NCT #NCT03564145

CLINICAL STUDY PROTOCOL

Title: A Multi-Center, Open-Label, Long-Term Safety Study of S5G4T-1 to Evaluate the Safety of S5G4T-1 in Papulopustular Rosacea Patients

Protocol No:	SGT-54-07: November 27, 2018
Protocol Version:	4.0
Original Version:	3.0
Sponsor:	Sol-Gel Technologies Ltd. 7 Golda Meir St. Weizmann Science Park Ness Ziona 7403650, Israel

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2. PROTOCOL APPROVAL- SPONSOR SIGNATURE PAGE

Protocol Title: A Multi-Center, Open-Label, Long-Term Safety Studly of S5G4T-l to Evaluate the Safety of S5G4T-1 in Papulopustular Rosacea Patients

Study Product: S5G4T-1

Sol-Gel Technologies Ltd. commits to conduct the study as described hen in 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 Nov 27, 2018 version of the SGT-54-07 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 28, 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, Ml 49401

Signature: [redacted]

Date: [redacted]

3. INVESTIGATOR PROTOCOL ACKNOWLEDGMENT

Protocol Title: A Multi-Center, Open-Label, Long-Term Safety Study of S5G4T-1 to Evaluate the Safety of S5G4T-1 in Papulopustular Rosacea Patients

Study Product: S5G4T-1

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 Multi-Center, Open-Label, Long-Term Safety Study of S5G4T-1 to Evaluate the Safety of S5G4T-1 in Papulopustular Rosacea Patients
Study Number:	SGT-54-07
Study Phase:	3
Indication:	Papulopustular rosacea
Study Period:	In treatment period: up to 52 weeks (365 days)
Study Products:	S5G4T-1: Encapsulated Benzoyl Peroxide (E-BPO) Cream, 5%, developed by Sol-Gel Technologies and manufactured by [redacted], Montreal, Canada.
Study Objectives:	To assess the safety of S5G4T-1 when applied once daily for up to 52 weeks in patients with papulopustular rosacea.
Study Design:	Patients from the double-blind, Phase 3 studies SGT-54-01 and SGT-54-02 may continue into this open-label, long-term safety study. Patients will be admitted into the study only after a written informed consent has been obtained and after completing Visit 6 within the Week 12 window and not missing more than 1 visit of Visits 3, 4 or 5 in these studies. Eligible patients for enrollment may apply the study product, S5G4T-1, daily for up to 40 weeks to complete long-term usage of the drug for up to 52 weeks. The sponsor may also recruit patients for the long-term safety study only (and not as an extension study for phase 3) for a total of 52 weeks. In this case, the subject must meet the same inclusion and exclusion criteria as the phase 3 SGT-54-01 or SGT-54-02 studies, see section 12.2 and 12.3. The study will enroll patients who completed the SGT-54-01 and SGT-54-02 studies first. Study sites should not enroll new patients into SGT-54-07 until the Sponsor provides approval to do so. The Sponsor may terminate the recruitment after 300 patients complete a total of 28 weeks and 100 patients complete a total of 52 weeks of treatment.
Study Population:	Approximately 700 male and female patients who meet the study Entry Criteria (applies for patients who completed Study SGT-54-01 or SGT-54-02) or who meet the Inclusion/Exclusion criteria (applies for new patients) will be enrolled with the intent that at least 300 patients will be followed for 28 weeks and at least 100 patients will be followed for 52 weeks. Drop-out patients will not be replaced.
Investigational Sites	It is estimated that up to 56 study centers in US will participate in this study.

Dosing:	Patients will apply the study product if applicable once daily for up to52 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.

Methodology:	Clinical and Safety Evaluations will be performed at: 1. Visit 1/Screening, only applies for new patients 2. Visit 2/Baseline, Day 1 can also be Visit 6/Week 12, Day 85 of Study SGT-54-01 or Study SGT-54-02 3. Visit 3/Week 4, Day 29 (± 10 Days) 4. Visit 4/Week 8, Day 57 (± 10 Days) 5. Visit 5/Week 12, Day 85 (± 10 Days) 6. Visit 6/Week 16, Day 113 (± 10 Days) 7. Visit 7/Week 20, Day 141 (± 10 Days) 8. Visit 8/Week 24, Day 169 (± 10 Days) 9. Visit 9/Week 28, Day 197 (± 10 Days) 10. Visit 10/Week 32, Day 225 (± 10 Days) 11. Visit 11/Week 36, Day 253 (± 10 Days 12. Visit 12/Week 40, Day 281 (± 10 Days)/ End of Treatment/End of Study for patients who complete the study, early terminate, or if the Sponsor terminates the study prematurely (only for patients that completed Study SGT-54-01 or Study SGT-54-02) Applies for new patients: 13. Visit 13/Week 44, Day 309 (± 10 Days) 14. Visit 14/Week 48, Day 337 (± 10 Days) 15. Visit 15/Week 52, Day 365 (+ 10 Days)/ End of Treatment/End of Study for patients who complete the study, early terminate, or if the Sponsor terminates the study prematurely. Patients will be admitted into the study only if they completed Study SGT-54-01 or Study SGT-54-02 at Week 12 within the window time or missed no more than one study Visit 3, 4 or 5 in these studies. For patients that were enrolled for study SGT-54-01 or study SGT-54-02 clinical exclusion criteria (IGA grade or lesion count) will not limit the enrollment for the study. New patients who meet specified inclusion criteria (including moderate to severe rosacea according to 5-point IGA scale and have a minimum total of 15 and a maximum total of 70 inflammatory lesions (papules and/or pustules) including those present on the nose) and none of the exclusion criteria will be admitted to the study. At each visit a 5-point IGA scale of rosacea; rosacea erythema, and telangiectasia; will be performed and recorded. If a patient is assessed as "mild", "moderate" or "severe" (2, 3 or 4 respectively), study product will be dispensed and the patient will use the study product daily according to patient instructions. If a patient is assessed as "clear" (0) or "almost clear" (1), the patient will not be dispensed the study product. In addition, 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). Rosacea Quality of Life Questionnaire (RosaQoL) will be completed at Baseline, Visits 5, 8, 11, 14 and at End of Study or at early termination. The RosaQoL data of patients who were enrolled from SGT-54-01 or SGT-54-02, will be used from the questionnaire completed at Visit 6/Week 12 of SGT-54-01 or SGT-54-02. Urine pregnancy tests will be performed on females of child-bearing potential at Screening (for new patient) and 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 stabilizes or resolves, based on investigator's medical judgment.

Clinical Trial Duration	Up to 52 weeks/365 days. The Sponsor may terminate the study once 100 patients complete a total of 52 weeks and 300 patients complete a total of 28 weeks of treatment (totals include 12 weeks from the double-blind treatment period of Study SGT-54-01 or Study SGT-54-02 for those previously enrolled in this studies). Patients have the right to stop the study for any reason at any given time.
Study product dosage and Reference therapy	Encapsulated Benzoyl Peroxide Cream, 5% will be dispensed every 4 weeks. The study product will be supplied in 55-gram pumps (total weight including pump is 85 grams).
Entry Criteria (applies for patients entering from Phase 3, SGT-54-01 or SGT-54-02)	Patients rolling over from either Study SGT-54-01 or Study SGT-54-02 may participate in the study if they meet the criteria below: 1. Patient must sign an Institutional Review Board (IRB) approved written informed consent for the extension study. 2. Complete 12 weeks or within the Week 12 window time (± 4 days) of the double-blind treatment period of Study SGT-54-01 or Study SGT-54-02 and missed not more than one visit of Visits 3, 4 or 5 in Study SGT-54-01 or Study SGT-54-02. 3. Patients who in the opinion of the investigator, are likely to be able to follow the restrictions of the protocol and complete the study.
Patient Inclusion Criteria (applies for new patients only)	New patients who were not previously enrolled in Study SGT-54-01 or Study SGT-54-02 must meet all 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: Metronidazole 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.
Patient Exclusion Criteria (applies for new patients only):	Patients who were not previously enrolled in Study SGT-54-01 or Study SGT-54-02 must be excluded from entry into the study according to the following criteria:

	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 erythematosus, 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 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. – 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.
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. 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

Statistical Method:	**General Statistical Methodology** All statistical processing will be performed using SAS® version 9.3 or later unless otherwise stated. Data will be summarized using descriptive statistics. No inferential testing or imputations for missing data will be performed. No interim analyses are planned for the co-primary variables. For categorical parameters, the number and percentage of patients in each category will be presented. For continuous parameters, descriptive statistics will include n (number of patients), mean, standard deviation, median, minimum and maximum. **Populations Analyzed** All analyses will be performed using the Safety Population of the study. Part of this population will be referred as the extension safety population, and part as a new enrolled safety population. All patients who receive at least one confirmed dose of S5G4T-1 (in either Study SGT-54-01 or Study SGT-54-02, and in this study or for new patients in this study) and have at least one assessment will be included in the Safety Population. The number of patients included in the Safety Population will be summarized. **Analysis of Efficacy** This study is not intended to assess efficacy, but rather the IGA is included to determine the need for treatment and subsequent re-treatment. after the initial 12-week treatment course (in either Study SGT-54-01 or Study SGT-54-02 or for those patients not previously enrolled in Study SGT-54-01 or Study SGT-54-02) and any subsequent 4-week courses, if applicable. Certain efficacy data and endpoints will, however, be summarized. Descriptive statistics will be used to summarize the assessment of efficacy. IGA scores will be summarized at Baseline Visit of Study SGT-54-01 or Study SGT-54-02 or at the Screening visit of SGT-54-07 for those patients not previously enrolled in Study SGT-54-01 or Study SGT-54-02, and entry into the study (SGT-54-07) and every 4 weeks through end of the study. The number and percentage of patients who achieve treatment success at the scheduled study visits will be tabulated. A patient will be considered a success if their IGA score is clear or almost clear. Rosacea Quality of Life Questionnaire (RosaQoL) will be completed at Baseline, Visits 5, 8, 11, 14 and End of Study visits. The RosaQoL data of patients who were enrolled from SGT-54-01 or SGT-54-02, will be used from the questionnaire completed at Visit 6/Week 12 of SGT-54-01 or SGT-54-02.

Safety Evaluation:	Safety will be evaluated by tabulations of adverse events (AEs), Cutaneous Safety Assessments (dryness and scaling), Local Tolerability Assessment (itching and burning) and assessments for erythema and telangiectasia 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. Safety data will be presented for patients in the Safety Population with tabulations for the following periods 12 to 28 weeks, > 28 to 52 weeks and > 52 weeks to the end of the study, as well as an overall for all periods.

5.2. Study Flow Chart for patients entered from Study SGT-54-01 or SGT-54-02

Procedure	**Visit 2[1],[2],[7]**	**Visit 3, 4, 6, 7, 9, 10**	**Visit 5, 8, 11**	**Visit 12 (EOT[3]/ EOS[4])**	**Unscheduled Visit[11]**
Name of Visit	**Baseline Day 1**	**Week 4, 8, 16, 20, 28, 32[5] Day 29, 57, 113, 141, 197, 225**	**Week 12, 24, 36[5] Day 85, 169, 253**	**Week 40 Day 281[6]**	
Visit window		**± 10 days**	**± 10 days**	**± 10 days**	
Entry Criteria	X				
Sign Informed Consent	X				
Demographics	X				
Medical History/Previous Therapies	X				
Con med	X	X	X	X	X
Pregnancy Test[7]	X	X	X	X	X
Brief Physical Examination	X		X	X	X
Cutaneous Safety Assessment and Local Tolerability Assessments	X	X	X	X	X
Administer/ Review Patient Instructions	X	X	X		X
IGA[8]	X	X	X	X	X
Rosacea Erythema Assessment	X	X	X	X	X
Telangiectasia Assessment	X	X	X	X	X
Weigh Study Product	X	X	X	X	X
Study Product Dispensed[9]	X	X	X		X
Provide Cleanser and Moisturizer/Sunscreen, if needed	X	X	X		X
Study Product Collected		X	X	X	
Diary Card dispensed	X	X	X		X
Diary Card collected		X	X	X	X
Adverse Events	X	X	X	X	X
Complete RosaQoL[10]	X		X	X	

[1] Patient will be eligible for the extension study only after completing 12 weeks of one of the two Phase 3 studies SGT-54-01 or SGT-54-02 at the Week 12 window time (± 4 days) and missed not more than one visit of Visits 3, 4 or 5 in these studies.

[2] Same Visit as Visit 6 in Phase 3 Study SGT-54-01 or Study SGT-54-02. All procedures that were performed in Visit 6 of Study SGT-54-01 or Study SGT-54-02 will be captured in the Study SGT-54-07 source document.

[3] EOT – end of treatment.

[4] EOS – end of study.

[5] All visits must be in reference to baseline and counted accordingly.

[6] All Week 40 procedures should be completed for Patients who terminate early.

[7] Urine test for women of childbearing potential.

[8] For product dispensing eligibility

[9] The dispensation and usage of the pump is based on IGA score.

[10] RosaQoL is a Rosacea Quality of Life questionnaire

[11] Perform procedures per PI discretion.

5.3. Study Flow Chart for new patients only

Procedure	**Visit 1[1]**	**Visit 2**	**Visit 3, 4, 6, 7, 9, 10, 12, 13**	**Visit 5, 8, 11, 14**	**Visit 15 (EOT[2]/ EOS[3])**	**Unscheduled Visit[9]**
Name of Visit	**Screening -35 to 0**	**Baseline Day 1**	**Week 4, 8, 16, 20, 28, 32, 40, 44 Day 29, 57, 113, 141, 197, 225, 281, 309**	**Week 12, 24, 36, 48 Day 85, 169, 253, 336**	**Week 52 Day 365[4]**	
Visit window			**± 10 days**	**± 10 days**	**± 10 days**	
Inclusion/Exclusion Criteria	X	X				
Demographics	X					
Medical History/Previous Therapies	X	X				
Sign Informed Consent	X					
Brief Physical Examination		X		X	X	X
Concomitant Therapy and Medication History Reviewed	X	X	X	X	X	X
Pregnancy Test[5]	X	X	X	X	X	X
Cutaneous Safety Assessment and Local Tolerability Assessments		X	X	X	X	X
Administer/ Review Patient Instructions		X	X	X		X
IGA[6]	X	X	X	X	X	X
Inflammatory Lesion Count	X	X				
Rosacea Erythema Assessment		X	X	X	X	X
Telangiectasia Assessment		X	X	X	X	X
Weigh Study Product		X	X	X	X	X
Study Product Dispensed[7]		X	X	X		X
Provide Cleanser and Moisturizer/ Sunscreen, if needed		X	X	X		X
Study Product Collected			X	X	X	
Diary Card dispensed		X	X	X		X
Diary Card collected			X	X	X	X
Adverse Events	X	X	X	X	X	X
Complete RosaQoL[8]		X		X	X	

[1] Patient will be eligible for the study only after meeting all Inclusion/Exclusion criteria.
[2] EOT – end of treatment.
[3] EOS – end of study.
[4] All Week 52 procedures should be completed for Patients who terminate early.
[5] Urine test for women of childbearing potential.
[6] For product dispensing eligibility
[7] The dispensation and usage of the pump is based on IGA score.
[8] RosaQoL is a Rosacea Quality of Life questionnaire
[9] Perform procedures per PI discretion.

6. LIST OF ABBREVIATIONS AND TERMS

AE(s)	Adverse Event(s)
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
EDC	Electronic Data Capture
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 Harmonization
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
OTC	Over-the-Counter
PP	Per Protocol
SAE	Serious Adverse Event
SOP	Standard Operating Procedure

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.

The most prevalent AEs associated with topical BPO were related to local irritation. These included dry skin, peeling, burning and erythema. For the published studies, the percentage of subjects with dermatological adverse events considered possibly related to BPO monotherapy ranged from 7% (Thiboutot *et al.* 2007) to 22% (Tschen *et al.* 2001). In studies sponsored by Sol-Gel, the percentage of subjects with dermatological adverse events associated with E-BPO, 7% ranged from 0% (Study SGT-03B) to 37% (Study SGT-04), and the incidence associated with lower concentrations of E-BPO was 2% or less.

Several published studies reported AEs that might be associated with sensitivity of subjects to BPO. Leyden *et al.* 2001 reported that 1 of 164 subjects (0.6%) receiving 5% BPO had an allergic reaction, and that allergic reactions occurred for 1.2% of subjects receiving 5% BPO plus 1% clindamycin and for 3.1% of subjects receiving 5% BPO plus 3% erythromycin. Tschen *et al.* 2001 reported a rash for l of 95 subjects (1%) that received 5% BPO monotherapy. Fyrand and Jakobsen 1986 reported that 2 of 49 subjects withdrew from the study due to severe dermatitis indicating possible sensitization. Montes *et al.* 1983 reported hypersensitivity to BPO in 4 of 31 subjects receiving 5% BPO acetone gel for rosacea. Weiss *et al.* 2002 reported that 2 of 257 subjects receiving BPO plus clindamycin developed urticaria. In Study KGL 5782, 1 subject developed possible delayed contact hypersensitivity to both E-BPO, 2.5%, and Proactiv, 2.5%, indicating the hypersensitivity was probably due to BPO not an excipient. None of these events that might possibly indicate sensitization were confirmed by patch testing.

8. OBJECTIVE

The objective of this long-term safety study is to determine the nature, severity and frequency of the AE rate, the Cutaneous Safety Assessment and the Local Tolerability Assessment of S5G4T-1 when applied once daily, if applicable, for up to 52 weeks

The safety endpoints to be assessed include the following:

- The frequency of both local and systemic adverse events
- Investigator Cutaneous Safety Assessment (dryness and scaling) and Local Tolerability Assessment (itching and burning/stinging) at Baseline and at all study visits.

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

Approximately 700 patients will be enrolled at up to 56 sites. All patients in this open-label, long-term safety study will be assigned to treatment with S5G4T-1.

Patients who complete the treatment period of the Phase 3 studies SGT-54-01 or SGT-54-02 will be offered to continue into this long-term safety, open-label extension study for up to an additional 40 weeks. These patients will be admitted into the study and assigned to S5G4T-1 only after completing Visit 6/Week 12 within the allowable window (± 4 days) and without protocol violation of missing visits (i.e., missing more than one of Visits 3, 4 or 5).

New patients with moderate to severe rosacea (rated 3 or 4 on the 5-point IGA scale) will be enrolled into this long-term safety, open-label study for 52 weeks. These patients will be admitted to this study after meeting inclusion/exclusion criteria. Subjects with severe rosacea who are appropriate for systemic treatment need to be counseled regarding their treatment options by the Principal Investigator. The study will enroll patients who completed the SGT-54-01 and SGT-54-02 studies first. Study sites should not enroll new patients into SGT-54-07 until the Sponsor provides approval to do so.

The objective of this study is to determine the long-term safety and tolerability of daily use of S5G4T-1 in papulopustular rosacea patients.

Patients who successfully completed the 12-week treatment period from Study SGT-54-01 or Study SGT-54-02 may be offered to continue in the long-term safety, open-label extension study (Study SGT-54-07) for up to an additional 40 weeks [sum of up to 52 weeks; 12 weeks treatment during the double-blind, pivotal studies (Study SGT-54-01 or Study SGT-54-02) and up to an additional 40 weeks in this long-term safety study (Study SGT-54-07)]. The Sponsor may terminate the study once 300 patients complete a total of 28 weeks of treatment and 100 patients complete a total of 52 weeks.

Patients who completed Phase 3 studies SGT-54-01 or SGT-54-02 will be admitted into the study after the Entry Criteria have been met and an ICF has been signed. Qualified patients will receive study product at Baseline visit and treated for up to 40 weeks. New patients will be admitted into the study after the Inclusion/Exclusion Criteria have been met. At each visit, the patients will be assessed for a 5-point scale IGA of rosacea. If a patient is assessed as “clear” (0) or “almost clear” (1), the patient will not be dispensed the study product. If a patient is assessed as “mild”, “moderate” or “severe” (2, 3 or 4, respectively), study product will be dispensed, and the patient will use the study product daily according to patient instructions. Rosacea Quality of Life Questionnaire (RosaQoL) will be completed at Baseline, Visits 5, 8, 11, 14 and at End of Study or at early termination. The RosaQoL data of patients who were enrolled from SGT-54-01 or SGT-54-02, will be used from the questionnaire completed at Visit 6/Week 12 of SGT-54-01 or SGT-54-02. 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 and dryness, scaling and Local Tolerability Assessments rating of itching and burning/stinging on a scale ranging from 0 (None) to 3 (Severe).

A urine pregnancy test is required at all Visits for all females of child-bearing potential.

Clinical Evaluations will be performed at:

1. Visit 1/Screening, only applies for new patients

2. Visit 2/Baseline, Day 1 can also be Visit 6/Week 12, Day 85 of Study SGT-54-01 or Study SGT-54-02
3. Visit 3/Week 4, Day 29 (± 10 Days)
4. Visit 4/Week 8, Day 57 (± 10 Days)
5. Visit 5/Week 12, Day 85 (± 10 Days)
6. Visit 6/Week 16, Day 113 (± 10 Days)
7. Visit 7/Week 20, Day 141 (± 10 Days)
8. Visit 8/Week 24, Day 169 (± 10 Days)
9. Visit 9/Week 28, Day 197 (± 10 Days)
10. Visit 10/Week 32, Day 225 (± 10 Days)
11. Visit 11/Week 36, Day 253 (± 10 Days)
12. Visit 12/Week 40, Day 281 (± 10 Days)/ End of Treatment/End of Study for patients who complete the study, early terminate, or if the Sponsor terminates the study prematurely (applies only to patients who completed Study SGT-54-01 or Study SGT-54-02)

Applies for new patients:

13. Visit 13/Week 44, Day 307 (± 10 Days)
14. Visit 14/Week 48, Day 337 (± 10 Days)
15. Visit 15/Week 52, Day 365 (+ 10 Days)/ End of Treatment/End of Study for patients who complete the study, early terminate, or if the Sponsor terminates the study prematurely.

Safety will be assessed by monitoring incidence of Cutaneous Safety Assessment and Local Tolerability Assessments, adverse events reporting; at Baseline, and at all treatment and end-of-treatment visits. The study product will be administered in an open-label fashion, i.e., the treatment assignment will be known to the patient, to study personnel and Sol-Gel personnel and its representatives.

12. STUDY POPULATION

Each patient who signs an informed consent and meets Entry Criteria or Inclusion/Exclusion Criteria will be enrolled in the study. Patients will receive study product in an open-label fashion (see instructions in Section 13.4) for entire trial period (i.e., the treatment assignment, E-BPO, 5% Cream (Encapsulated Benzoyl Peroxide Cream, 5%, S5G4T-1), will be known to the patient, to study personnel, Sol-Gel personnel and its representatives.

12.1. Entry Criteria (only applies for patients entering from Phase 3, SGT-54-01 or SGT-54-02)

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 the extension study.
2. Complete 12-week or within the week 12 window time (± 4 days) of the double-blind treatment period of study SGT-54-01 or Study SGT-54-02 and missed not more than one visit of Visits 3, 4 or 5 in Study SGT-54-01 or Study SGT-54-02.
3. Patients who in the opinion of the investigator, are likely to be able to follow the restrictions of the protocol and complete the study.

12.2. Patient Inclusion Criteria (applies only for new patients)

New patients who were not previously enrolled in Study SGT-54-01 or Study SGT-54-02 must meet all 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: Metronidazole 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. Patient Exclusion Criteria (applies only for new patients):

New patients who were not previously enrolled in Study SGT-54-01 or Study SGT-54-02 must be excluded from entry into 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 erythematosus, 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 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.
    - 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

12.4.1. Patients entering from Phase 3, SGT-54-01 or SGT-54-02

Any rosacea therapies must not be used as specified below:

- Therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed).
- Use of antipruritics (including antihistamines), spa or sauna treatments or chlorine exposure (swimming etc.) within 24 hours (1 day) before of all study visits (Visit 2 through End of Study.
- Use of medicated cleansers on the face (e.g., benzoyl peroxide, salicylic acid, sulfur or triclosan).
- Topical anti-rosacea treatments.
- Topical antibiotics, antimicrobials.
- Topical anti-inflammatories on the face such as corticosteroids and non-steroidalanti-inflammatory drugs (NSAID).
- Topical retinoids.
- Systemic rosacea treatments, corticosteroids, antibiotics.
- Systemic retinoids.

12.4.2. New Patients

Any rosacea therapies must not be used as specified below:

- 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 – 30 days prior to Baseline.
- Systemic retinoids – 6 months prior to Baseline.

12.4.3. All Patients

Other than the study products, no other topical medications are permitted to be used on the face. All topical or systemic medications listed above are prohibited. Other prohibited treatments include but are not limited to astringents, toners, clarifying lotions, medicated shaving products, chemical peeling products used on the face. A stable regimen of inhaled corticosteroids for stable medical conditions and antibiotic treatment are allowed during the study. No medicated cleansers or moisturizers are allowed on the face. Only study provided, or approved cleanser and 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. Provided or 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 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 Screening (Visit 1) for new patients OR at Baseline (visit 2) for patients proceed from SGT-54-01 or SFGT-54-02 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 (before going to bed) 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 study provided/approved moisturizer with SPF (minimum of SPF 15) 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

Patients entering from Phase 3, SGT-54-01 or SGT-54-02 will continue with the same number identification he/she received from study SGT-54-01 or SGT-54-02. When new patients sign an informed consent, he/she will be assigned a three (3)-digit patient number beginning with [redacted], as well as the 3-digit site number (e.g., [redacted]). In these studies, the complete patient ID consists 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.

13.2. Screen Failure and Discontinuation Criteria

For new patients, a screen failure is a patient who is not randomized/enrolled in the study due to ineligibility, after signing an Informed Consent Form, and did not receive 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.
- 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. Best effort should be performed 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
- Worsening of condition that requires alternate therapy.

In the event that the Sponsor terminates the study early, every effort will be made to allow patients to complete at least 6 months of treatment.

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 35 days from their initial informed consent/assent signing must be re-consented before any further study procedures can begin.

13.4. Method of Treatment Assignment

The patient assignment schedule will be a stratified by investigational site. Patients will be assigned through the IWRS a unique ID indicating pump number. The format of the supplied number of pump is XXXX. At each visit the patient will return the pump and will be dispensed the next pump according to the IWRS assignment.

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. For patients who continue from Phase 3, SGT-54-01 or SGT-54-02, a demographic profile and complete medical history will be recorded at Visit 2 in the Study SGT-54-07 source document. New patients will have demographic profile done at Visit 1/Screening and medical history done at Visits 1/Screening and 2/Baseline. Any adverse events that might be ongoing or chronic or new medical history should be also recorded.

13.6. Concomitant Medications

Concomitant medications taken 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. Brief physical examination will be performed by the investigator, sub-investigator or appropriately delegated and qualified designee every 12 weeks. For patients who enter from Phase 3, SGT-54-01 or SGT-54-02, the first physical examination of this study is the same as the Visit 6 examination from Study SGT-54-01 or Study SGT-54-02. A photocopy of the Visit 6 physical examination will be placed in the SGT-54-07 source document.

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 every 4 weeks starting at Visit 1/Screening or Visit 2/Baseline until End of Treatment/Early Termination Visit. For patients who proceed from a Phase 3 study, SGT-54-01 or SGT-54-02, the first urine pregnancy test of this study is the same as the Visit 6 examination from Study SGT-54-01 or Study SGT-54-02. A photocopy of the Visit 6 Urine Pregnancy Test will be placed in the SGT-54-07 source document. 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 for patients who entered from Study SGT-54-01 or SGT-54-02

Procedure	**Visit 2[1],[2],[7]**	**Visit 3, 4, 6, 7, 9, 10**	**Visit 5, 8, 11**	**Visit 12 (EOT[3]/ EOS[4])**	**Unscheduled Visit[11]**
Name of Visit	**Baseline Day 1**	**Week 4, 8, 16, 20, 28, 32[5] Day 29, 57, 113, 141, 197, 225**	**Week 12, 24, 36[5] Day 85, 169, 253**	**Week 40 Day 281[6]**	
Visit window		**± 10 days**	**± 10 days**	**± 10 days**	
Entry Criteria	X				
Sign Informed Consent	X				
Demographics	X				
Medical History /Previous Therapies	X				
Con med	X	X	X	X	X
Pregnancy Test[7]	X	X	X	X	X
Brief Physical Examination	X		X	X	X
Cutaneous Safety Assessment and Local Tolerability Assessments	X	X	X	X	X
Administer/ Review Patient Instructions	X	X	X		X
IGA[8]	X	X	X	X	X
Rosacea Erythema Assessment	X	X	X	X	X
Telangiectasia Assessment	X	X	X	X	X
Weigh Study Product	X	X	X	X	X
Study Product Dispensed[9]	X	X	X		X
Provide Cleanser and Moisturizer/Sunscreen, if needed	X	X	X		X
Study Product Collected		X	X	X	
Diary Card dispensed	X	X	X		X
Diary Card collected		X	X	X	X
Adverse Events	X	X	X	X	X
Complete RosaQoL[10]	X		X	X	

[1] Patient will be eligible for the extension study only after completing 12 weeks of one of the two Phase 3 studies SGT-54-01 or SGT-54-02 at the Week 12 window time (± 4 days) and missed not more than one visit of Visits 3, 4 or 5 in these studies.

[2] Same Visit as Visit 6 in Phase 3 Study SGT-54-01 or Study SGT-54-02. All procedures that were performed in Visit 6 of Study SGT-54-01 or Study SGT-54-02 will be captured in the Study SGT-54-07 source document.

[3] EOT – end of treatment.

[4] EOS – end of study.

[5] All visits must be in reference to baseline and counted accordingly.

[6] All Week 40 procedures should be completed for Patients who terminate early.

[7] Urine test for women of childbearing potential.

[8] For product dispensing eligibility

[9] The dispensation and usage of the pump is based on IGA score.

[10] RosaQoL is a Rosacea Quality of Life questionnaire

[11] Perform procedures per PI discretion.

13.10. Study Flow Chart for new patients only

Procedure	**Visit 1[1]**	**Visit 2**	**Visit 3, 4, 6, 7, 9, 10, 12, 13**	**Visit 5, 8, 11, 14**	**Visit 15 (EOT[2]/ EOS[3])**	**Unscheduled Visit[9]**
Name of Visit	**Screening -35 to 0**	**Baseline Day 1**	**Week 4, 8, 16, 20, 28, 32, 40, 44 Day 29, 57, 113, 141, 197, 225, 281, 309**	**Week 12, 24, 36, 48 Day 85, 169, 253, 337**	**Week 52 Day 365[4]**	
Visit window			**± 10 days**	**± 10 days**	**± 10 days**	
Inclusion/Exclusion Criteria	X	X				
Demographics	X					
Medical History/Previous Therapies	X	X				
Sign Informed Consent	X					
Brief Physical Examination		X		X	X	X
Concomitant Therapy and Medication History Reviewed	X	X	X	X	X	X
Pregnancy Test[5]	X	X	X	X	X	X
Cutaneous Safety Assessment and Local Tolerability Assessments		X	X	X	X	X
Administer/ Review Patient Instructions		X	X	X		X
IGA[6]	X	X	X	X	X	X
Inflammatory Lesion Count	X	X				
Rosacea Erythema Assessment		X	X	X	X	X
Telangiectasia Assessment		X	X	X	X	X
Weigh Study Product		X	X	X	X	X
Study Product Dispensed[7]		X	X	X		X
Provide Cleanser and Moisturizer/ Sunscreen, if needed		X	X	X		X
Study Product Collected			X	X	X	
Diary Card dispensed		X	X	X		X
Diary Card collected			X	X	X	X
Adverse Events	X	X	X	X	X	X
Complete RosaQoL[8]		X		X	X	

[1] Patient will be eligible for the study only after meeting all Inclusion/Exclusion criteria.
[2] EOT – end of treatment.
[3] EOS – end of study.
[4] All Week 52 procedures should be completed for Patients who terminate early.
[5] Urine test for women of childbearing potential.
[6] For product dispensing eligibility
[7] The dispensation and usage of the pump is based on IGA score.
[8] RosaQoL is a Rosacea Quality of Life questionnaire
[9] Perform procedures per PI discretion.

13.11. Screening Visit (Visit 1) for new patients only

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 36 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 Demographics and Medical History
- Record any adverse events
- 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
- 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 13.6
- 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

13.12. Baseline Visit (Visit 2, Day 1)

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 Entry Criteria for patients to proceed from Studies SGT-54-01 or SGT-54-02 as outlined in Section 12.1or Inclusion/Exclusion criteria for new patients as outlined in Section 12.2
- Ask the patient to complete Rosacea Quality of Life (RosaQoL) questionnaire (see Appendix 0). If the questionnaire was performed at the Visit 6/End of Treatment Visit of SGT-54-01 or SGT-54-02, attach a copy of the questionnaire to the source document
- Record Demographics and Medical History (For patients who continue from Phase 3, SGT-54-01 or SGT-54-02, a demographic profile and complete medical history will be recorded at Visit 2 in the Study SGT-54-07 source document)
- Record any adverse events
- Perform brief physical examination as described in Section 13.7 (If the last physical examination was done at Visit 6/End of Treatment Visit of SGT-54-01 or SGT-54-02 studies, attach a copy of it to the source document)
- 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. (If the last urine pregnancy test was done at Visit 6/End of Treatment Visit of SGT-54-01 or SGT-54-02 studies, attach a copy of it to the source document)

- Record the patient's concomitant therapies on Concomitant Therapy form as outlined in Section 13.6
- Perform Cutaneous Safety Assessment and Local Tolerability Assessment as described in Sections 15.1 to 15.2 (If the assessments were taken at Visit 6/End of Treatment Visit of SGT-54-01 or SGT-54-02 studies, attach a copy of the assessments to the source document)
- Perform the IGA, described in Section 14.1, rosacea erythema assessment and telangiectasia assessment, described in Sections 14.2 to 14.4. (If the assessments were performed at the Visit 6/End of Treatment Visit of SGT-54-01 or SGT-54-02, attach a copy of the assessments to the source document)
- Perform the inflammatory lesion count, described in (Section 14.2) for new patients only
- Weigh the study product before dispensing
- Instruct the patient on the study product application as described in Appendix 1. For new patients, pump usage shall 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)
- Dispense cleanser and moisturizer with sunscreen
- Instruct the patient that throughout the study overexposure of the face to sunlight should be avoided. Instruct the patient to use the sunscreen provided or approved; any exposure to tanning beds must be avoided during the study
- Assign 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

13.13. On-treatment (Visit 5, 8, 11; for new patients only: 14) – week 12, 24, 36; for new patients only: 48 - Day 85, 169, 253; for new patients: 337 (± 10 days)

The following procedures will be conducted at each visit:

- Ask the patient to complete Rosacea Quality of Life (RosaQoL) questionnaire (see Appendix 0)
- 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 the IGA described in Section 14.1, rosacea erythema assessment and telangiectasia assessment described in Sections 14.2 to 14.4
- Perform Cutaneous Safety Assessment and Local Tolerability Assessment as described in Sections 15.1 to 15.2
- Perform a urine pregnancy test for all females of childbearing potential (see Section 13.8)
- Perform a brief physical examination

- Review the patient's compliance with the study requirements; collect and review the Patient Diary Card
- Dispense a Diary Card to the patient
- Dispense cleanser and moisturizer with sunscreen if needed
- 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.

Remind patient to not wear make-up to all subsequent visits

13.14. On-treatment (Visit 3, 4, 6, 7, 9, 10; for new patients: 12, 13) – Week 4, 8, 16, 20, 28, 32; for new patients: 36, 40, 44 - Day 29, 57, 113, 141, 197, 225; for new patients: 281, 309 (± 10 days)

The following procedures will be conducted at each visit:

- 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 the IGA described in Section 14.1, rosacea erythema assessment and telangiectasia assessment described in Sections 14.2 to 14.4
- Perform Cutaneous Safety Assessment and Local Tolerability Assessment as described in Sections 15.1 to 15.2
- Perform a urine pregnancy test for all females of childbearing potential (see Section 13.8)
- Review the patient's compliance with the study requirements; collect and review the Patient Diary Card
- Dispense a Diary Card to the patient
- Dispense cleanser and moisturizer with sunscreen if needed
- 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.
- Remind patient to not wear make-up to all subsequent visits
- Schedule/confirm the next study visit

13.15. Patients Who entering from Studies SGT-54-01 or SGT-54-02: End of Treatment (Visit 12) – Week 40, Day 281 (± 10 days) or Early Termination by the Patient or Sponsor. New Patients: End of Treatment (Visit 15) – Week 52, Day 365 (± 10 days) or Early Termination by the Patient or Sponsor

The following procedures will be conducted at this visit:

- Ask the patient to complete Rosacea Quality of Life (RosaQoL) questionnaire (see Appendix 2)
- 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 brief physical examination as described in Section 13.7
- Perform efficacy evaluations: IGA described in Section 14.1, rosacea erythema assessment and telangiectasia assessment described in Sections 14.2 to 14.4
- Perform Cutaneous Safety Assessment and Local Tolerability Assessment as described in Sections 15.1 to 15.2
- Perform a urine pregnancy test for all females of childbearing potential (see Section 13.8)
- Review the patient's compliance with the study requirements
- Collect and review the Patient Diary Card
- Record number of missed doses on the appropriate eCRF page
- Collect and weigh returned study product pump
- Complete the End of Study/Study Termination eCRF
- Discharge the patient from the study

13.16. Unscheduled Visit

An unscheduled visit is allowed at any time if in the investigator's opinion it is warranted. The following procedures may be performed at the unscheduled visit, if required.

- 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 brief physical examination and vital signs as described in Section 13.7
- Perform a urine pregnancy test
- Perform the IGA described in Section 14.1, rosacea erythema assessment and telangiectasia assessment described in Sections 14.2 to 14.4
- Perform Cutaneous Safety Assessment and Local Tolerability Assessment as described in Sections 15.1 to 15.2
- Review the patient's compliance with the study requirements; collect and review the Patient Diary Card
- Dispense a Diary Card to the patient

- Dispense cleanser and moisturizer with sunscreen if needed
- Review the study product application instructions with the patient
- Weigh and dispense the next pump of study product
- Remind patient to not wear make-up to all subsequent visits
- Schedule/confirm the next study visit

14. CLINICAL OUTCOME ASSESSMENTS

14.1. Investigator Global Assessment (IGA)

The IGA will be performed at all study visits.

If a patient is assessed as “clear” (0) or “almost clear” (1), the patient will not be dispensed the study product. If a patient is assessed as “mild”, “moderate” or “severe” (2, 3 or 4, respectively), study product will be dispensed and the patient will use the study product daily according to patient instructions.

In the event a subject is not dispensed IP at a given visit due to an IGA of "clear" or "almost clear," and the subject's rosacea condition worsens, an unscheduled visit can be performed for assessing the subject and dispensing IP, if appropriate.

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 and Baseline, for new patients only, and they 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, and at all the study visits except the screening visit. 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 at all the study visits except the screening visit; 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. Rosacea Quality of Life (RosaQoL)

RosaQoL questionnaire will be taken at Baseline, Visits 5, 8, 11, 14 and at the End of Study Visit. There is a symptom subscale with seven questions (items 2, 6, 9, 16, 17, 18 and 19 in Appendix 2), a functional subscale with 3 questions (items 13, 15 and 21 in Appendix 2) and an emotion subscale with 11 questions (items 1, 3, 4, 5, 7, 8, 10, 11 12, 14 and 20 in Appendix 2) 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.
- 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 RosaQoL 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. SAFETY EVALUATIONS

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

15.1. Cutaneous Safety Assessments

A qualified designee will assess local application site cutaneous reactions by rating the dryness and scaling at Baseline, and at all the study visits except the screening visit. 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.

15.2. Local Tolerability Assessments

A qualified designee will assess local application site tolerability by rating the itching and burning/stinging at Baseline, and at all the study visits except the screening visit. 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 (such as pain) should be recorded as adverse events in the source document and eCRFs.

16. ADVERSE EVENTS

16.1. 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.

16.2. 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.

16.3. 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.

16.4. 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 16.2), 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. In any case, serious adverse events that are not resolved or considered to be chronic within 30 days of the final study treatment must be followed by the investigator until they become resolved 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.

16.5. 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.

16.6. 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

16.7. 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. Please see SAE and Pregnancy Form Report Instructions for safety reporting instructions.

16.8. 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.

16.9. Post Study Adverse Events

16.9.1. 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.

16.9.2. 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.

17. STUDY PRODUCTS / CLINICAL SUPPLIES

17.1. Method of Treatment Assignment

All eligible patients who complete the treatment phase of Phase 3 Study SGT-54-01 or Study SGT-54-02 within the Week 12 window and without protocol violation of missing visits (i.e., missing more than one of Visits 3, 4 or 5) will be offered to continue to this open-label, long- term safety study for up to 40 weeks. New patients, who were not previously enrolled in Study SGT-54-01 or Study SGT-54-02 will be enrolled to this open-label, long- term safety study for up to 52 weeks. During the study, patients will attend monthly visits. At Baseline, Visit 2, after satisfying all the Entry Criteria or Inclusion/Exclusion Criteria and after approval of the investigator, the patient will be assigned study product by the IWRS. Study medication will be marked in four (4)-digit pump number XXXX. At every visit, a new pump will be supplied to the patient.

17.2. Formulation

Study Product name:	Encapsulated Benzoyl Peroxide Cream, 5%
Sponsor name:	**S5G4T-1**
Active ingredients:	benzoyl peroxide
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 and water.

17.3. Study Products Packaging and Labeling

The study medication intended to be used will be stored together. The pump will carry a yellow, 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 label has spaces to enter the patient's initials and date of assignment and shows:

- Protocol number
- Patient number
- Pump number
- Patient Initials
- Dispense Date
- Dispenser Initials
- Contains: one (1) pump of Encapsulated Benzoyl Peroxide (E-BPO) Cream, 5%, 55g.
- 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 (or United States) Law to Investigational Use"
- Sponsor information

17.4. 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 according to Investigator Global Assessment at: Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32 and 36 for patients entering from study SGT-54-01 or study SGT-54-02 and for new patients at: Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48. Study product will be returned at: Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36 and 40 for patients entering from study SGT-54-01 or study SGT-54-02 and for new patients at: Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36,40,44, 48 and 52. Study product weight will be documented) prior to dispensing and after return of each pump per flow chart (Section 13.9 and Section 13.10).

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.

17.5. Dosing Instructions

Topical application of study product will be made to the face once daily at approximately the same time of the day, for the study period. 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, 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 sponsor provided or 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 apply the study cream on each area of the face as evenly as possible and gently rub the cream into the skin. Each pea-size amount should be used to evenly cover the following parts on the patient's face: chin, left cheek, right cheek, nose, left forehead and right forehead excluding the mouth, eyes 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 provided or 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 provided or 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.

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.

17.6. 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.

17.7. Return and Destruction of Study Product Supplies

Upon completion or termination of the study, all remaining pumps 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.

17.8. Additional Supplies Provided by Sponsor

- Regulatory study file system (Investigator Binder)
- Cleanser

- Moisturizer/sunscreen

18. STATISTICAL CONSIDERATIONS

18.1. General Statistical Methodology

All statistical processing will be performed using SAS® version 9.3 or later unless otherwise stated. Data will be summarized using descriptive statistics. No inferential testing or imputations for missing data will be performed. No interim analyses are planned for the co-primary variables.

For categorical parameters, the number and percentage of patients in each category will be presented. For continuous parameters, descriptive statistics will include n (number of patients), mean, standard deviation, median, minimum and maximum.

18.2. Populations Analyzed

All analyses will be performed using the Safety Population of the study. Part of this population will be referred as the extension safety population, and part as a new enrolled safety population. All patients who receive at least one confirmed dose of S5G4T-1 (in either Study SGT-54-01 or Study SGT-54-02, and in this study or for new patients in this study) and have at least one assessment will be included in the Safety Population.

The number of patients included in the Safety Population will be summarized.

18.3. Analysis of Efficacy

This study is not intended to assess efficacy, but rather the IGA is included to determine the need for treatment and subsequent re-treatment after treatment course (in either Study SGT-54-01 or Study SGT-54-02 or for new patients not previously enrolled in Study SGT-54-01 or Study SGT-54-02) and any subsequent 4-week courses, if applicable. Certain efficacy data and endpoints will, however, be summarized.

Descriptive statistics will be used to summarize the assessment of efficacy. IGA scores will be summarized at Baseline Visit of Study SGT-54-01 or Study SGT-54-02 or at the Screening visit of SGT-54-07 for those patients not previously enrolled in Study SGT-54-01 or Study SGT-54-02, and entry into the study (SGT-54-07) and every 4 weeks through end of the study. The number and percentage of patients who achieve treatment success at the scheduled study visits will be tabulated.

The number of retreatments is defined as the number of clinical confirmations of the condition for which the subject was initially treated after the first treatment period with S5G4T-1. For rollover subjects previously treated with Vehicle Cream, this is the number after the initial treatment in Study SGT-54-07. For rollover subjects previously treated with S5G4T-1, this is the number of treatments in Study SGT-54-07 following the cessation of the treatment which began in Study SGT-54-01 or Study SGT-54-02.

The number of treatment free days until the first retreatment (relapse) will be calculated and analyzed. For rollover subjects previously treated with Vehicle Cream, the number of treatment free days will be the number of days between the end of the initial treatment in study SGT-54-07 and the start of the next treatment in study SGT-54-07 if one should be needed or the end of the subject's participation in study SGT-54-07. For rollover subjects previously treated with S5G4T1, the number of treatment free days will be the of days between the end of the initial treatment that began in Study SGT-54-01 or Study SGT-54-02 and the start of the next treatment in study SGT-54-07 if one should be needed or the end of the subject's participation in the study SGT-54-07.

Descriptive statistics for retreatment rates will be presented. The time (number of days) to relapse will be analyzed using the Kaplan–Meier method. The median time to relapse will be calculated in addition to other appropriate descriptive statistics. Patients who discontinue study SGT-54-07 without relapse will considered censored in the Kaplan–Meier analysis.

18.4. Safety Evaluation

Safety will be evaluated by tabulations of adverse events (AEs), Cutaneous Safety Assessments for dryness and scaling, Local Tolerability Assessment for itching and burning and assessments for erythema and telangiectasia 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. Safety data will be presented for patients in the Safety Population with tabulations for the following periods 12 to 28 weeks, > 28 to 52 weeks and > 52 weeks to the end of the study, as well as an overall for all periods.

18.4.1. Exposure and Compliance

The extent of exposure to study product in each treatment group will be summarized by total number of days of exposure to S5G4T-1, total number of applications and number of missed applications. No formal evaluations of compliance are planned.

18.4.2. 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 period (and total) and by 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 period (and total) 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.

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 study product.

Serious adverse events (SAEs) will be tabulated.

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

TEAEs will be summarized by the number of patients reporting a TEAE, system organ class, preferred term, severity, relationship to study product (causality) and seriousness. When summarizing AEs by severity and relationship, each patient will be counted once within a system organ class or a preferred term by using the event with the highest severity and greatest relationship within each classification.

18.4.3. Vital Sign Measurements

Vital signs, as recorded during the brief physical examination, 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.

18.4.4. Exploratory Endpoint

The mean change in RosaQoL subscale scores from Baseline will be summarized for each treatment group at all applicable study visits.

19. ADMINISTRATIVE CONSIDERATIONS

19.1. 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.

19.2. 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.

19.3. 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.

19.4. 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).

19.5. 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 and diaries. 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.

19.6. 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.

19.7. 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.

19.8. 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.

20. REFERENCES

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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 study cream once a day every day during the study period unless instructed otherwise by the study team. The study doctor will discuss with you when you should apply the study cream if your skin is clear.
- 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 cream should be applied once daily (preferably at the same time each day) to the entire face during the study period.
- Apply one gentle pump application of study cream 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 study 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 cream. But do not wash your face for at least two hours after you apply study cream.
- Wait for at least 30 minutes before applying the study provided or approved moisturizer/sunscreen.
- If applicable, wait at least 30 minutes before applying only non-medicated make-up.

ADDITIONAL REMINDERS:

- Store study cream 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 STUDY CREAMTSHOULD 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 cream 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.
- If you use a moisturizer and/or sunscreen, you must use the one provided or approved 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 cream pump with you to every study visit.

STUDY VISIT SCHEDULE for patient entered from study SGT-54-01 or study SGT-54-02:

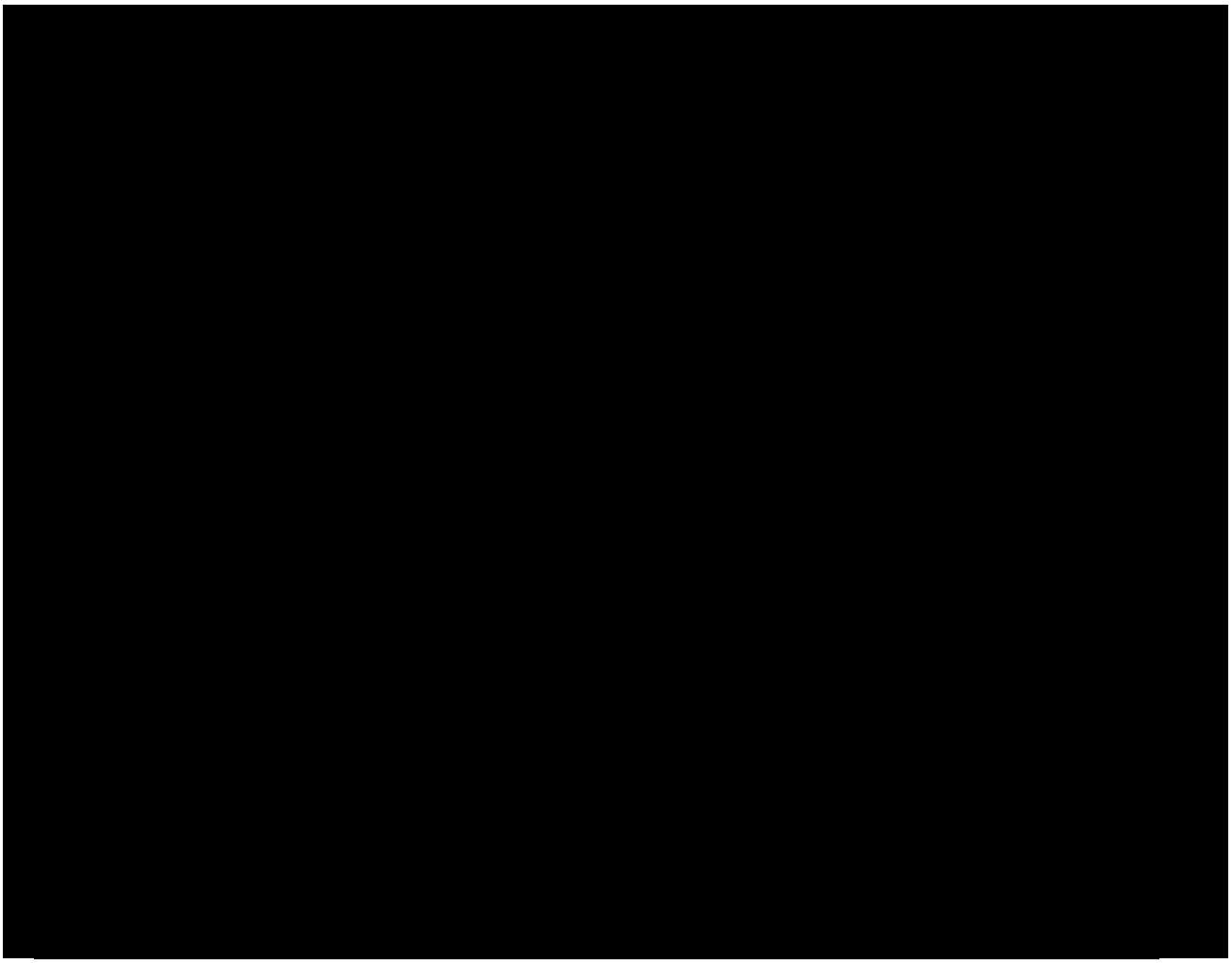
VISIT 2: Baseline, Day 1 Date: Time:	VISIT 5: Week 12, Day 85 Date: Time:	VISIT 9: Week 28, Day 197 Date: Time:
VISIT 3: Week 4, Day 29 Date: Time:	VISIT 6: Week 16, Day 113 Date: Time:	VISIT 10: Week 32, Day 225 Date: Time:
VISIT 4: Week 8, Day 57 Date: Time:	VISIT 7: Week 20, Day 141 Date: Time:	VISIT 11: Week 36, Day 253 (if applicable) Date: Time:
	VISIT 8: Week 24, Day 169 Date: Time:	VISIT 12: Week 40, Day 281 (if applicable) Date: Time:

STUDY VISIT SCHEDULE for new patient:

VISIT 2: Baseline, Day 1 Date: Time:	VISIT 7: Week 20, Day 141 Date: Time:	VISIT 12: Week 40, Day 281 (if applicable) Date: Time:
VISIT 3: Week 4, Day 29 Date: Time:	VISIT 8: Week 24, Day 169 Date: Time:	VISIT 13: Week 44, Day 309 (if applicable) Date: Time:
VISIT 4: Week 8, Day 57 Date: Time:	VISIT 9: Week 28, Day 197 Date: Time:	VISIT 14: Week 48, Day 337 (if applicable) Date: Time:
VISIT 5: Week 12, Day 85 Date: Time:	VISIT 10: Week 32, Day 225 (if applicable) Date: Time:	VISIT 15: Week 52, Day 365 (if applicable) Date: Time:
VISIT 6: Week 16, Day 113 Date: Time:	VISIT 11: Week 36, Day 253 (if applicable) Date: Time:	

Thank you for following these instructions.

APPENDIX 2: ROSACEA QUALITY OF LIFE QUESTIONNAIRE (ROSAQOL)



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