicylic acid, sulfur or triclosan) within 7 days of Baseline and throughout the study. 14. Patient consumes excessive alcohol, abuses drugs, or has a condition that could compromise the patient's ability to comply with study requirements and/or have drug or alcohol addiction requiring treatment in the past 12 months. 15. Use of topical astringents or abrasives (e.g., rubs, exfoliating cleansers and products containing salicylic acid and/or alcohol), topical preparations that contain spices or lime, medicated topical preparations (prescription and OTC products) within 7 days prior to Visit 2 (Baseline) and throughout the study. 16. Use of antipruritics (including antihistamines), spa or sauna treatments or chlorine exposure (swimming pool etc.) within 24 hours (1 day) of all study visits (Visit 2, Baseline, through End of Study).

5.1. Synopsis

Patient Exclusion Criteria (continued):	17. Participation in any clinical study involving an investigational product, agent or device that might influence the intended effects or mask the side effects of study product, within 30 days prior to Visit 2 (Baseline) and throughout the study. 18. Previous enrollment in this study or current enrollment in this study at another participating site. 19. Employee (or employee's family member) of the research center or private practice, or patients who have a conflict of interest. 20. Patients living (e.g., siblings, spouses, relatives) in the same household cannot be enrolled in the study at the same time. 21. Use of tanning booths, sun lamps or excessive UV radiation (e.g., phototherapy, daily extended exposure or occupational exposure to the sun), sunbathing or excessive exposure to the sun 1 week (7 days) prior to Baseline and throughout the study. 22. Patients who in the opinion of the investigator, are unlikely to be able to follow the restrictions of the protocol and complete the study.
Primary Efficacy Endpoints:	• Proportion of patients with the primary measure of success "Clear" (0) or "Almost clear" (1) in the IGA relative to Baseline at Week 12 • Absolute change in inflammatory lesion counts from baseline to Week 12
Secondary Efficacy Endpoints:	• Percent change in inflammatory lesion count from baseline to Week 12 • Absolute change in inflammatory lesion count from baseline to Week 8 • Proportion of patients with the primary measure of success "Clear" (0) or "Almost clear" (1) in the IGA relative to Baseline at Week 8 • Absolute change in inflammatory lesion count from baseline to Week 4 • Proportion of patients with the primary measure of success "Clear" (0) or "Almost clear" (1) in the IGA relative to Baseline at Week 4

5.1. Synopsis

Supportive efficacy endpoints:	• Percent change in inflammatory lesion count at Week 8 • Percent change in inflammatory lesion count at Week 4 • Mean change comparison in PAPSS item 1 (burning) between groups from Baseline to Weeks 4, 8 and 12 • Mean change comparison in PAPSS item 2 (itching) between groups from Baseline to Weeks 4, 8 and 12 • Mean change comparison in PAPSS item 3 (redness) between groups from Baseline to Weeks 4, 8 and 12 • Mean change comparison in PAPSS item 4 (bumps) between groups from Baseline to Weeks 4, 8 and 12 Rosacea erythema assessment at Week 12 • Telangiectasia assessment at Week 12 • The proportion of patients in treatment relative to control who report at least "minimally improved" as measured by the PGI-C at Week 12 • Mean change in the components of the PAPI score between groups from Baseline to Week 12 • Proportion of patients in the treatment relative to control achieving a three-point improvement in the components of the PAPI score from Baseline to Week 12 • Patient Global Impression of Symptom Severity (PGI-S) at Week 12 • Patient Global Impression of Treatment Satisfaction (PGI-TS) at Week 12 • A set of cumulative distribution function (CDF) curves will be generated to allow for the evaluation of within-person change by treatment group. Specifically, 5 plots will be generated showing the change from baseline to Week 12 [and/or other, earlier time points if so desired] by the cumulative percent of subjects for each of the treatment arms (change on the x-axis will be expressed as absolute change) on: o PAPSS total scale scores; o PAPSS item 1 (burning) scores; o PAPSS item 2 (itching) scores; o PAPSS item 3 (redness) scores; and o PAPSS item 4 (bumps) scores

5.1. Synopsis

Safety Endpoints:	• Adverse events (AEs), including serious adverse events (SAEs) occurring at any time during the trial. • Investigator Cutaneous Safety Assessment and Local Tolerability Assessments score at any time during the trial.
Safety:	The incidence of all adverse events reported during the study will be summarized by treatment group. Safety will be evaluated by comparing the nature, severity and frequency of their adverse event profiles. Safety variables include Investigator Cutaneous Safety Assessment score, treatment-emergent adverse events (AEs), SAEs, treatment related AEs, AEs leading to study discontinuation and concomitant medications

5.1. Synopsis

Statistical Method:	**General Statistical Methods** All statistical processing will be performed using SAS® version 9.3 or later unless otherwise stated. Statistical significance will be based on two-tailed tests of the null hypothesis resulting in p-values of 0.05 or less. **Analysis Populations** The intent-to-treat (ITT) population will consist of all randomized patients who were dispensed study product. The safety population will be comprised of all randomized patients who are presumed to have used the study product at least once and who provide at least one post-baseline safety evaluation. Patients will be considered per protocol (PP) if they complete the 12-week evaluation without noteworthy study protocol violations (i.e., any patient or investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy). Patients that discontinue from the study due to an adverse event related to study treatment or documented lack of treatment effect will be included in the PP population. Data for these subjects will not be imputed by multiple imputation but rather their data will be imputed with values consistent with their status as treatment failures. Prior to breaking the blind, other additional criteria may be added to the list to accommodate for unforeseen events that occurred during the conduct of the trial that result in noteworthy study protocol violations **Evaluations and Analyses** Inflammatory lesion count will be recorded for each patient at Baseline and at Weeks 2, 4, 8 and 12. The absolute and percent change from baseline of inflammatory lesions will be derived for each patient at Weeks 2, 4, 8 and 12. The IGA will be recorded for each patient at Baseline, Weeks 2, 4, 8 and 12. The IGA will be dichotomized into “success” and “failure” at Weeks 2, 4, 8 and 12 with a patient considered a success for those visits if the IGA is at least 2 grades less than baseline and are Clear or Almost Clear. The Rosacea erythema assessment, and telangiectasia assessment will be recorded at Baseline, Weeks 2, 4, 8 and 12. Patients will be asked to complete a Patient Reported Outcome, PRO questionnaire at Baseline, Weeks 2, 4, 8 and 12 and a Rosacea Quality of Life, RosaQoL questionnaire at Baseline and Week 12(or at the early termination visit). All assessments will be conducted for both ITT and PP.

5.1. Synopsis

Statistical Method (continued):	**Statistical Hypothesis Testing** Tests of superiority for the absolute change from Baseline in inflammatory lesions will be based on either parametric or non-parametric methods consistent with the statistical assumptions required to support the analyses. Specifically, the tests of superiority will be based on an ANCOVA with factors of treatment and analysis center and the respective Baseline lesion count as a covariate or on ranked data submitted to an ANCOVA with factors of treatment and analysis center and the respective Baseline lesion count as a covariate. If the treatment-by-analysis center interaction effect is significant at an alpha less than 0.10, then the effect will be included in the model; otherwise it will be removed. A skewness test, based on the methods presented by Zar 1984, will be applied to the residuals resulting from an ANCOVA. A two-sided p-value for the skewness test significant at 0.01 will imply the use of the non-parametric method. If a parametric analysis is indicated, the results of the parametric analysis will be considered the primary analysis. Should a non-parametric analysis be indicated, the absolute or percent changes in inflammatory lesions will be rank-transformed prior to submitting them to the ANCOVA. Results of the rank-transformed analyses then will be considered the primary analysis; however, results of the non- rank-transformed analyses will also be presented. The IGA will be dichotomized into "success" and "failure" with a patient considered a success for those visits if the Investigator's Global Assessment is at least 2 grades less than Baseline and "Clear" or "Almost Clear". The analysis of the dichotomized IGA will be based on a logistic regression test with factors of treatment group and analysis center. **Missing Efficacy Data Imputations** Missing Week 12 data will be estimated by multiple imputation and subsequently analyzed. Missing lesion count data will be derived for the analysis using the method of Markov Chain Monte Carlo (MCMC) multiple imputation. The pattern of missing observations in each treatment group cannot influence the missing value estimation in the other because the imputation will be conducted independently for each treatment group.
Safety Evaluation:	Safety will be evaluated by tabulations of adverse events (AEs), Cutaneous Safety Assessments for dryness and scaling, assessments for scores (erythema and telangiectasia) and Patient Global Impression of Treatment Side-Effects (PGI-SE) will be presented with descriptive statistics at Baseline and at the scheduled study visits. Frequencies and percentages for each outcome category will be included in these statistics.

5.2. Study Flow Chart

Procedures	**Visit 1[1]**	**Visit 2[2]**	**Visit 3[2]**	**Visit 4[2]**	**Visit 5[2]**	**Visit 6[2,3] (EOT[4]/ EOS[5])**
Name of Visit	**Screening -35 – 0**	**Baseline Day 1**	**Week 2 Day 15**	**Week 4 Day 29**	**Week 8 Day 57**	**Week 12 Day 85**
Visit window			**± 3 days**	**± 3 days**	**± 3 days**	**± 4 days**
Informed Consent	X					
Demographics	X					
Medical History/Previous Therapies	X	X				
Brief Physical Examination		X				X
Inclusion/Exclusion Criteria	X	X				
Urine Pregnancy Test[6]	X	X		X	X	X
IGA	X	X	X	X	X	X
Inflammatory Lesion Counts	X	X	X	X	X	X
Assessment of Eligibility		X				
Rosacea Erythema Assessment		X	X	X	X	X
Telangiectasia Assessment		X	X	X	X	X
Randomization		X				
Cutaneous Safety Assessment and Local Tolerability Assessments		X	X	X	X	X
Administer/ Review Patient Instructions		X	X	X	X	
Weigh Study Product		X		X	X	X
Study Product Dispensed		X[7]		X	X	
Provide Cleanser and Moisturizer/Sunscreen[8]		X				
Diary Card dispensed		X		X	X	
Study Product Collected				X	X	X
Diary Card collected				X	X	X
Patient Compliance Reviewed (Diary)			X	X	X	X
Concomitant Therapy and Medication History Reviewed	X	X	X	X	X	X
Adverse Events	X[9]	X	X	X	X	X
Photography (select site(s))		X	X	X	X	X
Complete PAPSS, PAPI and PGI-S[10,11]		X	X	X	X	X
Complete PGI-C, PGI-TS and PGI-SE[12]			X	X	X	X
Complete RosaQoL[13]		X				X

[1] If no washout is needed, Visits 1 and 2 may occur on the same day. If a washout is needed, Visit 2 must occur within one month 35 days of Visit 1.

[2] All visit dates are in reference to Baseline, e.g., Visit 5 occurs 8 weeks ± 3 days after Baseline Visit.

[3] All Week 12 procedures should be completed for Patients who terminate early.

[4] EOT – end of treatment

[5] EOS – end of study

[6] All women of childbearing potential

[7] Dispense one pump of test material at the Baseline Visit and dispense additional pump at Visit 4 and 5.

[8] Or study approved cleanser and moisturizer

[9] Adverse events after ICF is signed will be collected.

[10] PAPSS is Patient Assessment of Papulopustular rosacea Signs and Symptoms; PAPI is Patient Assessment of Papulopustular rosacea Impacts; PGI-S is Patient Global Impression of Symptom Severity. Questionnaires will be completed prior to PI assessment.

[11] In case Screening Visit and Baseline are on the same day, the PRO questionnaires should be completed prior to screening procedures.

[12] PGI-C is Patient Global Impression of Change; PGI-TS is Patient Global Impression of Treatment Satisfaction; PGI-SE is Patient Global Impression of Treatment Side-Effects. Questionnaires will be completed prior to PI assessment.

[13] RosaQoL is a Rosacea Quality of Life questionnaire.

6. LIST OF ABBREVIATIONS AND TERMS

AE(s)	Adverse Event(s)
ANCOVA	Analysis of Covariance
BPO	Benzoyl Peroxide
°C	Degrees Centigrade
CFR	Code of Federal Regulations
CRO	Contract Research Organization
E-BPO	Encapsulated Benzoyl Peroxide
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
g	Grams
cGCP	current Good Clinical Practice
h	hour(s)
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IGA	Investigator's Global Assessment
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
min	Minutes
mg	Milligram
NRS	Numerical Rating Scale
OTC	Over-the-Counter
PAPI	Patient Assessment of Papulopustular Rosacea Impacts
PAPSS	Patient Assessment of Papulopustular Rosacea Signs and Symptoms
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Symptom Severity
PGI-SE	Patient Global Impression of Treatment Side-Effects
PGI-TS	Patient Global Impression of Treatment Satisfaction
PI	Principal Investigator
PRO	Patient Reported Outcome

PP	Per Protocol
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
VRS	Verbal Rating Scale

7. INTRODUCTION AND BACKGROUND

S5G4T-1 is an innovative topical formulation containing 5% encapsulated benzoyl peroxide (E-BPO) that Sol-Gel is developing for the treatment of rosacea. If approved, S5G4T-1 will be the first product containing E-BPO for the treatment of rosacea. Sol-Gel believes S5G4T-1 has the potential to be as tolerable as, and more effective than, currently marketed rosacea drugs.

Rosacea is a chronic and recurrent inflammatory dermatological disorder of unknown etiology. The disease is common, especially in fair-skinned people of Celtic and northern European heritage. The onset of the disorder is usually between the ages of 30 and 50. Early stages of the disease affect women more often than men at a ratio of 3 to 1 (Jansen and Plewig 1997 and McDonnell and Tomecki 2000). Rosacea usually starts as flushing and subtle redness on the cheeks, nose, chin or forehead. Alcohol, hot drinks, spicy foods, stress, sunlight and extreme heat or cold can trigger the onset of this disease. If left untreated, rosacea can slowly worsen over time. As the condition progresses, patients experience inflammatory lesions (papules and pustules), vivid erythema and telangiectasia. Patients may develop furuncles, cystic nodules, granulomas and tissue hypertrophy, sometimes leading to rhinophyma.

The first report on the treatment of rosacea with benzoyl peroxide as a single agent was described by in Montes *et al.* in 1983. In this limited study, 5% benzoyl peroxide, after 5 to 8 weeks of treatment, demonstrated superiority compared to control with respect to papules, pustules and erythema but not telangiectasia. The formulation was a basic formulation with benzoyl peroxide dissolved and delivered in acetone. Irritation and burning was reported in both groups, most likely due to the well-known effects of benzoyl peroxide.

More recently, Breneman *et al.* 2004 published the results of a study in collaboration with J. Leyden. This study was a double-blind, vehicle-controlled study, using a combination gel product of 5% benzoyl peroxide and 1% clindamycin to treat patients having moderate to severe rosacea. The most dramatic effect of the benzoyl peroxide/clindamycin treatment was on the reduction of papules and pustules. Side effects included the well-known effects of benzoyl peroxide, burning and itching.

Yamasaki *et al.* published a paper in 2007 which may explain why benzoyl peroxide potentially has a therapeutic benefit in the treatment of rosacea. The team reported that a protease that splits the antimicrobial peptide, cathelicidin, from its protein precursor is elevated in inflammatory rosacea. Cathelicidin subsequently induces the formation of the pro-inflammatory cytokine IL-8. It has also been previously reported that *Propionibacterium acnes* induces elevated levels of cathelicidin in the skin. These observations support the hypothesis that *P. acnes* has a major role in the etiology of rosacea, and provide a mechanistic understanding of why benzoyl peroxide may have a therapeutic benefit in the treatment of rosacea.

Rosacea is treated with both systemic and topical therapies. However, topical therapies are preferable because of side effects caused by the use of systemic therapies.

According to the U.S. National Rosacea Society, approximately 16 million people in the United States are affected by rosacea. According to a study commissioned by the Sponsor, approximately 4.8 million people in the United States experience subtype II symptoms and physicians estimate that only 20% of the U.S. rosacea population is treated. The topical drugs approved by the FDA to treat subtype II rosacea generated aggregate revenues of approximately $392 million in the United States for the 12 months period ending June 30, 2017.

8. OBJECTIVE

- **The primary objective of this pivotal study is:**

1. To assess the efficacy and safety of S5G4T-1 compared to S5G4T-1 Vehicle when applied once daily for 12 weeks in patients with papulopustular rosacea.

The co-primary efficacy endpoints are to be evaluated using the following parameters:

- Proportion of patients with the primary measure of success "Clear" (0) or "Almost clear" (1) in the IGA relative to Baseline at Week 12.
- Absolute change in inflammatory lesion counts from baseline to Week 12.

- **The secondary objective of this pivotal study is:**

To demonstrate statistical superiority in efficacy of S5G4T-1 compared to the vehicle with regard to percent change from baseline.

The co-secondary efficacy endpoints are:

- Percent change in inflammatory lesion count from baseline to Week 12
- Absolute change in inflammatory lesion count from baseline to Week 8
- Proportion of patients with the primary measure of success "Clear" (0) or "Almost clear" (1) in the IGA relative to Baseline at Week 8
- Absolute change in inflammatory lesion count from baseline to Week 4
- Proportion of patients with the primary measure of success "Clear" (0) or "Almost clear" (1) in the IGA relative to Baseline at Week 4

- **The supportive objective of this pivotal study is:**

To determine the time required to observe improvement in the efficacy parameters associated with clearance of rosacea for S5G4T-1 compared to vehicle.

Supportive efficacy endpoints include the following:

- Percent change in inflammatory lesion count at Week 8
- Percent change in inflammatory lesion count at Week 4
- Mean change comparison in PAPSS item 1 (burning) between groups from Baseline to Weeks 4, 8 and 12
- Mean change comparison in PAPSS item 2 (itching) between groups from Baseline to Weeks 4, 8 and 12
- Mean change comparison in PAPSS item 3 (redness) between groups from Baseline to Weeks 4, 8 and 12
- Mean change comparison in PAPSS item 4 (bumps) between groups from Baseline to Weeks 4, 8 and 12 Rosacea erythema assessment at Week 12
- Telangiectasia assessment at Week 12
- The proportion of patients in treatment relative to control who report at least "minimally improved" as measured by the PGI-C at Week 12

- Mean change in the components of the PAPI score between groups from Baseline to Week 12
- Proportion of patients in the treatment relative to control achieving a three-point improvement in the components of the PAPI score from Baseline to Week 12
- Patient Global Impression of Symptom Severity (PGI-S) at Week 12
- Patient Global Impression of Treatment Satisfaction (PGI-TS) at Week 12.
- A set of cumulative distribution function (CDF) curves will be generated to allow for the evaluation of within-person change by treatment group. Specifically, 5 plots will be generated showing the change from baseline to Week 12 [and/or other, earlier time points if so desired] by the cumulative percent of subjects for each of the treatment arms (change on the x-axis will be expressed as absolute change) on:

  PAPSS total scale scores;

  PAPSS item 1 (burning) scores;

  PAPSS item 2 (itching) scores;

  PAPSS item 3 (redness) scores; and

  PAPSS item 4 (bumps) scores

- **The safety objective of this pivotal study is:**

The safety objectives of this study are to determine the nature, severity and frequency of the adverse event rate, the Cutaneous Safety Assessment and the Local Tolerability Assessment of S5G4T-1 compared to the vehicle.

The safety endpoints to be assessed include the following:

- Adverse events (AEs), including serious adverse events (SAEs) occurring at any time during the trial.
- Investigator Cutaneous Safety Assessment and Local Tolerability Assessments score at any time during the trial.

9. ETHICS

This study will be conducted in compliance with FDA regulations, the ethical principles of the Declaration of Helsinki, and the current ICH- Good Clinical Practice (cGCP) guidelines. The investigator and all study staff will conduct the study in compliance with this protocol.

The protocol, informed consent documents, any information provided to patients, recruitment advertisements and any amendments to these items will have Institutional Review Board (IRB) approval prior to their use in the study. Voluntary informed consent will be given by every patient prior to the initiation of any study related procedures. The rights, safety and well-being of the study patients are the most important considerations and prevail over the interests of science and society.

All personnel involved in the conduct of this study must be qualified by education, training and experience to perform their assigned responsibilities.

10. INSTITUTIONAL REVIEW BOARD (IRB) AND INFORMED CONSENT

Before study initiation, this protocol, the investigational brochure for encapsulated benzoyl peroxide cream (E-BPO) in the treatment of rosacea, the informed consent form, and any other written information given to patients, and any advertisement for patient recruitment must have IRB approval. The investigator will submit documentation of the IRB approval to the Sponsor, Sol-Gel Technologies Ltd., or their CRO designee.

The IRB-approved consent form must include all elements required by FDA, state, and local regulations, and may include appropriate additional elements.

The investigator/designee will explain the study to each potential patient and the patient must indicate voluntary consent by signing and dating the approved informed consent form. The consent process will be conducted prior to the start of any study-related procedures including a washout period. The investigator must provide the patient with a copy of the consent form, in a language the patient understands.

The investigator will maintain documentation that informed consent was obtained prior to the initiation of any study-related procedures.

11. OVERALL STUDY DESIGN

This study will be a randomized, double-blind, multicenter, parallel group, active- and vehicle-controlled pivotal study of the efficacy, and safety of S5G4T-1 and its vehicle for the treatment of papulopustular rosacea for 12 weeks. Approximately 350 patients with moderate to severe rosacea (rated 3 or 4 on the 5-point IGA scale) will be enrolled at up to 28 sites. Patients in this randomized, double-blind, vehicle-controlled, parallel-group multi-center study will be randomly assigned in a 2:1 ratio to S5G4T-1 or vehicle, respectively. Subjects with severe rosacea who are appropriate for systemic treatment need to be counseled regarding their treatment options by the Principal Investigator.

Patients will receive once daily treatment with S5G4T-1 or vehicle cream for 12 weeks. After the screening period, qualified patients will be randomly assigned at the Baseline visit and treated for 12 weeks. Efficacy assessments will include facial inflammatory lesion counts and IGA assessment ranging from 0 (Clear) to 4 (Severe). Investigators will be provided with instructions for lesion counts to ensure consistency of procedure. Patient reported outcomes (PRO) will be assessed with the PAPSS (Patient Assessment of Papulopustular rosacea Signs and Symptoms), PAPI (Patient Assessment of Papulopustular rosacea Impacts) and PGI-S (Patient Global Impression of Symptom Severity) that will be administered at Baseline, Weeks 2, 4, 8 and 12, or at early termination. In addition, the PGI-C (Patient Global Impression of Change), PGI-TS (Patient Global Impression of Treatments Satisfaction) and PGI-SE (Patient Global Impression of Treatments Side Effects) will be administered at Weeks 2, 4, 8 and 12, or at early termination [FDA Guidance 2009]. Rosacea Quality of Life (RosaQoL) questionnaire will be administered at Baseline, and Week 12, or at early termination. Safety will be assessed at all visits and will include monitoring local and systemic adverse events (AEs); the investigator Cutaneous Safety Assessment rating of erythema, dryness and scaling and Local Tolerability Assessments rating of itching and burning/stinging on a scale ranging from 0 (None) to 3 (Severe).

Patients will return to centers for IGA, lesion counts, PRO questionnaire, , Investigator Cutaneous Safety Assessment and Local Tolerability Assessments at Weeks 2, 4, 8 and 12. At Week 12 (or at the early termination visit) patients will be asked to complete RosaQoL questionnaire. Adverse events and concomitant medications will be assessed throughout the treatment period. A urine pregnancy test is required at Visit 1, 2, 4, 5 and 6 for all females of child-bearing potential.

Clinical Evaluations will be performed at:

- Visit 1/Screening
- Visit 2/Baseline, Day 1
- Visit 3/Week 2, Day 15 (± 3 Days)
- Visit 4/Week 4, Day 29 (± 3 Days)
- Visit 5/Week 8, Day 57 (± 3 Days)
- Visit 6/Week 12, Day 85 (± 4 Days)/End of Treatment)

12. STUDY POPULATION

12.1. Randomization and Blinding

It is planned that approximately 350 patients who meet the inclusion/exclusion criteria will be enrolled in this study at up to 28 U.S. study sites. Patients will be at least 18 years of age and older, of either gender. Efforts will be made to enroll patients ages matching the target study population.

The study product will be administered in a double-blinded fashion, i.e., the treatment assignment will not be known to the patient, to study personnel, or Sol-Gel and its representatives. Patients will be instructed not to discuss the study product with the study personnel. Patients will be randomly assigned in a 2:1 ratio as follows:

- E-BPO Cream, 5% (S5G4T-1) (234 patients)
- Vehicle Cream (S5G4T-2) (117 patients)

Each patient who signs an informed consent, meets inclusion/exclusion criteria, and successfully completes the screening procedures, will be enrolled in the study. The patient randomization schedule will be a permuted block design stratified by investigational site. Blocks will be composed of 3 treatment assignments in a ratio of 2:1 study product and vehicle, respectively. Complete blocks from the randomization schedule will be allocated to investigational sites as they randomize patients to maintain the randomization ratio of 2:1 study product and vehicle, respectively.

Additionally, the staff involved in data management and statistical evaluation will remain blinded until identification of the per protocol population is finished and a database lock memo is issued.

The randomization schedule and treatment code will not be revealed to the patients, study personnel, Sol-Gel or its representatives until after the database lock, except to the Medical Monitor or Principal Investigator for an emergency. Access to the randomization list will be maintained by and limited to the unblinded Biostatistician and the designated personnel directly responsible for labeling of study materials. The Medical Monitor will not have access to the randomization list, but may determine that unblinding one or all patients may be necessary in the case that the safety of study patients is at risk. In an emergency, the study blind may be broken only if:

- In the opinion of the Medical Monitor and/or the PI, it is in the patient's best interest to do so
- Knowledge of the treatment will alter the clinical management of the patient

In the case of an emergency that requires unblinding, the Investigator can request to unblind the patient without prior contact with the Medical Monitor although follow-up between the Investigator and Medical Monitor must occur so that all parties are aware of the unblinding. Although it is recommended that the Investigator contact the Medical Monitor prior to unblinding any patient, in instances where this is not feasible or advisable the PI may directly access the patient's treatment assignment. In all situations, the Interactive Web Response System (IWRS) will be used to obtain treatment assignment information with limited access to only the above-designated individuals, and any unblinding will be documented as a protocol deviation.

12.2. Inclusion Criteria

To be included in the study, patients must meet the following eligibility /inclusion criteria:

1. Patient must sign an Institutional Review Board (IRB) approved written informed consent for this study.
2. Male and female 18 years of age and older.
3. Patients must have clinical diagnosis of moderate to severe rosacea with a Baseline (IGA Score of 3 (moderate severity) or 4 (severe) on a severity scale of 0 to 4.
4. Have a minimum total of 15 and a maximum total of 70 inflammatory lesions (papules and/or pustules) including those present on the nose.
5. Have two nodules or less (nodule defined as a papule or pustule greater than 5 mm in diameter) at Baseline.
6. Patients must be willing and able to understand and comply with the requirements of the study, apply the medication as instructed, refrain from use of the following medications (during the study, return for the required treatment period visits, comply with therapy prohibitions, and are able to complete the study):
    - topical rosacea medication including: Metronizadole 0.75% to 1%, Azelaic acid, Brimonidine, Oxymetazoline, Sodium Sulfacetamide 10%, Sulfur 5%, Benzoyl Peroxide, Clindamycin, Erythromycin, Benzoyl Peroxide and Clindamycin, Sulfur lotions, retinoids, Ivermectin Cream 1%, Ivermectin lotion 0.5%, or
    - topical and systemic (oral and injectable) antibiotics known to impact rosacea e.g., tetracycline and its derivatives, erythromycin and its derivatives, doxycycline and its derivatives, minocycline and its derivatives, azithromycin and its derivatives, clarithromycin and its derivatives, metronidazole and its derivatives, sulfamethoxazole, or trimethoprim and retinoids (e.g., isotretinoin)
7. Patients must be willing to minimize or not significantly alter controllable external factors that might trigger rosacea flare-ups (such as spicy food, thermally hot foods, soups and drinks, hot environments, prolonged sun exposure, strong winds, alcoholic beverages, etc.) throughout their participation in the study.
8. Patients must be generally healthy and free from any clinically significant disease, other than rosacea, that might interfere with the study evaluations.
9. Sexually active females of child-bearing potential, excluding women who are sterilized (including Essure procedure, tubal ligation, bilateral oophorectomy or hysterectomy) or post- menopausal for at least 2 years, must use one of the following birth control options*:
    - Intrauterine device (IUD)
    - Hormonal (injections, implants, transdermal patch, vaginal ring)
    - Abstinence
    - Oral contraceptives,
    - Female condom
    - Diaphragm with spermicides

- Cervical cap with spermicides
- Contraceptive sponge

* In addition, patients entering the trial that are on hormonal contraceptives must have been on this method for at least 3 months (90 days) prior to the trial and continue the method for the duration of the trial. Patients who had used hormonal contraception and stopped must have stopped no less than 3 months prior to Baseline. Patients entering the study who had an Essure procedure must have had this procedure at least 3 months prior to the study and have undergone an Essure confirmation test to ensure its efficacy. A sterile sexual partner is not considered an adequate form of birth control.

12.3. Exclusion Criteria

Patients are excluded from the study if any of the following criteria are met:

1. Females, who are pregnant, breastfeeding, or planning a pregnancy within the period of their study participation or were found to have positive pregnancy test at baseline or screening visits.
2. Presence of more than 2 facial nodules or any nodule greater than 1 cm.
3. Current or past ocular rosacea (e.g., conjunctivitis, blepharitis, or keratitis) of sufficient severity to require topical or systemic antibiotics.
4. Presence of any other facial skin condition that might interfere with rosacea diagnosis and/or assessment including but not limited to (e.g., on the face: rosacea conglobata, rosacea fulminans, acne vulgaris, acne conglobata, acne fulminans, or secondary acne (chloracne, drug-induced acne, etc.), facial pustulosis of the chin, dermatitis (including peri-orbital and seborrheic dermatitis), demodicidosis, facial keratosis pilaris, acute lupus erythematous, psoriasis, eczema, acneiform eruptions caused by medications, steroid acne, steroid folliculitis, sunburn, rhinophyma, or bacterial folliculitis).
5. Any uncontrolled, chronic or serious disease or medical condition that would prevent participation in a clinical trial or, in judgment of the Investigator, would put the patient at undue risk or might confound the study assessments.
6. Excessive facial hair (e.g., beards, sideburns, moustaches, etc.) that would interfere with diagnosis or assessment of rosacea.
7. History of unresponsiveness to topical benzoyl peroxide.
8. Concurrent use of drugs causing acneiform eruptions (e.g., azathioprine, haloperidol, halogens, lithium, systemic corticosteroids, phenytoin, phenobarbital, testosterone, anabolic steroids, isoniazid).
9. Known sensitivities to the study product ingredients. Allergy to benzoyl peroxide, parabens and glycerin or other ingredients listed in the investigator brochure.
10. Use:
    - within 180 days prior to Baseline or during the study of oral retinoids (e.g., Accutane®) or therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed).
    - within 90 days prior to Baseline radiation therapy and/or anti-neoplastic agents.

- start or change of dose within 90 days prior to Baseline or during the study of vasodilators, vasoconstrictors, anticoagulation or beta-blockers therapy and use throughout the study. Use of such therapy must remain constant throughout the study.
- start or change of dose within 90 days prior to Baseline of hormonal treatment (oral, implanted, topical contraceptives and androgens). Use of such therapy must remain constant during the study.
- within 30 days prior to Baseline or during the study of therapeutic Vitamin D supplements of greater than 2,000 units/day (daily multivitamins with Vitamin D not exceeding more than 2000 IU/day are allowed). If a patient on a constant stable prescribed weekly dose, they should remain on this dose during the study.
- within 30 days prior to Baseline or during the study of (1) systemic steroids, (2) topical retinoids to the face (e.g., tretinoin) (3) systemic (e.g., oral or injectable) antibiotics known to impact rosacea (e.g., tetracycline and its derivatives, erythromycin and its derivatives, doxycycline and its derivatives, minocycline and its derivatives, macrolides and its derivatives, azithromycin and its derivatives, clarithromycin and its derivatives, metronidazole and its derivatives, sulfamethoxazole, bactrim or trimethoprim); short term treatment of all other antibiotics (not affecting rosacea for) ≤ 14 days for non-rosacea related conditions is acceptable, (4) immunosuppressive agents, or immunomodulators (e.g. cyclosporine, tacrolimus, pimecrolimus).
- of medicated make-up (including anti-aging make-up) throughout the study and significant change in the use of consumer products within 14 days of study entry and throughout the study.
- of niacin and niacinamide (Vitamin B3) within 24 hours of study entry and throughout the study.
- of intranasal and inhaled corticosteroids do not require a washout and may be used throughout the study if at a stable and standard dose.

11. Facial use within 14 days prior to Baseline or during the study of (1) topical steroids, (2) topical anti-inflammatory agents or topical non-steroidal anti-inflammatory drugs (NSAID), (3) topical antimycotics, (4) any topical rosacea treatments (e.g., Metronizadole 0.75% to 1%, Azelaic acid, Brimonidine, Oxymetazoline, Sodium Sulfacetamide 10%, Sulfur 5%, Benzoyl Peroxide, Clindamycin, Erythromycin, Benzoyl Peroxide and Clindamycin, Sulfur lotions, Retinoids, Ivermectin) or (5) topical antibiotics.
12. Use on the face within 30 days prior to Baseline or during the study of (1) cryodestruction or chemodestruction, (2) dermabrasion, (3) photodynamic therapy, (4) acne surgery, (5) intralesional steroids, (6) laser resurfacing or electrodessication, (7) x-ray therapy, (8) pulse dye laser, (9) long-pulsed Nd-YAG laser, (10) Intense pulse light or pulse light laser, (11) electrocautery or electrocoagulation, (12) CO_2 laser, Fractioned lasers, or loop electrosurgery, (13) facial peels or other facial cosmetic surgery (e.g., Thermage®, etc.).
13. Use of medicated cleansers on the face (e.g., benzoyl peroxide, salicylic acid, sulfur or triclosan) within 7 days of Baseline and throughout the study.
14. Patient consumes excessive alcohol, abuses drugs, or has a condition that could compromise the patient's ability to comply with study requirements and/or have drug or alcohol addiction requiring treatment in the past 12 months.

15. Use of topical astringents or abrasives (e.g., rubs, exfoliating cleansers and products containing salicylic acid and/or alcohol), topical preparations that contain spices or lime, medicated topical preparations (prescription and OTC products) within 7 days prior to Visit 2 (Baseline) and throughout the study.
16. Use of antipruritics (including antihistamines), spa or sauna treatments or chlorine exposure (swimming pool etc.) within 24 hours (1 day) of all study visits (Visit 2, Baseline, through End of Study).
17. Participation in any clinical study involving an investigational product, agent or device that might influence the intended effects or mask the side effects of study product, within 30 days prior to Visit 2 (Baseline) and throughout the study.
18. Previous enrollment in this study or current enrollment in this study at another participating site.
19. Employee (or employee's family member) of the research center or private practice, or patients who have a conflict of interest.
20. Patients living (e.g., siblings, spouses, relatives) in the same household cannot be enrolled in the study at the same time.
21. Use of tanning booths, sun lamps or excessive UV radiation (e.g., phototherapy, daily extended exposure or occupational exposure to the sun), sunbathing or excessive exposure to the sun 1 week (7 days) prior to Baseline and throughout the study.
22. Patients who in the opinion of the investigator, are unlikely to be able to follow the restrictions of the protocol and complete the study.

12.4. Prohibited, Previous and Concomitant Therapies

Any previous rosacea therapies must be stopped for the appropriate washout period as specified below and as noted in the exclusion criteria:

- Topical astringents or abrasives or preparations that contain spices or lime, medicated topical preparations applied to the face (prescription and OTC products) within 7 days prior to Baseline.
- Use of medicated cleansers on the face (e.g., benzoyl peroxide, salicylic acid, sulfur or triclosan) within 7 days of Baseline.
- Topical anti-rosacea treatments – 2 weeks prior to Baseline.
- Topical antibiotics, antimicrobials – 2 weeks prior to Baseline.
- Topical anti-inflammatories on the face such as corticosteroids, vasoconstrictors and non-steroidal anti-inflammatory drugs (NSAID) – 2 weeks prior to Baseline.
- Topical retinoids – 30 days prior to Baseline.
- Systemic rosacea treatments, corticosteroids, antibiotics – 4 weeks prior to Baseline.
- Systemic retinoids – 6 months prior to Baseline.

Other than the study products, no other topical medications are permitted to be used on the face. All topical or systemic medications listed above and under exclusion criteria are prohibited. Other prohibited treatments include but are not limited to astringents, toners, clarifying lotions, medicated shaving products, cosmetic procedures and chemical peeling products used on the face. A stable regimen of inhaled corticosteroids for stable medical conditions (in the 2 months preceding enrollment) and antibiotic treatment of an infection of less than 14 days are allowed during the study.

No medicated cleansers or moisturizers are allowed on the face. Only the sponsor-provided cleanser and moisturizer/sunscreen (or a study-approved cleanser or moisturizer/sunscreen) will be allowed to be used on the face during the study. Study product shall be applied to clean skin and no cleanser should be applied to the face within two hours of study product application. Approved moisturizer/sunscreen may be applied after 30 minutes or more of study product application. Patients who use make-up must have used the same brands/types of make-up for a minimum period of 1 month (30 days) prior to study entry and must agree to not change make-up brand/type or frequency of use throughout the study. Patients should not apply the moisturizer or sunscreen or combination of them or wear make-up during study visits as it may interfere with the evaluator's assessments.

All concomitant therapies used during the study must be recorded on the Concomitant Therapy electronic case report form (eCRF).

Therapies (medication and non-medication therapies) not restricted by the protocol may be used during the study for the treatment or prevention of disease or to maintain good health. Vitamins and mineral supplements are permitted at dosages considered by the investigator as reasonable for maintaining good health. Non-prohibited chronic therapies being used at Baseline (Visit 2) may be continued. Patients may use systemic anti-inflammatory agents [i.e., NSAIDs (ibuprofen or aspirin) for pain relief] as needed (with no more than 7 days of consecutive use) throughout the study. Prophylactic use of low dose aspirin (81 mg) is allowed. Patients may use acetaminophen for pain relief, as needed throughout the study.

Any changes in concomitant therapies during the study must be recorded on the Concomitant Therapy form at each visit. The reason for any change in concomitant therapies should be reported as, or in conjunction with, an adverse event except as noted below:

- Prophylactic therapies, such as vaccines, must be recorded on the Concomitant Therapy form, but the reasons for these therapies should not be reported as adverse events.
- Changes in therapy for pre-existing conditions that are not related to a worsening of the condition must be reported on the Concomitant Therapy form, but the reasons for these changes should not be reported as adverse events. The condition must be reported in the Medical History.

If a patient receives prohibited treatment during the study, the patient may be allowed to continue in the study at the discretion of the investigator and Sponsor / Medical Monitor.

Patients should avoid UV exposure by sun bathing or tanning parlors.

12.5. Precautions

The following precautions are to be taken during this study:

1. Patients should avoid contact of the study product with the eyes, mouth, and lips or on any cuts or broken skin. In case of accidental exposure, the eyes should be rinsed with plenty of water.
2. The study product should not be applied to cuts, abrasions, eczematous or sunburned skin.
3. Patients should wash hands before and after applying study product.
4. Patients should allow the treated area to completely dry for at least 30 minutes after applying the study product to avoid spreading it on other areas of the face (e.g., eyes, ears, neck, etc.) and pillow cases.
5. The study product should be spread evenly in a thin layer on each area of the face (chin, left cheek, right cheek, nose, left forehead and right forehead); excessive rubbing must be avoided.
6. The study product should not be applied more than once daily and patients should not use more than the recommended amount.
7. Patients should not wash their face more than 2 or 3 times a day.
8. Facial makeup (non-medicated) may be applied according to the patient's normal daily routine (but not prior to 30 minutes after study product application).
9. Patients should not apply moisturizers, make-up, creams, lotions, powders or any topical product they do not routinely use on their face
10. Patients should not cover the treated area with a bandage (occlusive dressing) or other types of dressing after applying the study product.
11. Patients should limit sun exposure, including sunlamps (non-prescription UV light sources); avoid tanning beds/booths/parlors and sauna while using the study product.
12. Patient should use moisturizer with SPF supplied by the Sponsor or from study-approved list product and protective apparel (e.g. wide- brimmed hat) when outdoors. Patients should wait approximately 30 minutes after study product is applied on the face before applying a sunscreen. Weather extremes, such as wind or cold, may be irritating to patients receiving treatment.
13. UVA/UVB treatments are also prohibited.
14. Patients must not wear make-up to any study visits, so as not to interfere with the evaluations. If a patient comes to his/her visits with make-up on his/her face, the patient will be allowed to wash his/her face with a non-medicated cleanser and must wait at least 30 minutes before any study evaluation is made by the Principal Investigator (PI) or Sub-Investigator (Sub-I).
15. Patients should consult the investigator with any questions regarding concomitant medications.
16. Abrasive cleansers or washes, alcoholic toners, astringents are prohibited throughout the study.
17. "Waxing" as a depilatory method should be avoided on skin treated with study product.
18. Patients should be informed that local skin reactions [dryness, burning/stinging, pruritus (itching), scaling/peeling] may occur.
19. Patients should minimize or not significantly alter consumption of any foods and beverages that might provoke erythema, flushing, and blushing (including spicy food, alcoholic beverages, and thermally hot drinks, including hot coffee and tea) throughout the study.

13. STUDY PROCEDURES

13.1. Study Patient Identification

When the patient signs the informed consent, he/she will be assigned a three (3)-digit patient number. The complete patient ID will consist of the 3-digit site number followed by the 3-digit patient number: e.g., [redacted] (first patient screened at site [redacted]). This number will remain with the patient for the duration of the study and will not be reassigned to another patient should the patient screen fail.

13.2. Screen Failure and Discontinuation Criteria

A screen failure is a patient who is not randomized/enrolled in the study due to ineligibility, after signing an Informed Consent Form, and would not have received study product. The Informed Consent Form signed by the patient should be kept with the source document for patients who do not pass the screening procedures. The documentation should include identification of the eligibility criterion or criteria that were and were not met. The patient should not be re-screened for this study without Sol-Gel's approval.

Although encouraged to complete the study whenever possible, patients are free to discontinue their participation in this study at any time and for any reason without prejudice. A patient may be withdrawn from the study prior to study completion for any of the following reasons:

- Investigator opinion that it is not in the patient's best interest to continue.
- Patient Request /Withdraw Consent – Whenever the patient decides it is in his/her best interest to withdraw.
- Lack of Efficacy/ Worsening of Condition.
- Adverse Event – when the investigator thinks it's in the patient's best interest
- Lost to Follow-up – Documentation confirmed at minimum by two phone calls and certified letter. Every effort should be made to capture an explanation for the lost-to follow-up event.
- Protocol Violation – When requirements of the protocol are not respected, especially when patient safety is concerned.
- Pregnancy.
- Unblinding of study product.

Study staff should make efforts to encourage patients to complete the study on time. If a patient prematurely withdraws during the study, every effort should be made to complete at least the Week 12/End of Study assessments.

In the case of patients who discontinue due to an Adverse Event, the Investigator will conduct follow-up contacts with the patient until the Investigator, Sponsor and Medical Monitor agree the event is satisfactorily resolved and/or stabilized.

Patients discontinued early from the study shall not be replaced.

13.3. Patient Screening and Enrollment

The study personnel will review the IRB approved informed consent form with each patient and give the patient an opportunity to have all questions answered before proceeding. The consent form must be signed by each patient before the patient is enrolled into the study. A copy of the signed consent will be given to every patient (or legally authorized representative) and the original will be maintained with the patients' records.

Patients that require a wash-out of more than 30 days from their initial informed consent/assent signing must be re-consented before any further study procedures can begin.

13.4. Assignment of Randomization

The patient randomization schedule will be a permuted block design stratified by investigational site. Blocks will be composed of 3 treatment assignments in a ratio of 2:1 study product and vehicle, respectively. Complete blocks from the randomization schedule will be allocated to investigational sites as they randomize patients. Patients will be randomized through the IWRS and assigned a unique randomization ID indicating treatment group. The study product supplies will be packed in 4 pumps per kit and will be numbered in a scrambled randomized method. The kits will be dispensed by the IWRS according to the randomized treatment group.

The first supplied pump in each kit is marked A (e.g. number of pump within a kit is XXXXA), at Visit 4/ Week 4 the patient will return the pump and will be dispensed with the next pump which is marked B. At Visit 5/ Week 8, the patient will return the pump and will be dispensed with a pump marked C. Pump marked as D may be dispensed to patients who lost/damaged/ran-out of study product.

13.5. Demographics/Medical History

A demographic profile and complete medical history will be recorded prior to starting study product. The medical history will include a complete review of all current diseases and their respective treatments.

13.6. Concomitant Medications

Concomitant medications and any medications taken in the 30 days prior to signing informed consent will be recorded as prior/concomitant medications (using their generic name, if known) with the corresponding indication. The medications to be recorded will include prescription and over-the-counter (OTC) medications and dietary supplements. All medications taken on either a regular or "prn" basis, including vitamins, aspirin and acetaminophen, should be recorded on this page prior to commencing the use of the study product.

13.7. Physical Examination

The investigator, sub-investigator or appropriately delegated and qualified designee will perform a brief physical examination, prior to the patient starting study product. The exam will include heart, lung, abdomen evaluation as well as recording height, weight and vital signs. Vital signs are to include sitting blood pressure, oral temperature, heart rate and respiratory rate.

13.8. Urine Pregnancy Test

Females of childbearing potential (excluding women who are surgically sterilized or post-menopausal for at least 2 years), in addition to having a negative urine pregnancy test, must be willing to use an acceptable form of birth control during the study. An investigator could repeat the pregnancy test at any time during the study if there is any suspicion or possibility that the patient is pregnant. Urine pregnancy test will also be conducted starting at Visit 1/Screening and at each visit [Baseline, Weeks 2, 4, 8 and 12 (End of Study)]. For the purpose of this study, the following are considered acceptable methods of birth control: intrauterine device (IUD); hormonal (injections, implants, transdermal patch, vaginal ring); abstinence; oral contraceptives; female condom; diaphragm with spermicides; cervical cap with spermicides; contraceptive sponge.

Patients entering the trial that are on hormonal contraceptives must have been on this method for at least 3 months (90 days) prior to the trial and continue the method for the duration of the trial. Patients who had used hormonal contraception and stopped must have stopped no less than 3 months prior to Baseline. Patients entering the study who had an Essure procedure must have had this procedure at least 3 months prior to the study and have undergone an Essure confirmation test to ensure its efficacy. A sterile sexual partner is not considered an adequate form of birth control.

13.9. Study Flow Chart

Procedures	**Visit 1[1]**	**Visit 2[2]**	**Visit 3[2]**	**Visit 4[2]**	**Visit 5[2]**	**Visit 6[2,3] (EOT[4]/ EOS[5])**
Name of Visit	**Screening -35 – 0**	**Baseline Day 1**	**Week 2 Day 15**	**Week 4 Day 29**	**Week 8 Day 57**	**Week 12 Day 85**
Visit window			**± 3 days**	**± 3 days**	**± 3 days**	**± 4 days**
Informed Consent	X					
Demographics	X					
Medical History/Previous Therapies	X	X				
Brief Physical Examination		X				X
Inclusion/Exclusion Criteria	X	X				
Urine Pregnancy Test[6]	X	X		X	X	X
IGA	X	X	X	X	X	X
Inflammatory Lesion Counts	X	X	X	X	X	X
Assessment of Eligibility		X				
Rosacea Erythema Assessment		X	X	X	X	X
Telangiectasia Assessment		X	X	X	X	X
Randomization		X				
Cutaneous Safety Assessment and Local Tolerability Assessments		X	X	X	X	X
Administer/ Review Patient Instructions		X	X	X	X	
Weigh Study Product		X		X	X	X
Study Product Dispensed		X[7]		X	X	
Provide Cleanser and Moisturizer/Sunscreen[8]		X				
Diary Card dispensed		X		X	X	
Study Product Collected				X	X	X
Diary Card collected				X	X	X
Patient Compliance Reviewed (Diary)			X	X	X	X
Concomitant Therapy and Medication History Reviewed	X	X	X	X	X	X
Adverse Events	X[9]	X	X	X	X	X
Photography (select site(s))		X	X	X	X	X
Complete PAPSS, PAPI and PGI-S[10,11]		X	X	X	X	X
Complete PGI-C, PGI-TS and PGI-SE[12]			X	X	X	X
Complete RosaQoL[13]		X				X

[1] If no washout is needed, Visits 1 and 2 may occur on the same day. If a washout is needed, Visit 2 must occur within 35 days of Visit 1.

[2] All visit dates are in reference to Baseline, e.g., Visit 5 occurs 8 weeks ± 3 days after Baseline Visit.

[3] All Week 12 procedures should be completed for Patients who terminate early.

[4] EOT – end of treatment

[5] EOS – end of study

[6] All women of childbearing potential

[7] Dispense one pump of test material at the Baseline Visit and dispense additional pump at Visit 4 and 5.

[8] Or study approved cleanser and moisturizer

[9] Adverse events after ICF is signed will be collected.

[10] PAPSS is Patient Assessment of Papulopustular rosacea Signs and Symptoms; PAPI is Patient Assessment of Papulopustular rosacea Impacts; PGI-S is Patient Global Impression of Symptom Severity. Questionnaires will be completed prior to PI assessment.

[11] In case Screening Visit and Baseline are at the same day, the PRO questionnaires should be completed prior to screening procedures.

[12] PGI-C is Patient Global Impression of Change; PGI-TS is Patient Global Impression of Treatment Satisfaction; PGI-SE is Patient Global Impression of Treatment Side-Effects. Questionnaires will be completed prior to PI assessment.

[13] RosaQoL is a Rosacea Quality of Life questionnaire

13.10. Screening Visit (Visit 1)

If no washout is needed, Visits 1 (Screening) and 2 (Baseline) may occur on the same day. If a washout is needed, Visit 2 (Baseline) must occur within 35 days of Visit 1 (Screening). The following procedures will be conducted at this visit:

- Obtain a signed and dated, written informed consent for all patients prior to any study related procedures.
- Confirm the patient meets the inclusion/exclusion criteria as outlined in Section 12.2 and Section 12.3.
- Record any adverse events.
- Perform a urine pregnancy test for all females of childbearing potential (see Section 12.2); the results must be negative for the patient to be enrolled.
- Report the medical history and demographics for the patient.
- Record the patient's concomitant medications and/or therapies on Concomitant Therapy form as outlined in Section 13.8.
- Perform investigator's global assessment (IGA) to determine eligibility (See Section 14.1)
- Perform facial inflammatory lesion counts to determine eligibility: (Section 14.2).
- Determine if patient requires washout and schedule Baseline Visit.

13.11. Baseline Visit (Visit 2, Day 1)

The following procedures will be conducted at this visit:

- Confirm the patient continues to meet the inclusion/exclusion criteria.
- Update since Screening Visit the medical history for the patient.
- Ask the patient to complete PAPSS, PAPI questionnaire (see Appendix 2 and Appendix 3). Patient will also complete the PGI-S questionnaire (see Appendix 4). The PAPSS, PAPI and PGI-S questionnaires are to be completed prior to any other assessments or procedures as described in Section 14.5. In case Screening Visit and Baseline are at the same day, the PRO questionnaires should be completed prior to screening procedures.
- Ask the patient to complete Rosacea Quality of Life (RosaQoL) questionnaire (see Appendix 8).
- Perform brief physical examination as described in Section 13.7.
- Perform a urine pregnancy test for all females of childbearing potential (see Section 13.8); the results must be negative for the patient to be enrolled.
- Update since screening the patient's concomitant therapies on Concomitant Therapy form as outlined in Section 13.6.
- Perform the efficacy evaluations including the Investigator's Global Assessment, inflammatory lesion counts, rosacea erythema assessment, and telangiectasia assessment described in Sections 14.1 to 14.4. Every effort shall be made to have the same investigator perform the Baseline and Visit 6/Week 12 evaluations for the same patient.
- Perform Cutaneous Safety Assessment and Local Tolerability Assessment as described in Sections 16.1 to 16.2.

- Take standardized photography of face (at selected sites, see separate photographic manual for instructions) as described in Section 15.
- Weigh the study product before dispensing.
- Instruct the patient on the study product application as described in Appendix 1. Pump usage will be demonstrated by the site personnel on a sample pump at the clinic to help assure the patient understands the procedure.
- Dispense the Patient Instruction Sheet and Diary Card to the patient (see Appendix 1 for appropriate instructions for study patients).
- Record any adverse events.
- Instruct the patient that throughout the study overexposure of the face to sunlight should be avoided. Instruct the patient to use the sponsor-provided cleanser and moisturizer/sunscreen; any exposure to tanning beds must be avoided during the study.
- Perform randomization for study product by using IWRS.
- Dispense study product pump to patient.
- Remind patient to not wear make-up to all subsequent visits
- Schedule the next study visit.

13.12. On treatment (Visit 3) – Week 2, Day 15 (± 3 days)

The following procedures will be conducted at this visit:

- Ask the patient to complete PAPSS, PAPI questionnaire (see Appendix 2 and Appendix 3). Patient will also complete the PGI-S questionnaire (see Appendix 4), PGI-C (see Appendix 5), PGI-TS (see Appendix 6) and PGI-SE (see Appendix 7). The PAPSS, PAPI, PGI-S, PGI-C PGI-TS and PGI-SE questionnaires are to be completed prior to any other assessments or procedures as described in Section 14.5.
- Observe and query the patient in a non-directive fashion about any adverse events since the previous study visit. Initiate or update the appropriate adverse event form as required.
- Query the patient about any changes in concomitant therapies since the previous study visit and update the Concomitant Therapy eCRF as required.
- Perform the efficacy evaluations including the Investigator's Global Assessment, inflammatory lesion counts, rosacea erythema assessment, and telangiectasia assessment described in Sections 14.1 to 14.4.
- Perform Cutaneous Safety Assessment and Local Tolerability Assessment as described in Sections 16.1 to 16.2.
- Take standardized photography of face (at selected sites, see separate photographic manual for instructions) as described in Section 15.
- Review the patient's compliance with the study requirements (review patient diary).
- Record number of missed doses on the appropriate eCRF page.
- Review the study product application instructions with the patient.
- Schedule/confirm the next study visit.

13.13. On-treatment Visits (Visits 4 and 5) – Weeks 4 and 8, Days 29 and 57 (± 3 days)

The following procedures will be conducted at these visits:

- Ask the patient to complete PAPSS, PAPI questionnaire (see Appendix 2 and Appendix 3). Patient will also complete the PGI-S questionnaire (see Appendix 4), PGI-C (see Appendix 5), PGI-TS (see Appendix 6) and PGI-SE (see Appendix 7). The PAPSS, PAPI, PGI-S, PGI-C PGI-TS and PGI-SE questionnaires are to be completed prior to any other assessments or procedures as described in Section 14.5.
- Observe and query the patient in a non-directive fashion about any adverse events since the previous study visit. Initiate or update the appropriate adverse event form as required.
- Query the patient about any changes in concomitant therapies since the previous study visit and update the Concomitant Therapy eCRF as required.
- Perform a urine pregnancy test for all females of childbearing potential (see Section 12.2).
- Perform efficacy evaluations: IGA, inflammatory lesion counts, rosacea erythema assessment, and telangiectasia assessment described in Sections 14.1 to 14.4.
- Perform Cutaneous Safety Assessment and Local Tolerability Assessment as described in Sections 16.1 to 16.2. Take standardized photography of face (at selected sites, see separate photographic manual for instructions) as described in Section 15.
- Review the patient's compliance with the study requirements; collect and review the Patient Diary Card.
- Dispense a Diary Card to the patient
- Record number of missed doses on the appropriate eCRF page.
- Review the study product application instructions with the patient.
- Collect and weigh returned study product pump.
- Weigh and dispense the next pump of study product.
- Schedule/confirm the next study visit.

13.14. On-treatment (Visit 6) – Week 12, Day 85 (± 4 days) or End of Treatment or Early Termination

The following procedures will be conducted at this visit:

- Ask the patient to complete PAPSS, PAPI questionnaire (see Appendix 2 and Appendix 3). Patient will also complete the PGI-S questionnaire (see Appendix 4), PGI-C (see Appendix 5), PGI-TS (see Appendix 6) and PGI-SE (see Appendix 7). The PAPSS, PAPI, PGI-S, PGI-C PGI-TS and PGI-SE questionnaires are to be completed prior to any other assessments or procedures as described in Section 14.5.
- Ask the patient to complete Rosacea Quality of Life (RosaQoL) questionnaire (see Appendix 8).
- Observe and query the patient in a non-directive fashion about any adverse events since the previous study visit.
- Query the patient about any changes in concomitant therapies since the previous study visit and update the Concomitant Therapy eCRF.
- Perform physical examination as described in Section 13.7.

- Perform efficacy evaluations: IGA, inflammatory lesion counts, rosacea erythema assessment, and telangiectasia assessment described in Sections 14.1 to 14.4. The evaluator who performed the Baseline evaluations should perform all subsequent evaluations for a patient. when this is not possible, it is recommended that another delegated evaluator with overlapping experience with the patient may perform the evaluations.
- Perform Cutaneous Safety Assessment and Local Tolerability Assessment as described in Sections 16.1 to 16.2.
- Take standardized photography of face (at selected sites, see separate photographic manual for instructions) as described in Section 15.
- Review the patient's compliance with the study requirements; collect and review the Patient Diary Card.
- Record number of missed doses and report the last date the patient applied the study product.
- Perform a urine pregnancy test for all females of childbearing potential (see Section 12.2).
- Collect and weigh the study product.
- Complete the End of Study/Study Termination eCRF.
- Discharge the patient from the study.

14. CLINICAL OUTCOME ASSESSMENTS

The determination of efficacy will be based on investigator evaluations of the signs and symptoms of rosacea. Evaluators must be a physician or have appropriate documented experience and training. Every effort will be made to ensure appropriate training is provided to the investigators for consistent diagnosis and evaluation of rosacea.

For consistency of evaluations, the same designated evaluator who performs the Baseline assessments shall perform the assessments at Visit 6/Week 12; when this becomes impossible, another delegated evaluator may perform the assessments.

14.1. Investigator Global Assessment (IGA)

The Investigator Global Assessment (IGA) will be performed at Screening/Baseline, Weeks 2, 4, 8 and 12 (End of Study) visits.

Patients are eligible for enrollment if they have facial rosacea with a global severity of a 3 (moderate) or a 4 (severe) on the IGA scale.

The IGA scale provided in Table 1 will be used to describe the severity grade and subsequent score:

Table 1: Investigator Global Assessment (IGA) Scale

Grade	Description
0 – Clear	Skin clear of inflammatory papules or pustules
1 – Almost Clear	Very few small papules or pustules and very mild dull erythema is present
2 – Mild	Few small papules or pustules and mild dull or light pink erythema is present
3 – Moderate	Several to many small or larger papules or pustules and moderate light to bright red erythema is present
4 – Severe	Numerous small and/or larger papules or pustules and severe erythema that is bright red to deep red is present

14.2. Inflammatory Lesion Counts

Inflammatory lesions (papules and pustules) counts will be performed at Screening, Baseline, Weeks 2, 4, 8 and 12 (End of Study) visits. At Screening/Baseline patients must have at least 15 and not more than 70 inflammatory lesions (papules, pustules) on the face.

Papules and pustules are defined as follows:

- **Papule** – A solid, elevated inflammatory lesion equal to or less than 5 mm in diameter
- **Pustule** – An elevated inflammatory lesion equal to or less than 5 mm in diameter, contains pus (yellow-white exudate)

Nodules will not be included in the inflammatory lesion count and are defined as:

- **Nodule/Cyst** – Palpable solid inflammatory lesion, greater than 5 mm in diameter, has depth, not necessarily elevated

14.3. Erythema Severity Assessments

Erythema is defined as redness of the skin. It will be scored on a scale of 0 (none) to 3 (severe) at Baseline, Weeks 2, 4, 8, and 12 (End of Study) visits. The Rosacea Erythema Assessment Scale is provided in Table 2.

Table 2: Rosacea Erythema[a] Assessment Scale

Grade	Description
0 – None	No visible erythema
1 – Mild	Slight erythema (dull or light pink), centro-facial
2 – Moderate	Definite erythema (light to bright red), either centro-facial or generalized to whole face
3 – Severe	Severe erythema (bright red to deep red), either centro-facial or generalized to whole face

[a] Generalized erythema associated with rosacea

14.4. Telangiectasia Assessment

Facial telangiectasia will be evaluated on a scale of 0 to 3 at Baseline and Weeks 2, 4, 8 and 12 (End of Study) visits; the Telangiectasia is provided in Table 3

Table 3: Telangiectasia Assessment Scale

Grade	Description
0 – None	No Telangiectasia
1 – Mild	Only a few fine vessels discernible, involves approximately 10% or less of facial area
2 – Moderate	Multiple and more prominent fine vessels, involves approximately 10 – 30% of the facial area
3 – Severe	Numerous and prominent fine and/or courser vessels, involves more than 30% of the facial area

14.5. Patient Reported Outcomes (PRO)

There are six PRO questionnaires to be administered in the study and each is summarized below. Each will be administered to all patients during the designated study visits with instruction from the Study Staff that they be completed:

- Only by the patient without amendment or interpretation of the patient's response by a clinician or anyone else.
- Prior to any other assessments or procedures.

In the event the patient skips any questionnaire items; the Study Staff will ask the patient to complete the form. The PRO questionnaire data will be entered into EDC, and a copy will be placed with the patient source at the site according to the ICH-GCP guideline (4.9.5).

The PAPSS (Appendix 2): The PAPSS is a 4-item questionnaire that asks patients to assess the severity of their rosacea symptoms (burning, itching, redness, and bumps) in the 24 hours prior to assessment on an 11-point numeric rating scale (NRS) ranging from "0=none" to "10=worst possible symptom". The questionnaire can be completed in less than one minute and is administered via pen-and-paper at the Baseline visit and site visits at Weeks 2, 4, 8 and 12 (End of Study) or early termination. Items can be scored individually as well as together to form a total score. In the present context, within visit scores from Items 1 (burning), 2 (itching), and 4 (bumps) are summed and averaged to create a total score that will be used to evaluate efficacy hypotheses.

The PAPI (Appendix 3): The PAPI is a 3-item questionnaire that asks patients to assess the papulopustular rosacea related embarrassment, self-consciousness, and frustration in the 7 days prior to assessment on an 11-point NRS ranging from 0 ["not (concept) at all"] to 10 ["extremely (concept)"]. The questionnaire can be completed in less than one minute and is administered via pen-and-paper at the Baseline visit and site visits at Weeks 2, 4, 8 and 12 (End of Study) or early termination. Items can be scored individually as well as together to form a total score.

PGI-S (Appendix 4): The PGI-S is a single item questionnaire that asks respondents to describe the severity of their rosacea symptoms "right now" (i.e., at the present moment) on a five-point verbal response scale ranging from "Clear" (face is clear, no redness) to "Severe" (face has numerous small and/or large bumps, severe redness). Patients are encouraged to look in a mirror to help with their response and the questionnaire can be completed in less than 30 seconds. The PGI-S is administered via pen-and-paper at the Baseline visit and site visits at Weeks 2, 4, 8 and 12 (End of Study) or early termination. Though data generated from the PGI-C can be supportive of efficacy hypotheses, the primary purpose of the tool is to support anchor-based analyses that will inform how researchers may interpret the meaning of change in the primary and secondary assessments.

PGI-C (Appendix 5): The PGI-C is a single item questionnaire that asks respondents to describe the change they have noticed in their rosacea symptoms since the start of the study a 7-point VRS ranging from "Very much improved" to "Very much worse". Patients are encouraged to look in a mirror to help with their response and the questionnaire can be completed in less than 30 seconds. The PGI-C is administered via pen-and-paper at the site visits at Weeks 2, 4, 8 and 12 (End of Study) or early termination. Though data generated from the PGI-C can be supportive of efficacy hypotheses, its primary purpose is to support anchor-based analyses that will inform how researchers may interpret the meaning of change in the primary and secondary assessments.

PGI-TS (Appendix 6): The PGI-TS is a single item questionnaire that asks respondents to describe how satisfied they are "right now" with the rosacea treatment administered as part of the study on a 5-point VRS ranging from "I am very satisfied" to "I am very dissatisfied". The questionnaire can be completed in less than 30 seconds and is administered via pen-and-paper at the site visits at Weeks 2, 4, 8 and 12 (End of Study) or early termination. Though data generated from the PGI-TS can be used for other purposes, its primary purpose is to support anchor-based analyses that will inform how researchers may interpret the meaning of change in the primary and secondary assessments.

PGI-SE (Appendix 7): The PGI-SE is a single item questionnaire that asks respondents to describe how bothered they are "right now" with the rosacea treatment administered as part of the study on a 5-point VRS ranging from "I am not bothered" to "I am extremely bothered". The questionnaire can be completed in less than 30 seconds and is administered via pen-and-paper at the site visits at Weeks 2, 4, 8 and 12 (End of Study) or early termination. Though data generated from the PGI-TSE can be used for other purposes, its primary purpose is to support anchor-based analyses that will inform how researchers may interpret the meaning of change in the primary and secondary assessments.

14.6. Rosacea Quality of Life (RosaQoL)

There is a symptom subscale with seven questions (items 2, 6, 9, 16, 17, 18 and 19 in Appendix 8), a functional subscale with 3 questions (items 13, 15 and 21 in Appendix 8) and an emotion subscale with 11 questions (items 1, 3, 4, 5, 7, 8, 10, 11 12, 14 and 20 in Appendix 8) to be administered in the study. The questionnaire will be administered to all patients during the designated study visits with the appropriate instructions from the Study Staff. The questionnaire should be completed:

- Only by the patient without amendment or interpretation of the patient's response by a clinician or anyone else.
- After completion of the Patient Reported Outcomes (PRO) questionnaires

In the event the patient skips any questionnaire items; the Study Staff will ask the patient to complete the form. The QoL questionnaire data will be entered into the EDC system by the Study Staff, and a copy will be placed with the patient source documents at the site according to the ICH-GCP guideline (4.9.5).

All items should be scored for the following answers:

- Never: 1
- Rarely: 2
- Sometimes: 3

- Often: 4
- All the time: 5

The Site Staff and anyone else provided with a copy of the RosaQoL instrument for the purpose of the study will be instructed that the RosaQoL instrument is protected by Common Law copyright. No part of this may be reproduced or transmitted in any form or by any means, now known or to be invented or adapted, for purpose of financial gain or profit.

An overall total score will be calculated; this score will be the unweighted mean of all RosaQoL questions. In addition to the total score, each subscale (symptom, functional and emotion) will also have a score calculated; these scores will the unweighted mean of the group of questions that comprise the subscale. Further details on the handling of missing responses and calculation of the subscale scores will be detailed in the Statistical Analysis Plan (SAP).

15. PHOTOGRAPHY

Standardized photography of facial rosacea at Baseline, and at the site visits at Weeks 2, 4, 8 and 12 (End of Study) will be performed at select sites. These photographs will be optional for patients at the selected sites and will not be used for efficacy assessment purposes. Participating investigators shall refer to separate photographic manual for instructions.

16. SAFETY EVALUATIONS

Safety will be assessed by monitoring incidence of Cutaneous Safety Assessment, Local Tolerability Assessment and adverse events reporting; at Baseline, at all treatment and end-of-treatment visits.

16.1. Cutaneous Safety Assessments

The evaluator will assess local application site cutaneous reactions by rating the dryness and scaling at the Baseline visit and site visits at Weeks 2, 4, 8 and 12 (End of Study) or unscheduled visits. The evaluator will determine the score for each of these variables by direct evaluation. The definitions of grades provided in Table 4 will be applied to these evaluations. The Cutaneous Safety Assessment of dryness and scaling will be made by the investigator at the time of the visit.

Table 4: Cutaneous Safety Assessment Scale

Grade	Description
Dryness	
0 – None	No dryness
1 – Mild	Slight but definite dryness
2 – Moderate	Moderate dryness
3 – Severe	Marked dryness and/or cracking
Scaling	
0 – None	No scaling
1 – Mild	Barely perceptible scaling
2 – Moderate	Obvious but not profuse scaling
3 – Severe	Heavy scale production and/or peeling

Application site reactions (dryness and scaling) are not to be recorded as adverse events unless they result in either:

- The temporary discontinuation of the study product.
- The discontinuation of the patient from the study.
- The use of a new concomitant medication in order to treat this event.

Any other application site reaction not listed above (such as pain) should be recorded as adverse events in the source document and eCRFs.

16.2. Local Tolerability Assessments

The evaluator will assess local application site tolerability by rating the itching and burning/stinging at the Baseline visit and site visits at Weeks 2, 4, 8 and 12 (End of Study) or unscheduled visits. The evaluator will determine the score for each of these variables by asking the patient to grade their experience over the **past 24 hours**. The definitions of grades provided in Table 5 will be applied to these evaluations. The Local Tolerability Assessment evaluations of itching and burning/stinging will be made by the investigator at the time of the visit.

Table 5: Local Tolerability Assessment Scale

Grade	Description
Itching	
0 – None	No itching
1 – Mild	Slight itching, not really bothersome
2 – Moderate	Definite itching that is somewhat bothersome
3 – Severe	Intense itching that may interrupt daily activities and/or sleep
Burning/Stinging	
0 – None	No burning/stinging
1 – Mild	Slight burning/stinging sensation; not really bothersome
2 – Moderate	Definite warm, burning/stinging sensation that is somewhat bothersome
3 – Severe	Hot burning sensation that causes definite discomfort and may interrupt daily activities or sleep

Application site reactions (itching and burning/stinging) are not to be recorded as adverse events unless they result in either:

- The temporary discontinuation of the study product.
- The discontinuation of the patient from the study.
- The use of a new concomitant medication in order to treat this event.

Any other application site reaction not listed above should be recorded as adverse events in the source document and eCRFs.

17. ADVERSE EVENTS

17.1. Departure from the Protocol for Individual Patients

When an emergency occurs requiring a departure from the protocol for a patient, departure will be only for that patient. In such circumstances, the investigator or other physician in attendance will contact the Medical Monitor or the Sponsor by telephone and follow up with a written description as soon as possible. The overseeing IRB should also be notified.

17.2. Definitions

An adverse event (AE) is defined as any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

A serious adverse event (SAE) is an adverse event that results in any of the following outcomes:

- Death
- Life-threatening event (i.e., the patient was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death)
- Requires in-patient hospitalization or prolongs hospitalization
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect
- Other adverse events that may be considered serious based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Immediately Reportable Adverse Events (IRAE) is any serious AE or any AE that necessitates discontinuation of study product, including pregnancy.

Unexpected Adverse Event is any adverse drug experience, the specificity or severity of which is not consistent with the current approved product labeling (package insert) for the study product, the Investigator's Brochure, or as described in the clinical protocol and consent materials.

Intensity of Adverse Events are the maximum intensity of an AE during a day should be recorded on the eCRF. If the intensity of an AE changes over a number of days, then separate entries should be made having distinct onset dates for the changes in severity.

- Mild - AEs are usually transient, requiring no special treatment, and do not interfere with patient's daily activities.
- Moderate - AEs typically introduce a low level of inconvenience or concern to the patient and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.
- Severe - AEs interrupt a patient's usual daily activity and traditionally require systemic drug therapy or other treatment.

17.3. Causal Relationship to Study product

The following criteria should be used in assessing the apparent causal relationship of an AE to study product:

Definitely - The AE:

- follows a reasonable temporal sequence from study product administration
- abates upon discontinuation of the study product (de-challenge)
- is confirmed by reappearance of the reaction on repeat exposure

Probably - The AE:

- follows a reasonable temporal sequence from study product administration
- abates upon discontinuation of the study product (de-challenge).
- cannot be reasonably explained by the known characteristics of the patient's state.

Possible - The AE:

- follows a reasonable temporal sequence from study product administration
- but that could readily be produced by a number of other factors.

Unlikely - The AE:

- follows a reasonable temporal sequence from study product administration.
- could have been produced by either the patient's clinical state or by study product administration.

Not related - The AE:

- does not have a reasonable temporal association with the administration of study product
- has some other obvious explanation for the event.

17.4. Eliciting and Reporting of Adverse Events

The investigator will periodically assess patients for the occurrence of adverse events. In order to avoid bias in eliciting adverse events, the patient or parent/legally authorized representative should be asked a non-specific question (e.g., "How have you been feeling since your last visit?") to assess whether any AE has been experienced since the last visit. All adverse events (as defined in Section 17.2), either observed by the Investigator or one of his/her medical collaborators, or reported by the patient spontaneously, or in response to direct questioning, will be reported and documented in the source and the study reporting forms. When reporting an adverse event, the Investigator must assign a severity grade to each event and declare an opinion on the relatedness of the event to the study product or procedure. Serious or unexpected adverse events must be reported to the CRO within 24 hours of when the Investigator first learns of the occurrence of the event.

Adverse events will be documented in the source document and recorded in a timely manner on case report forms. Adverse events that are identified at the last assessment visit (or the Early Termination Visit) must be recorded on the AE eCRF with the status of the AE noted.

Adverse event reporting begins from the signing of informed consent/assent. Study product-related adverse events should be followed until resolved or 30 days after the final study treatment. Regardless the duration of the study, patients that exhibit serious adverse event (SAE), will be followed up until the SAE resolves, based on investigator's medical judgment or are considered to be chronic (stabilized for at least 30 days). All events that are ongoing at this time will be recorded as ongoing on the eCRF.

17.5. Expedited Reporting Responsibilities of the Study Center

For any serious or unexpected adverse event, the Sponsor or its designee must be notified within 24 hours of when the Investigator first learns of the occurrence of the event. Expedited reporting requirements for serious adverse events are described below. Adequate information must be collected with supporting documentation to complete a standard report for submission to Sol-Gel. The adverse event term on the AE eCRF and the SAE report should agree exactly. Special attention should be given to recording hospitalizations and concomitant medications.

Patients with unresolved study or product-related adverse event(s) or serious adverse event(s) should be followed by the investigator until the events are resolved, events determined to be chronic or the patient is lost to follow-up. Resolution means the patient has returned to the Baseline state of health, or the investigator does not expect any further improvement or worsening of the adverse event. The investigator should continue to report any significant follow-up information to the sponsor up to the point that the event has resolved. Any serious adverse event reported by the patient to the investigator that occurs within 30 days after the last assessment, and are determined by the investigator to be reasonably associated with the use of the study product, should be reported to the sponsor within 24 hours of when the Investigator first learns of the occurrence of the event.

When reporting a serious adverse event (SAE) the Investigator (or the Study Coordinator) will promptly report any serious adverse event or pregnancy to the Sponsor or its designee by telephone email, immediately after the investigator becomes aware of the event. An SAE form should be completed and sent by fax, email, or overnight courier to the Sponsor or its designee within 24 hours of knowledge of the event by the site. In many cases, only preliminary information will be available. Appropriate follow up information should be sought (hospital discharge summaries, operative reports etc.) and a follow up SAE report form submitted. A designation of causality from the study product should always be included with a follow up report. Assess and report the causality of the event.

17.6. Submitting an Expedited Safety Report to the IRB

Once all supporting documentation is received for the reported event, the Medical Monitor, in conjunction with Sol-Gel, will determine if the safety report is eligible for expedited review. When expedited safety reporting to regulatory authorities is indeed required, the Investigator should review and update any newly available materials at once. Follow-up queries may be sent to the study center to further clarify the event.

The Sponsor, or its designee, is responsible for submitting reports of serious, unexpected related AEs to regulatory authorities on an expedited basis, according to the ICH E2A Guideline and to other regulatory authorities according to national and local regulations as required. The Sponsor, or its designee, is responsible for prompt submission to the IRB or EC of any expedited SAE reports submitted to regulatory authorities. All investigators participating in ongoing clinical studies will receive copies of the SAE reports submitted on an expedited basis to regulatory authorities

17.7. SAE & AEs Requiring Discontinuation of Study Drug, including Pregnancies

ANY SAE, WHICH OCCURS AFTER A PATIENT HAS ENTERED THE STUDY, WHETHER OR NOT RELATED TO STUDY PRODUCT, MUST BE REPORTED TO THE SPONSOR OR ITS DESIGNEE IMMEDIATELY (WITHIN 24 HOURS) VIA TELEPHONE, EMAIL OR FACSIMILE. IF INITIALLY REPORTED VIA TELEPHONE, THIS MUST BE FOLLOWED-UP BY A FACSIMILE OR EMAIL OF THE WRITTEN SAE REPORT WITHIN 24 HOURS OF THE CALL TO THE SPONSOR OR ITS DESIGNEE.

Non-serious events that require discontinuation of study product (including laboratory abnormalities) should be reported to the Sponsor or its designee immediately and within 1 working day.

Patients who discontinue due to experiencing study product-related adverse events should be followed clinically until their health has returned to baseline status, or until all parameters have returned to normal. It is expected that the investigator will provide or arrange appropriate supportive care for the patient.

A patient who experiences a severe adverse event related to study product will be discontinued from the study, but, regardless of the duration of the study, patients that exhibit serious adverse event (SAE), will be followed up until the SAE resolves, based on investigator's medical judgment or are considered to be chronic (stabilized for at least 30 days). For safety reporting instructions see SAE and Pregnancy Form Report Instructions.

17.8. Pregnancy

At the time, Principal Investigator or site personnel becomes aware that a study patient became pregnant following study participation, the Principal Investigator or designee will report the pregnancy immediately by phone and/or by faxing a completed Pregnancy Report to the Sponsor or its designee within one working day of being notified of the pregnancy report.

The report will include the following elements:

- Patient (mother's) coded study identifier;
- Date of patient's last menstrual period;
- Total accumulated dose of study treatment administered to date;
- Date of study product administration.

The investigator will follow the patient until completion of the pregnancy and must assess the outcome in the shortest possible time but not more than 30 days within completion of the pregnancy.

Upon delivery, miscarriage or abortion, the Principal Investigator or designee must forward a follow-up Pregnancy Report with any relevant information on the present condition of the fetus to the Sponsor or its designee, including:

- Mother's coded study identifier(s);
- Gestational age at delivery, miscarriage or abortion;
- Birth weight, gender, length and head circumference, if available;
- Apgar scores recorded after birth, if available;
- Any abnormalities.

If the outcome of the pregnancy meets the criteria for immediate classification of an SAE (e.g., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the investigator will report the event by phone and by faxing a completed SAE report form to the Sponsor or its designee within one working day of being notified of the pregnancy report.

If the trial is completed before the outcome of the pregnancy is known, the Sponsor or its designee will assume the responsibility for following up on the pregnancy. The Sponsor or its designee will contact the Investigator or Study coordinator on or around the potential expected date of delivery to follow-up on the outcome of pregnancy and will also check on the status of the infant 8 weeks post-delivery. Upon awareness of the pregnancy outcome and known status of the infant following 8 weeks of delivery, the investigator will complete the applicable pregnancy report forms and fax to the Sponsor or its designee within 1 day of being notified.

17.9. Post Study Adverse Events

17.9.1. Non-serious Adverse Events

Adverse events that are identified at the last assessment visit (or the Early Termination Visit) must be recorded on the AE eCRF with the status of the AE noted.

17.9.2. Serious Adverse Events

Serious adverse events that are identified on the last assessment visit (or the Early Termination Visit) must be recorded on the AE eCRF page and reported to Sol-Gel according to the procedures outlined above. Patients with unresolved previously reported serious adverse events, or any new serious adverse events identified on the last assessment visit, should be followed by the investigator until the events are resolved, or the patient is lost to follow-up. Resolution means the patient has returned to the baseline state of health, or the investigator does not expect any further improvement or worsening of the adverse event. The investigator should continue to report any significant follow-up information to Sol-Gel up to the point that the event has resolved. Any serious adverse event reported by the patient to the investigator that occurs after the last assessment, and are determined by the investigator to be reasonably associated with the use of the study product, should be reported to Sol-Gel.

18. STUDY PRODUCTS / CLINICAL SUPPLIES

18.1. Method of Treatment Assignment

Patients who satisfy all the inclusion and none of the exclusion criteria will be randomized to one of two treatment arms. Randomization will be performed in the IWRS according to a computer-generated randomization schedule. The randomization schedule will be generated by the unblinded statistician and uploaded to the IWRS. The randomization schedule will be maintained securely within the IWRS. Patients will be randomized to Encapsulated Benzoyl Peroxide Cream, 5%, or Vehicle Cream, once daily on a 2:1 basis for twelve (12) weeks.

Once a patient is determined eligible for the study at the Baseline visit, the patient will be randomized to study product assignment by the IWRS. Each study product carton will contain four pumps of the same product; The first supplied pump in each kit is marked A (e.g. number of pump within a kit is XXXXA), at Visit 4/ Week 4 the patient will return the pump and will be dispensed with the next pump which is marked B. At Visit 5/ Week 8, the patient will be dispensed with a pump marked C. The pump marked as D is a backup pump. The patient number will be added to both parts of the kit label (open part and tear-off label and to the pump label).

18.2. Formulations

Study Product name:	Encapsulated Benzoyl Peroxide Cream, 5%
Sponsor name:	**S5G4T-1**
Active ingredients:	benzoyl peroxide
Inactive ingredients:	see list below
Placebo Product:	Vehicle Cream (for study product)
Sponsor name:	**S5G4T-2**
Active ingredients:	none
Inactive ingredients:	see list below

The inactive ingredients include: silicon dioxide, cetrimonium chloride, polyquaternium-7, lactic acid, hydrochloric acid, polyoxyl 100 stearate, cetyl alcohol, cyclomethicone 5, glyceryl monostearate, citric acid anhydrous, sodium hydroxide, edetate disodium, glycerin, phenoxy ethanol, methylparaben (only in vehicle) and water.

18.3. Study Products Packaging and Labeling

The study product (Encapsulated Benzoyl Peroxide Cream, 5%), S5G4T-1, and placebo for the study product (Vehicle Cream), S5G4T-2, will be packaged and labeled in 55-g airless pump. At the first 12 weeks of treatment, a double-blind technique will be used. In order to maintain the blind, the study product and vehicle will be supplied in identically-appearing labeled pump cartons. Neither the patient nor the investigational staff (sponsor, investigator, and evaluators) will know which treatment a patient is receiving.

The study products will be shipped to sites in blocks of three (3) products to keep ratio 2:1 between study product and vehicle. The study products will be labeled with the following:

- Protocol Number

- Patient Number
- Kit Number
- Pump Number
- Patient Initials
- Dispense Date
- Dispenser Initials
- Contains: one (1) pump of S5G4T-1 (Encapsulated Benzoyl Peroxide) Cream, 5% or its Vehicle Cream, 55 g
- Directions for use: Apply as directed, for topical use only.
- Storage conditions "Store at Room Temperature 20 to 25°C (68 to 77°F). Excursions permitted between 15 to 30°C (59 to 86°F)."
- Keep container tightly closed.
- Do not freeze and do not refrigerate.
- Keep out of reach of children.
- Study product warning. "Caution: New Drug - Limited by Federal Law to Investigational Use"
- Sponsor Information

Each Study Product Kit Box will contain four (4) pumps and will carry a two-part label with a perforation. The tear-off section of the label will be attached to the study product dispensing log at the time the study product is dispensed. The other label part must remain attached to the box. Both label parts will have spaces to enter the patient's initials, date dispensed, dispenser's initials. The constant label part shows:

- Protocol Number
- Patient Number
- Patient Initials
- Kit Number
- Randomization Date
- Contains: four (4) pumps of Encapsulated Benzoyl Peroxide (E-BPO) Cream, 5% or its Vehicle Cream, 55 g.
- Directions for use: Apply as directed, for topical use only.
- Storage conditions "Store at Room Temperature 20 to 25°C (68 to 77°F). Excursions permitted between 15 to 30°C (59 to 86°F)."
- Keep container tightly closed.
- Do not freeze and do not refrigerate.
- Keep out of reach of children.
- Study product warning. "Caution: New Drug - Limited by Federal Law to Investigational Use"
- Sponsor Information

18.4. Preparation, Dispensing and Storage Instructions

The study product must be dispensed only to study patients and only at study sites specified on the form FDA 1572 by authorized personnel as required by applicable regulations and guidelines.

Study product will be dispensed at: Baseline, Weeks 4 and 8. Study product will be returned at: Weeks 4, 8 and 12. Study product weight will be documented in EDC prior to dispensing and after return of each pump per flow chart (Section 13.9 and Section 5.2).

Each Patient will be instructed on the importance of returning his or her study product at each designated visit. If a Patient does not return his or her study product, he or she will be instructed to return it at the next visit.

The study coordinator will question the patient on history of study product use since the last visit and will record any missed doses (as recorded on the patient diary) in both the source documents and the appropriate eCRF. A patient who deviates significantly from the prescribed dosage will be counseled.

Study product should be stored at room temperature 20 to 25°C (68 to 77°F). Excursions permitted between 15 to 30°C (59 to 86°F). Do not freeze or refrigerate the product.

18.5. Dosing Instructions

Topical application of study product will be made to the face once daily at approximately the same time of the day, for a period of twelve (12) weeks. Study product will be applied as a thin coating that is gently rubbed in to the skin.

Each patient will receive both verbal and written instructions (see Appendix 1) as to the proper dosing and study product application techniques.

Patients will be instructed to apply the study product for 12 weeks, once a day after cleansing. No time interval between dosing and meals or any other activity is specified.

Patients will cleanse their face with the given cleanser or sponsor approved cleanser using only the hands and pat dry with a soft clean towel. Patients will use a “pea-size” amount for each area of the face (chin, left cheek, right cheek, nose, left forehead and right forehead). The Patient should gently rub the cream into the skin. This amount of cream should be sufficient to cover the area on the face excluding the mouth, eyes, inside the nose, and lips. The Patient should wash his/her hands after application but should not wash face at least 2 hours after study product application. Patients should wait at least 30 minutes before applying moisturizer/sunscreen after application of study product to the face. During the trial that investigators remind patients to avoid exposure to sunlight and sunlamps and to wear sunscreen when sun exposure cannot be avoided.

The Patients will be instructed to continue using the same supplied/approved facial cleanser and not to change products during the study. At each visit, Patients are to be asked if they have changed their cleansing routine. The supplied/approved cleanser and moisturizer/sunscreen should be applied according to the directions on the pump. Facial makeup (non-medicated) may be applied according to the patient’s normal daily routine (but not prior to 30 minutes after study product application); however, patients should be instructed not to apply the moisturizer or sunscreen or combination of them or wear make-up during study visits as it may interfere with the evaluator’s assessments. No other products should be used on the face.

Pump usage will be demonstrated by the site personnel on a sample pump at the clinic to help assure the patient understands the procedure. The patient will be provided a set of instructions (Appendix 1) that includes study reminders and restrictions as described in this protocol. Patients will be instructed to bring the study product to each visit and to not apply study product one hour prior to the study visit. Patients should be instructed to store the study product at room temperature, not in the refrigerator or freezer and informed that the test article may bleach colored fabric.

18.6. Study Product Accountability and Study Records at Sites

Upon receipt of the clinical supplies, the study staff will conduct a complete inventory of study products and assume responsibility for their storage and dispensing. In accordance with federal regulations, the Investigators must agree to keep all study products in a secure, temperature-controlled location with restricted access.

All supplies sent to the Investigators will be accounted for and in no case used in any unauthorized manner. All used and unused study product will be appropriately inventoried by the clinical site, and verified by the clinical monitor.

Study product will be weighed before dispensing and upon return and weights will be recorded on the appropriate source document and eCRF.

18.7. Return and Destruction of Study Product Supplies

Upon completion or termination of the study, all remaining pumps (in kits) must be appropriately inventoried and returned to Sponsor or designee by a traceable method. All missing pumps of study products must be explained on the completed Clinical Supplies Return Form. The study site must keep a copy of the Clinical Supplies Return Form in the study file.

18.8. Additional Supplies Provided by Sponsor

- Regulatory study file system (Investigator Binder)
- Urine pregnancy test kits
- Cleanser
- Moisturizer/sunscreen

19. STATISTICAL CONSIDERATIONS

19.1. General Statistical Methods

All statistical processing will be performed using SAS® version 9.3 or later unless otherwise stated. Statistical significance will be based on two-tailed tests of the null hypothesis resulting in p-values of 0.05 or less. These methods are intended to analyze the results of the study.

The primary method of handling missing efficacy data will be based on estimation using the method of Markov Chain Monte Carlo (MCMC) imputation. This method provides robust estimation when the pattern of missingness is arbitrary. Additionally, the estimation will be done for each treatment group separately so that the pattern of missingness for one group does not influence the estimation of missing data for another group. Groups of complete datasets following the estimation will be concatenated to form analysis datasets for the comparative analyses and subsequent imputation result inference with SAS PROC MIANALYZE. Descriptive statistics will also be derived from the multiply imputed datasets.

Additionally, a model-based multiple imputation process will be used as a sensitivity analysis to the MCMC imputation. Finally, the absolute change in lesion count will be analyzed using a repeated measures ANCOVA for lesion count data or a repeated measures logistic regression model (generalized estimating equations) for the dichotomized Investigator's Global Assessment, IGA.

A statistical analysis plan (SAP), describing all statistical analyses will be provided as a separate document. The SAP will be finalized prior to unblinding of the study treatments.

19.1.1. Patient Disposition

A tabulation of patient disposition will be provided. The tabulation will include the numbers of patients who enter the study, complete the study, and discontinue the study. The reasons for discontinuation will be included.

19.1.2. Demographics and Baseline Characteristics

Patient demographic and baseline characteristics will be summarized by treatment group for the ITT, PP, and safety populations. For continuous variables (e.g. age) comparisons among the two treatment groups will be conducted using a two-way analysis of variance (ANOVA) with factors of treatment group and analysis center (see Section 19.4.6 for definition of "analysis center"). Ethnicity and race will be analyzed with a Cochran-Mantel-Haenszel test stratified by analysis center. Past and current medical conditions, as well as history of disease will be presented in a data listing.

19.1.3. Protocol Deviations

All protocol deviations will be reported to the sponsor and recorded throughout the study. A tabulation of protocol deviations will be presented in a data listing.

19.1.4. Analysis Populations

Approximately 350 male and female patients at least 18 years of age with moderate or severe papulopustular rosacea with 3 or 4 [moderate to severe] on the IGA scale will be enrolled and randomized in the study with a 2:1 randomization ratio, it is anticipated that:

- 234 patients will be randomized to receive S5G4T-1, Encapsulated Benzoyl Peroxide (E-BPO) Cream, 5%
- 117 patients will be randomized to receive S5G4T-2, Vehicle Cream

The ITT population will consist of all randomized patients who were dispensed study product. The safety population will be comprised of all randomized patients who are presumed to have used the study product at least once and who provide at least one post-baseline safety evaluation.

An intent-to-treat (ITT) analysis will be conducted on all study patients. A per-protocol (PP) analysis will also be conducted. Patients will be eligible for the PP analysis if they complete the 12-week evaluation without noteworthy study protocol violations (i.e., any patient or investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy). The PP population will include patients in the ITT population who do not meet any of the following criteria:

- Failed any of the inclusion/exclusion criteria;
- Have taken any interfering concomitant medications;
- Did not attend the Week 12 Visit;
- Missed more than 1 post baseline study visit prior to Week 12
- Have not been compliant with the dosing regimen (i.e., Patients may not miss more than five consecutive days of dosing and must take 80 to 120% of expected doses. The number of expected doses will be determined for each patient based on the length of their participation in the study);
- Out of visit window (± 4 days) at the 12-week Visit.

Patients that discontinue from the study due to an adverse event related to study treatment or documented lack of treatment effect will be included in the PP population. Data for these subjects will not be imputed by multiple imputation but rather their data will be imputed with values consistent with their status as treatment failures. Prior to breaking the blind, other additional criteria may be added to the list to accommodate for unforeseen events that occurred during the conduct of the trial that result in noteworthy study protocol violations.

19.2. Study Product Evaluations and Analyses

Inflammatory lesion count will be recorded for each patient at the Baseline and at Weeks 2, 4, 8 and 12. The absolute and percent change from baseline of inflammatory lesions will be derived for each patient at Weeks 2, 4, 8 and 12.

The IGA will be recorded for each patient at the Baseline visit and site visits at Weeks 2, 4, 8 and 12 (End of Study). The IGA will be dichotomized into “success” and “failure” at Weeks 2, 4, 8 and 12 with a patient considered a success for those visits if the IGA is at least 2 grades less than baseline and are Clear or Almost Clear.

The Rosacea Erythema assessment, and Telangiectasia assessment will be recorded at Baseline and at Weeks 2, 4, 8 and 12.

Patients will be asked to complete Patient Reported Outcome, PRO, questionnaires at appropriate time points.

All statistical analysis will be conducted for both PP and ITT population.

19.3. Assessment of Efficacy

Primary, secondary, and supportive efficacy analyses will be conducted on the ITT (primary) population. Primary efficacy analyses will be conducted on the PP (supportive) population.

19.3.1. Primary Efficacy

There are two co-primary efficacy endpoints:

- Proportion of patients with the primary measure of success "Clear" (0) or "Almost clear" (1) in the IGA relative to Baseline at Week 12.
- Absolute change in inflammatory lesion counts from baseline to Week 12.

19.3.2. Secondary Efficacy

The secondary efficacy endpoints will be the following:

- Percent change in inflammatory lesion count from baseline to Week 12
- Absolute change in inflammatory lesion count from baseline to Week 8
- Proportion of patients with the primary measure of success "Clear" (0) or "Almost clear" (1) in the IGA relative to Baseline at Week 8
- Absolute change in inflammatory lesion count from baseline to Week 4
- Proportion of patients with the primary measure of success "Clear" (0) or "Almost clear" (1) in the IGA relative to Baseline at Week 4
- .

19.3.3. Supportive Efficacy

Supportive efficacy endpoints include the following:

- Percent change in inflammatory lesion count at Week 8
- Percent change in inflammatory lesion count at Week 4
- Mean change comparison in PAPSS item 1 (burning) between groups from Baseline to Weeks 4, 8 and 12
- Mean change comparison in PAPSS item 2 (itching) between groups from Baseline to Weeks 4, 8 and 12
- Mean change comparison in PAPSS item 3 (redness) between groups from Baseline to Weeks 4, 8 and 12
- Mean change comparison in PAPSS item 4 (bumps) between groups from Baseline to Weeks 4, 8 and 12 Rosacea erythema assessment at Week 12
- Telangiectasia assessment at Week 12
- The proportion of patients in treatment relative to control who report at least "minimally improved" as measured by the PGI-C at Week 12
- Mean change in the components of the PAPI score between groups from Baseline to Week 12
- Proportion of patients in the treatment relative to control achieving a three-point improvement in the components of the PAPI score from Baseline to Week 12

- Patient Global Impression of Symptom Severity (PGI-S) at Week 12
- Patient Global Impression of Treatment Satisfaction (PGI-TS) at Week 12
- A set of cumulative distribution function (CDF) curves will be generated to allow for the evaluation of within-person change by treatment group. Specifically, 5 plots will be generated showing the change from baseline to Week 12 [and/or other, earlier time points if so desired] by the cumulative percent of subjects for each of the treatment arms (change on the x-axis will be expressed as absolute change) on:
    - PAPSS total scale scores;
    - PAPSS item 1 (burning) scores;
    - PAPSS item 2 (itching) scores;
    - PAPSS item 3 (redness) scores; and
    - PAPSS item 4 (bumps) scores

19.4. Statistical Hypothesis Testing

19.4.1. Test of Superiority for Lesion Count Variables

This section provides the basic model and statistical approach which is used in combination with the multiple imputation procedures described in Section 19.4.6. Tests of superiority for the absolute change from Baseline in inflammatory lesions will be based on non-parametric methods consistent with the statistical assumptions required to support the analyses. Specifically, the tests of superiority will be based on ranked data submitted to an ANCOVA with factors of treatment and analysis center and the respective Baseline lesion count as a covariate.

For informational purposes, a skewness test, based on the methods presented by Zar 1984, will be applied to the residuals resulting from an ANCOVA using the untransformed lesion count data. A two-sided p-value for the skewness test significant at 0.05 would validate the use of the non-parametric method. The results of a non-ranked ANCOVA with factors of treatment and analysis center and the respective Baseline lesion count as a covariate will also be presented for informational purposes.

19.4.2. Test of Superiority for IGA

The IGA will be dichotomized into “success” and “failure” with a patient considered a success for those visits if the Investigator’s Global Assessment is at least 2 grades less than Baseline and “Clear” or “Almost Clear”. The analysis of the dichotomized IGA will be based on a logistic regression test with factors of treatment group and analysis center.

19.4.3. Test of Superiority for Secondary Efficacy and Control of Multiplicity

Appropriate descriptive statistics will be computed for all Secondary Efficacy parameters. Additionally, all inferential testing will follow the methods for the primary lesion count analyses as well as those for the dichotomized IGA success rates (as appropriate).

The overall Type I error will be controlled by requiring the two co-primary efficacy endpoints to be statistically significant. Specifically, failure of either one of the primary efficacy endpoints will invalidate the statistical significance of the secondary efficacy endpoints.

A stepwise process will be conducted for testing the secondary efficacy endpoints in order to control for multiplicity. These tests will be performed for only the ITT population. The testing process will terminate whenever a statistical test for a step is not significant. All subsequent tests for the remaining steps will be considered not significant. The order of testing is provided in Table 6.

Table 6: Process for Testing the Secondary Efficacy Endpoints

Step Number	Secondary Endpoint
1	Percent change in inflammatory lesion count from baseline to Week 12
2	Absolute change in inflammatory lesion count from baseline to Week 8
3	Proportion of patients with the primary measure of success "Clear" (0) or "Almost clear" (1) in the IGA relative to Baseline at Week 8
4	Absolute change in inflammatory lesion count from baseline to Week 4
5	Proportion of patients with the primary measure of success "Clear" (0) or "Almost clear" (1) in the IGA relative to Baseline at Week 4

19.4.4. Supportive Efficacy Analyses

Appropriate descriptive statistics will be computed for all Supportive Efficacy parameters. Additionally, inferential testing for the following endpoints will use an ANOVA with factors of treatment, analysis center and the respective Baseline score. The overall Type I error will be controlled by the Benjamini-Hochberg method. Missing values will not be imputed.

- Mean change comparison in PAPSS item 1 (burning) between groups from Baseline to Week 12
- Mean change comparison in PAPSS item 2 (itching) between groups from Baseline to Week 12
- Mean change comparison in PAPSS item 3 (redness) between groups from Baseline to Week 12
- Mean change comparison in PAPSS item 4 (bumps) between groups from Baseline to Week 12

19.4.5. Exploratory Endpoint

The mean change in RosaQoL subscale scores from Baseline to Week 12.

19.4.6. Pooling Analysis

The clinical study will be conducted under a common protocol for each investigational site with the intention of pooling the data for analysis. Every effort will be made to promote consistency in study execution at each investigational site. The study is intended to be conducted in a manner such that a minimum of 5 patients will be enrolled in each treatment arm for any investigator. In the event that there are too few patients in a treatment arm for an investigator, then this investigator's data will be combined to achieve the desired sample size minimum per arm. The combining of investigator's data will be accomplished by taking the investigator with the smallest enrollment and combining it with the investigator with the largest enrollment. If there is a further need to combine data, then the data of the investigator with the second smallest enrollment will be combined with the investigator's data which had the second largest enrollment and so on. This process will continue for all investigators who did not have a minimum of 5 patients per treatment arm. The process of combining investigator data that have insufficient patients per treatment arm will result in redefining the groups of investigators for the purposes of statistical analyses. These combined groups will be referred to as "analysis centers" in the statistical analyses based on ANCOVA and stratified logistic testing.

Prior to investigating the treatment effect within the analysis centers, the magnitude of the site mail effect will be investigated to determine if the main site-to-site variability is such that it could mask the analysis center effects. Thus, if computationally possible, a one-way ANCOVA (for lesion count variables) or a logistic regression analysis (for IGA) with a factor of site will be conducted prior to pooling. If the data structure interferes with the logistic regression, a descriptive analysis of the site effect will be undertaken. Conclusions appropriate to the findings of this step will be presented.

The consistency of treatment response will be investigated across the analysis centers subsequent to combining the data as described above. Statistical tests will be conducted to identify if there are extreme analysis centers that could affect the interpretation of common statistical and clinical conclusions. An analysis center by treatment interaction will be included in the primary variable analyses to test for parallel treatment effect at an alpha level of 0.10. Change from baseline in inflammatory lesions will be analyzed with an ANCOVA (unranked or ranked) with factors of treatment, analysis center, and treatment by analysis center interaction and the respective baseline lesion count variable as a covariate. For the purpose of testing consistency of treatment response, the dichotomized IGA will be analyzed with a logistic regression procedure with factors of treatment, analysis center, and treatment by analysis center interaction. Further examination will follow for any variables that have a significant ANCOVA or logistic regression interaction term. In the event that the ANCOVA or logistic regression interaction (referred to henceforth as the "appropriate test") p-value is less than or equal to 0.10, a sensitivity analysis that excludes analysis centers with the extreme efficacy result will be performed to determine the robustness of the treatment effect. On the other hand, if the outcome of the appropriate test has a p-value greater than 0.10, then the conclusions from the pooled data will be considered to be free of the impact of extreme analysis centers.

The first step in conducting a sensitivity analysis is to identify the extreme analysis center or centers that contribute to the statistical significance of the appropriate test. The process involves submitting subsets of analysis centers to the appropriate test and observing the appropriate test p-value for the subset. Subsets with p-values greater than 0.10 for the appropriate test are considered homogeneous.

The search for an extreme analysis center begins by analyzing all subsets that can be created by excluding one analysis center. If one or more of the subsets result in an appropriate test p-value greater than or equal to 0.10, then the analysis center excluded from the subset with the largest p-value for the appropriate test is deemed to be the extreme analysis center.

If all appropriate test subset p-values are less than or equal to 0.10, then the process will analyze the appropriate test for all subsets that can be created by excluding two analysis centers. If one or more of these subsets generate appropriate test p-values larger than 0.10, then the analysis centers excluded from the subset with the largest appropriate test p-value are deemed the extreme analysis centers.

Thus, the process of identifying the extreme analysis centers will continue in a stepwise manner by first excluding one, then two, then three, etc., analysis centers until the appropriate test p-value exceeds 0.10.

Once the extreme analysis center or centers have been identified, then the treatment p-values of the remaining analysis centers will be computed. Inferences will be drawn from the treatment p-value, as well as any pertinent observations regarding the extreme analysis center or centers. Additionally, it is noted that this process excludes patients from the analysis in a non-random manner and has an unpredictable impact on the power of the treatment effect test. In the event that the treatment effect of the remaining subset is not statistically significant, due consideration of the post-hoc aspects of the process will be given when the results are interpreted. Conclusions will be presented by the sponsor as appropriate to the findings of the sensitivity analysis.

19.4.7. Missing Efficacy Data Imputations

19.4.7.1. Lesion Count Variable Missing Data Imputation

Missing Week 12 data will be estimated by multiple imputation and subsequently analyzed. Missing lesion count data will be derived for the analysis using the method of Markov Chain Monte Carlo (MCMC) multiple imputation. The pattern of missing observations in each treatment group cannot influence the missing value estimation in the other because the imputation will be conducted independently for each treatment group.

Multiple imputation and subsequent analysis will involve 3 distinct phases with these principal tasks:

1. Create a data set of patients, one for each treatment group, with observed values and those needing estimation by MCMC. The missing lesion count values in each data set will be filled in using the MCMC method 5 times to generate 5 data sets. The resulting data sets for each treatment arm will be combined into one complete data set for each imputation. Syntax:

```
proc mi data=datain out=dataout seed=&seed.  nimpute=5
<options>;
  where trtpn=(1, or 2);
  mcmc chain=multiple;
  var baseline week2 week4 week8 week12;
run;
```

2. For each complete data set, the variable of interest for baseline minus the Week 12 value will be computed. Each complete data set will be analyzed as specified for the particular analysis.
3. The results from these analyses will be combined into a single inference using SAS PROC MIANALYZE.

A total of 6 random seeds are needed to impute inflammatory lesion counts. These random seeds have been pre-specified by using a random number generator:

- Inflammatory Lesion Counts Week 12 S5G4T-1: Seed = 2046620966
- Inflammatory Lesion Counts Week 12 Vehicle: Seed = 693843173
- Inflammatory Lesion Counts Week 8 S5G4T-1: Seed = 385596352
- Inflammatory Lesion Counts Week 8 Vehicle: Seed = 386411964
- Inflammatory Lesion Counts Week 4 S5G4T-1: Seed = 796550211
- Inflammatory Lesion Counts Week 4 Vehicle: Seed = 40534656

19.4.7.2. IGA Missing Data Imputation

A similar procedure will be used for the analyses based on proportion of IGA successes wherein the ANCOVA analysis is replaced with a logistic regression analysis. Specifically, missing 12 week IGA values from which the dichotomized IGA is derived will be estimated by (MCMC). The pattern of missing observations in each treatment group cannot influence the missing value estimation in the other because the imputation is being conducted independently for each treatment group.

The missing 12-week IGA values will be derived for the analysis using the method of Markov Chain Monte Carlo (MCMC) multiple imputation. Multiple imputation and subsequent analysis will involve 4 principal tasks:

1. Create a data set, one for each treatment group, of patients with observed values and those needing estimation by MCMC. The missing IGA values in each data set will be filled in using the MCMC method 5 times to generate 5 data sets. The resulting data sets for each treatment arm will be combined into one complete data set by imputation. Syntax:

```
proc mi data=datain out=dataout seed=&seed.  nimpute=5
<options>;
  where trtpn=(1, or 2);
  mcmc chain=multiple;
  var baseline week2 week4 week8 week12;
run;
```

2. For each complete data set, the dichotomous success rate (clear or almost clear with a 2-point change from baseline) will be computed. The 12-week estimated global values will be rounded to the nearest integer value prior to evaluating the success rate. Each complete data set will be analyzed with a logistic regression with factors of treatment group and analysis center.
3. The results from these analyses will be combined into a single inference using SAS PROC MIANALYZE.

A total of 2 random seeds will be needed to impute IGA for the two treatment groups. Those 2 random seeds have been pre-specified by using a random number generator:

- IGA Week 12 S5G4T-1: Seed = 712066910
- IGA Week 12 Vehicle: Seed = 1200150465
- IGA Week 8 S5G4T-1: Seed = 1871392013
- IGA Week 8 Vehicle: Seed = 1866129897
- IGA Week 4 S5G4T-1: Seed = 301965746
- IGA Week 4 Vehicle: Seed = 812607204

19.4.8. Sensitivity Efficacy Analyses

19.4.8.1. Sensitivity Analyses for Absolute Change in Lesion Count

The first sensitivity analysis for absolute change in lesion count will use a repeated measures ANCOVA, with treatment, analysis center, and visit (i.e., Weeks 2, 4 and 8) as independent factors and a covariate of baseline lesion count. In this analysis, data from all post-baseline visits will be included with no imputation for missing data.

The second sensitivity analysis will use the model based multiple imputation method to impute missing data for the absolute change in lesion counts at Week 12. Although the full details will be presented in the Statistical Analysis Plan (SAP), the multiple imputation will involve 4 principal tasks:

1. Missing values will be filled in 5 times to generate 5 complete data sets. The imputation model used will be an ANCOVA with factors of treatment group and analysis center, and a covariate of baseline lesion count (i.e., the imputation model will be the same as the analysis model). Appropriate modifications will be made should the analysis be based on a non-parametric method.
2. Each complete data set will be analyzed with an ANCOVA with factors of treatment group, and analysis center, and a covariate of baseline lesion count.
3. Results from these analyses will be combined into a single inference.

19.4.8.2. Sensitivity Analyses for IGA

The first sensitivity analysis for the dichotomized IGA success will use a repeated measures logistic regression model (generalized estimating equations), with dichotomized IGA success as the dependent variable and treatment, analysis center, and visit (i.e., Weeks 2, 4 and 8) as independent factors. In this analysis, data from all post-baseline visits will be included with no imputation for missing data.

The second sensitivity analysis will use the model based multiple imputation method to impute missing data for the dichotomized IGA data. Although the full details will be presented in the SAP, the multiple imputation will involve 4 principal tasks:

1. Missing values will be filled in 5 times to generate 5 complete data sets. The imputation model used logistic regression with factors of treatment group and analysis center (i.e., the imputation model will be the same as the analysis model).
2. Each complete data set will be analyzed with a logistic regression a factors of treatment group and analysis center.
3. Results from these analyses will be combined into a single inference.

19.4.9. Subgroup Analyses

Subset analyses will be conducted for the ITT populations for the subgroups baseline global severity, gender, age, ethnicity, race, and geographic region. Age will be dichotomized to less than the median age of patients and greater than or equal to the median age of patients. Subset analyses will be conducted on the variables absolute change from baseline in inflammatory lesions at Week 12 as well as the dichotomized global severity score at Week 12. These analyses will contain only descriptive statistics.

19.5. Assessment of Safety

Safety will be evaluated by tabulations of adverse events (AEs), Cutaneous Safety Assessments for dryness and scaling, assessments for scores (erythema and telangiectasia) and Patient Global Impression of Treatment Side-Effects (PGI-SE) will be presented with descriptive statistics at Baseline and at Weeks 2, 4, 8 and 12 for each treatment group. Frequencies and percentages for each outcome category will be included in these statistics. Mean values will be presented graphically by week and treatment group.

19.6. Adverse Events

All adverse events occurring during the study will be recorded and classified on the basis of MedDRA terminology. Descriptions of AEs will include the date of onset, the date the AE ended, the severity of the AE, the relationship to study product, the action taken regarding study product usage, the action taken to treat the AE, and the outcome. All reported treatment-emergent AEs (TEAEs) will be summarized by the number of Patients reporting AEs, system organ class, severity, seriousness, and relationship to study product. TEAEs are those AEs with an onset on or after the date of the first study product application.

Adverse events will be summarized by treatment group and severity. Each patient will be counted only once within a system organ class or a preferred term by using the adverse events with the highest severity within each category.

Adverse events will be summarized by treatment group and relationship to study product. Each patient will be counted only once within a system organ class or a preferred term by using the adverse events with the greatest relationship within each category.

Comparisons among treatment groups will be made by tabulating the frequency of patients with one or more AEs (classified into MedDRA terms) during the study. The Fisher's Exact test will be used to compare the proportion of patients in each treatment group who report any adverse event at a significance level of 0.05. The specific system organ classes and preferred terms analyzed will be those that are reported by at least one percent of the patients in any treatment group.

All information pertaining to AEs noted during the study will be listed by patient, detailing verbatim given by the investigator, preferred term, system organ class, start date, stop date, severity, actions taken, and drug relatedness. The AE onset will also be shown relative (in number of days) to the day of initial dose of the randomized study product.

Serious adverse events (SAEs) will be tabulated by patient within treatment groups.

In addition, a list of patients who discontinued from the study and a list of patients who experienced SAEs will also be provided.

19.6.1. Vital Sign Measurements

Vital signs as well as changes from Baseline in vital sign measurements will be summarized with descriptive statistics for each treatment group at all applicable study visits.

19.6.2. Concomitant Medications

All previous therapies and concomitant medications will be classified based on terminology from the WHO Drug Dictionary. Previous therapies and concomitant medications data will be presented in data listings.

19.7. Sample Size Determination

The following power calculations are based on the observed Week 12 results of the Phase 2 study, SGT-EBP01-09. This study was a three-arm trial including E-BPO Cream, 1% and 5%, and Vehicle in the Treatment of Rosacea. Estimates from the E-BPO Cream, 5% arm were used in the power assessments. The anticipated randomization ratio is 2:1 for E-BPO Cream, 5% and Vehicle, respectively. The computations were performed with nQuery Advisor Version 7.0 using a two-sided test with a statistical significance value of 0.05.

A sample size of 86 in the E-BPO Cream, 5% and 43 in the Vehicle has group has 95% power to detect a statistically significant difference in the proportion of patients who have at least a 2-grade reduction at Week 12 from baseline in IGA and are Clear or Almost Clear. The estimated percentages with a 2-grade reduction at Week 12 from baseline in the IGA and Clear or Almost Clear are 53.3% and 20.0% for the E-BPO Cream and Vehicle, respectively.

A sample size of 200 in the E-BPO Cream, 5% and 100 in the Vehicle group has 95% power to detect a statistically significant difference in inflammatory lesions. The estimated absolute change from baseline in treatment means were -14.1 and -7.4 for the E-BPO Cream and Vehicle, respectively, with a standard deviation of 6.70 and 17.24, respectively.

The sample sizes above will be increased to give a planned enrollment of 234 in the E-BPO Cream, 5% group and 117 in the Vehicle group since the Phase 3 trial is expected to enroll patients who are as a group more severe than those of the Phase 2 trial. This is a consequence of some changes in the inclusion criteria.

20. ADMINISTRATIVE CONSIDERATIONS

20.1. Protocol Compliance

The IRB-approved protocol must be followed except in the case of a change that is intended to eliminate an immediate risk to patients. All protocol deviations must be documented in the source documents and in the comment CRFs.

20.2. Protocol Revisions

Sponsor or designee must prepare all protocol revisions. All protocol amendments must receive IRB approval prior to implementation. All administrative letters must be submitted to the IRB for their information. Copies of all correspondence with the IRB regarding this study must be sent to Sponsor or CRO designee. New or altered consent forms required by the IRB due to a protocol revision must be signed by all patients currently enrolled in the study and must be used for any subsequent patient enrollment.

20.3. Protocol Monitoring

Representatives of Sponsor must be allowed to visit all study sites, to review study records and to directly compare them with source documents (including, but not limited to patient and hospital records), to discuss the study conduct with the investigator and study staff; and to verify that the investigator, study staff and facilities remain acceptable for the conduct of the study. Representatives of government regulatory authorities (i.e., FDA) may also evaluate the study records, source documents, investigator, study staff, and facilities.

The investigator must immediately notify Sponsor of any audits by any regulatory agency, and must promptly provide copies of any audit reports.

20.4. Required Study Documents

The investigator must provide the following documents to Sponsor or CRO designee before any patients are enrolled and/or study product may be shipped to the study site:

- The signed INVESTIGATOR PROTOCOL ACKNOWLEDGEMENT page from the Sponsor and IRB approved protocol.
- Documentation of IRB approval of the protocol, informed consent form, any other written information provided to patients and any recruitment advertisements.
- A copy of the IRB approved informed consent form
- A current IRB assurance number and/or a membership roster.
- A completed, signed and dated Form FDA 1572.
- The appropriate financial disclosure documentation.
- A current signed and dated curriculum vitae and a copy of the current medical license for the investigator and sub-investigators listed on the Form FDA 1572.
- The signed agreement between the investigator and Sponsor, or designee, and related financial information for the study (this file is confidential and currently FDA has no authority to review this information. Keep this information in a separate file).

20.5. Electronic Case Report Forms (eCRF)/Source Documents

Electronic case report forms (eCRFs) called also electronic data capture (EDC) system, will be used for recording all data from source documents for each patient. Source documents are the point of first entry for all data collected. Whenever possible, an original recording of an observation should be retained as source document.

The investigator will ensure that the eCRFs are properly and completely filled in. The eCRFs must be completed for all patients who have signed an informed consent form. The eCRFs will be monitored against source documents. If data in the eCRF is not duplicated in a source document, a source document should be created and maintained by the site to capture that information. Source documentation for patients includes but is not limited to the physician's patient records, diaries, photographs. All source documents will be maintained at the study site.

The Investigator or delegate may enter corrections in the eCRFs, which will create an auditable history of all changes and by whom they were made. The final eCRF will be approved by the Investigator by electronic signature.

20.6. Reports to the IRB/Ethics Committee (EC)

Before study initiation, the investigator must have written and dated approval from the IRB for the protocol, consent form, patient recruitment materials /process (e.g., advertisements), and any other written information to be provided to patient. The investigator should also provide the IRB with a copy of the Investigator's Brochure and/or package insert. The investigator should provide the IRB with reports, updates, and other information (e.g., safety updates, protocol amendments, and administrative letters) according to regulatory requirements or Institution procedures.

20.7. Quality Assurance Audits

Representatives from Sponsor and/or a third party selected by Sponsor may conduct a quality assurance audit of this study. During the audit, the Investigator must provide the auditor with direct access to all relevant documents and discuss any findings with the auditor.

In the event of an inspection by the Food and Drug Administration or other regulatory authorities, the Investigator will notify the Sponsor /CRO as soon as possible of such notice and must give the inspector direct access to relevant documents and discuss any findings with the inspector.

20.8. Records Retention

The investigator must maintain records of the study product disposition, copies of the case report forms and all source documents for the maximum period of five years after NDA approval as required by Sponsor. The investigator must contact Sponsor prior to destroying any records associated with this study.

If the location of the study files changes from the address noted on the FDA Form 1572, written notification of the new location must be given to Sponsor. If the investigator withdraws from participation in the study the records shall be transferred to a mutually agreed-to designee. Written notification of such a transfer must be given to Sponsor.

21. REFERENCES

Breneman D., Savin R., VandePol C., Vamvakias G., Levy S., Leyden J. Double-blind, randomized, vehicle-controlled clinical trial of once-daily benzoyl peroxide/clindamycin topical gel in the treatment of patients with moderate to severe rosacea. Int. J of Derm. 2004; 43(5):381-387.

Jansen T. and Plewig G. Rosacea: classification and treatment. JR Soc Med. 1997; 90(3):144-150.

McDonnell JK and Tomecki KJ. Rosacea: an update. Clev Clinic J Med. 2000; 67(8):587-590.

Montes LF., Cordero AA., Kriner J., Loder J., Flanagan AD. Topical treatment of acne rosacea with benzoyl peroxide acetone gel. Cutis 1983; 32(2):185-190.

Yamasaki K., Di Nardo A., Bardan A., Murakami M., Ohtake T. Coda A., Dorschner RA., Bonnart C., Descargues P., Hovnanian A., Morhenn VB. and Gallo RL. Increased serine protease activity and cathelicidin promotes skin inflammation in rosacea. Nat. Med. 2007; 13:975-980.

Zar, JH. Bio-statistical analysis, 1984 2nd ed. Englewood Cliffs (NJ) Prentice-Hall. (*Available upon request).*

APPENDIX 1: PATIENT INSTRUCTION SHEET

Please follow these instructions carefully. Contact the study staff at the telephone number noted below if you have any questions about the study:

Contact: _____ At: _____

STUDY PRODUCT APPLICATION:

- At first application, priming is required.
- Apply the cream once a day every day during the study period [twelve (12) weeks].
- Wash your face gently with the mild cleanser provided by the doctor or by study approved cleanser for this study from the sponsor and water. Rinse thoroughly and gently pat dry.
- A thin coating of study product should be applied once daily (preferably at the same time each day) to the entire face during the study period [twelve (12) weeks].
- Apply one gentle pump application of test material from pump onto the tip of your finger the size of a pea for each area of the face (chin, left cheek, right cheek, nose, left forehead and right forehead), as instructed at your first study visit.
- Apply the cream on each area of the face as evenly as possible and gently rub into the skin. Each pea-size amount should be used to evenly cover the following parts on your face: chin, left cheek, right cheek, nose, left forehead and right forehead excluding the mouth, eyes and lips.
- Do NOT treat specific lesions but rather the entire face.
- Be sure to wash your hands after you apply the study product. But do not wash your face for at least two hours after you apply study product.
- Wait for at least 30 minutes before applying the moisturizer/sunscreen provided by the doctor for this study.
- If applicable, wait at least 30 minutes before applying only non-medicated make-up.

ADDITIONAL REMINDERS:

- Store study product at Room Temperature 20 to 25°C (68 to 77°F). Excursions permitted between 15 to 30°C (59 to 86°F). Do not freeze, refrigerate or expose to extreme temperature."
- Avoid contact with the eyes, inside the nose, mouth and all mucous membranes.
- Caution: This product contains benzoyl peroxide which can bleach hair or colored fabric.
- THE PRODUCT SHOULD BE USED ONLY BY THE PERSON FOR WHOM IT WAS PRESCRIBED and it should be kept out of the reach of children or others of limited capacity to read or understand.
- Pumps of study product must be returned to the study facility, even if they are empty.

- If you miss any doses, at your next visit inform the study doctor of the date(s) of the missed dose(s). Please record all doses on the Diary Card provided to you; indicate reason for any missed dose on the Diary Card.
- Throughout the study, continue to use on your face only the same cleanser provided by the doctor for this study.
- If you use a moisturizer and/or sunscreen, you must use the one provided by the doctor for this study.
- **On the day of your study visit, do not apply moisturizer/sunscreen, or make-up.**
- You must not use any other treatment for your rosacea while you are participating in this study.
- Avoid unnecessary sun exposure and tanning booths. When sun exposure cannot be avoided, use the approved moisturizer/sunscreen and wear a wide-brimmed hat.

It is important that you inform the study site about any medications (i.e., prescriptions, over-the-counter medications, street drugs, or herbal medications) that you have taken during thestudy.

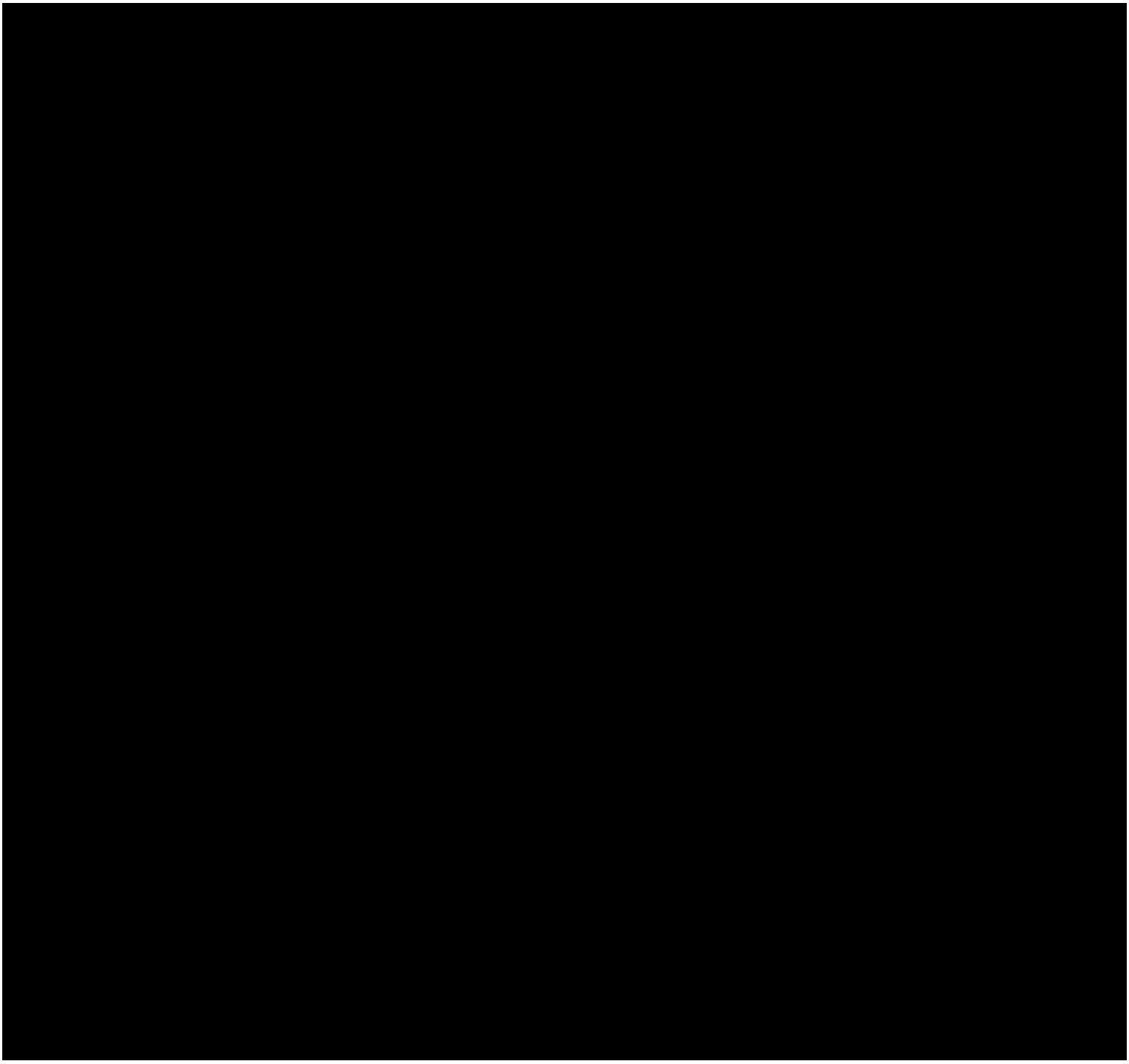
Bring this sheet, your updated Diary Card, and your study product pump with you to every study visit.

STUDY VISIT SCHEDULE:

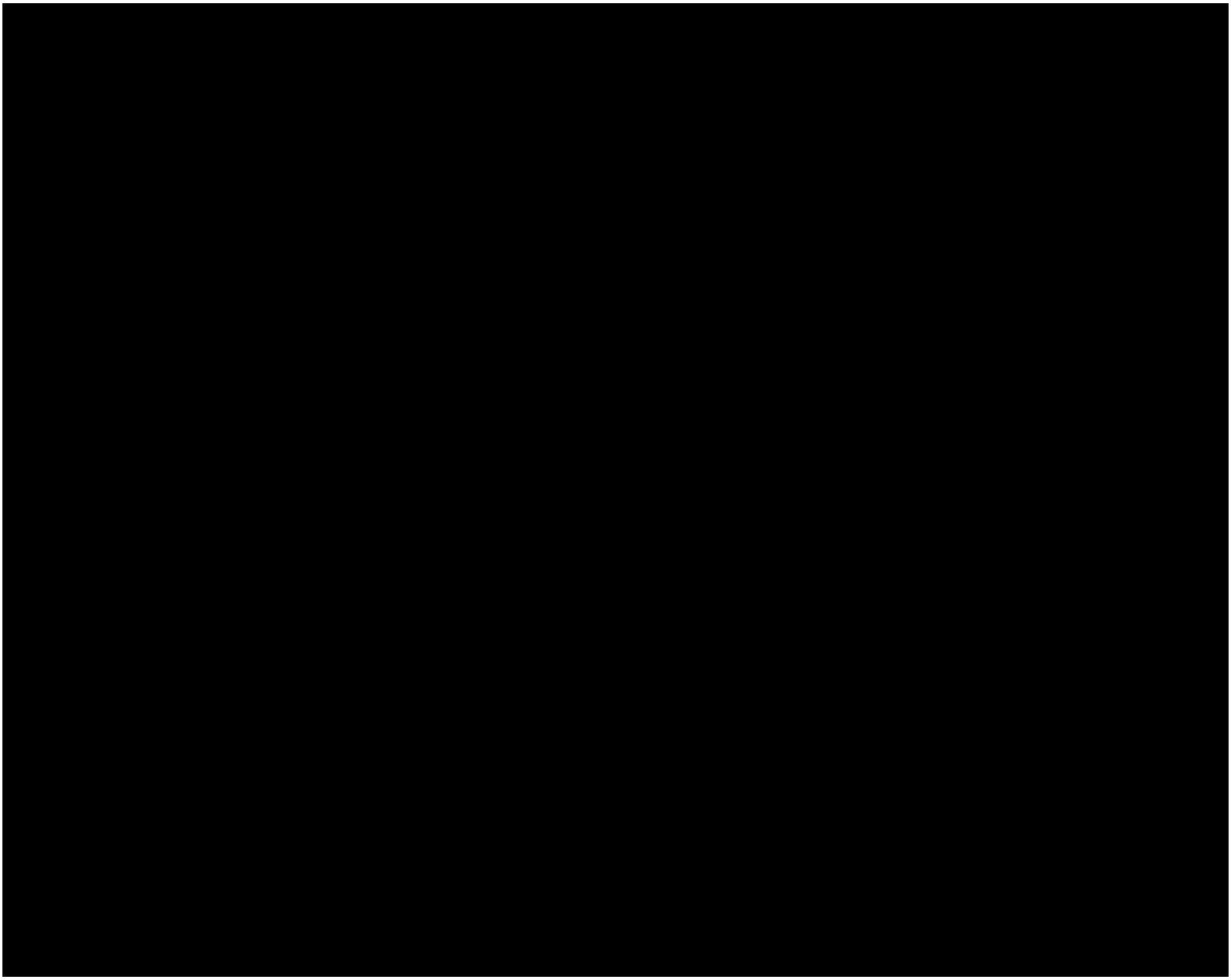
VISIT 2: Baseline Day 1 Date: Time:
VISIT 3: Week 2, Day 15 Date: Time:
VISIT 4: Week 4, Day 29 Date: Time:
VISIT 5: Week 8, Day 57 Date: Time:
VISIT 6: Week 12, Day 85 Date: Time:

Thank you for following these instructions.

APPENDIX 2: PRO – PAPSS



APPENDIX 3: PRO – PAPI



APPENDIX 4: PRO – PGI-S

APPENDIX 5: PRO – PGI-C

APPENDIX 6: PRO – PGI-TS

APPENDIX 7: PRO – PGI-SE

APPENDIX 8: ROSACEA QUALITY OF LIFE QUESTIONNAIRE (ROSAQOL)