NCT # NCT03761784

CLINICAL STUDY PROTOCOL

Title: A Phase 3 Multi-Center, Double-Blind, Randomized, Vehicle-Controlled Study of S6G5T-3 in the Treatment of Acne Vulgaris

Protocol No:	SGT-65-04
Protocol Version:	2.0
Amendment 1.0 version:	01-Nov-2018
Original Version:	23-Mar-2018

Sponsor : Sol-Gel Technologies Ltd.
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1 PROTOCOL APPROVAL – SPONSOR SIGNATURE

Protocol Title: A Phase 3 Multi-Center, Double-Blind, Randomized, Vehicle-Controlled Study of S6G5T-3 in the Treatment of Acne Vulgaris

Study Products: Product S6G5T-3 compared to Vehicle.

Sol-Gel Technologies Ltd. commits to conduct the study as described herein in accordance with the current International Conference on Harmonization (ICH) – Good Clinical Practices (cGCPs) and the World Medical Association Declaration of Helsinki and in compliance with the obligations and requirements of the Sponsor as listed in 21 CFR Part 312.The following individuals approve the 01-Nov-2018 version of the SGT-65-04 protocol. All changes to this version of the protocol must have prior written approval and require an amendment or administrative letter.

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2 INVESTIGATOR PROTOCOL ACKNOWLEDGMENT

Protocol Title: A Phase 3 Multi-Center, Double-Blind, Randomized, Vehicle-Controlled Study of S6G5T-3 in the Treatment of Acne Vulgaris

Study products: Product S6G5T-3 compared to Vehicle.

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

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

I agree to completely inform all Study 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

Protocol number: SGT-65-04, Version 2.0

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4 PROTOCOL SYNOPSIS

Title:	A Phase 3 Multi-Center, Double-Blind, Randomized, Vehicle-Controlled Study of S6G5T-3 in the Treatment of Acne Vulgaris
Study Number:	SGT-65-04
Study Phase:	3
Indication:	Acne vulgaris
Study Period:	12 weeks (84 Days)
Study Products:	1. S6G5T-3: E-BPO/E-ATRA 3%/0.1% developed by Sol-Gel Technologies and manufactured by [redacted] New-Zealand. 2. S6G5T-8: Vehicle Cream, developed by Sol-Gel Technologies and manufactured by [redacted] New Zealand.
Study Objectives:	To assess the efficacy and safety of S6G5T-3 compared to its Vehicle when applied once daily for 12 weeks in Patients with acne vulgaris.
Study Design:	Study Patients will be admitted into this multi-center, double-blind, randomized, vehicle-controlled, parallel-group pivotal study only after a written informed consent has been obtained and after all inclusion/exclusion criteria have been met. Male and female Patients at least 9 years of age with moderate or severe facial acne vulgaris. Investigator Global Assessment (IGA) grade 3 or 4 will be eligible for enrollment for daily treatment with S6G5T-3 or its vehicle, S6G5T-8, for 12 weeks.
Study Population:	Approximately 420 male and female Patients, at least 9 years of age, who meet the inclusion/exclusion criteria will be enrolled in this study.
Investigational sites:	Approximately 25 study centers in the US will participate in this study.
Dosing:	Patients will be randomized in a 2:1 ratio to the study product or vehicle treatment groups, respectively. Patients will apply the study product once daily for 12 weeks. Patients will use a “pea-size” amount for each area of the face (chin, left cheek, right cheek, nose, left forehead and right forehead). Study product will be spread as a thin layer, avoiding the eyes, lips, inside the nose, mouth and all mucous membranes. Patients will receive detailed instructions on the method of application and quantity of use in order to assure that treatment is consistent among all Patients to best extent possible.
Methodology:	Clinical and Safety Evaluations will be performed at: 1. Visit 1/Screening 2. Visit 2/Baseline, Day 1 3. Visit 3/Week 2, Day 15 (± 3 Days) 4. Visit 4/Week 4, Day 29 (± 3 Days) 5. Visit 5/Week 8, Day 57 (± 3 Days)

	6. Visit 6/Week 12, Day 85 (± 4 Days)/ End of Study or Early Termination. Patients will be admitted into the study after written informed consent has been obtained, and all inclusion/exclusion criteria have been met, including a clinical diagnosis of acne vulgaris. Patients with severe acne vulgaris who are appropriate for systemic treatment need to be counseled regarding their treatment options by the Principal Investigator. Prior to any treatment related assessments, questionnaires are to be completed by all patients, starting the age of 9 years old: 1. Patient reported outcomes (PRO) will be assessed with the Patient-Reported Evaluation of Facial Acne (PRE-FACE) and the Patient Global Impression of Symptom Severity (PGI-S) at: Screening, Baseline, Weeks 2, 4, 8, and 12/ Early Termination. The Patient Global Impression of Change (PGI-C), Patient Global Impression of treatment Side Effects (PGI-SE), and Patient Global Impression of Treatment Satisfaction (PGI-TS) will be assessed at: Weeks 2, 4, 8, and 12/ End of Study or Early Termination. 2. Acne Quality of Life (QoL) questionnaire at Baseline and week 12/ End of Study or Early Termination At each visit, a 5-point scale Investigator Global Assessment (IGA) ranging from 0 (Clear) to 4 (Severe) of acne assessment and facial lesion counts (inflammatory and non-inflammatory) will be performed. Investigators will be provided with instructions for IGA assessments and lesion counts to ensure consistency of procedures. Safety will be assessed at all visits and will include monitoring of adverse experiences; the Investigator Cutaneous Safety Assessment rating of pigmentation, erythema, dryness and scaling on a scale ranging from 0 (None) to 3 (Severe); and the Patient assessment of Local Tolerability rating itching burning and stinging on a scale ranging from 0 (None) to 3 (Severe). Urine pregnancy tests will be performed for all females of child-bearing potential and premenarchal females, at every visit: Screening, Baseline, Weeks 2, 4, 8 and 12/ End of Study or Early Termination. Standardized optional photography of the face at Baseline and all study visits will be performed at select sites. Regardless of the duration of the study, all 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:	Planned enrollment duration: about 9 months The maximal duration for each participating patient is up to 119 days as follows:

	Screening Period: up to 35 days prior to baseline (Screening evaluations should be repeated if Baseline is >35 days after screening) Treatment Period: 12 weeks/84 days In addition, patients that experience an adverse event (AE) will be followed up until the AE stabilizes or resolves, based on the Investigator's medical judgment.
Study Products:	Encapsulated Benzoyl Peroxide 3%/Encapsulated All-Trans-Retinoic Acids 0.1% Cream or Vehicle Cream will be dispensed every 4 weeks (Baseline, Week 4 and Week 8) to Patients and used daily during the study. The study product and vehicle will be supplied in 52-gram pumps.
Patient Inclusion Criteria:	Patients may participate in the study if they meet all the following criteria: 1. Patient must consent to participate, verified by signing an approved written Informed Consent Form (ICF). For Patients under the age of consent, both a signed assent form and a signed ICF from the parent/guardian are required in accordance with local and federal regulations. 2. Male and female 9 years of age and older. 3. Willingness and capacity for protocol compliance (for Patients under the age of consent, the parent/guardian must be willing and able to comply with study requirements). 4. Have a diagnosis of facial acne with ≥30 and ≤150 non-inflammatory lesions and ≥20 and ≤100 inflammatory lesions including the nose. 5. Have a score of "3" or "4" (Moderate or Severe) on the IGA scale. 6. Have two (2) or fewer cysts or nodules (defined as an inflammatory lesion greater than or equal to 5 mm in diameter). 7. All females of child-bearing potential and premenarchal, excluding women who are surgically sterile (including Essure procedure, tubal ligation, bilateral oophorectomy or hysterectomy) or post-menopausal: [defined as amenorrhea >12 consecutive months; or women on hormone replacement therapy (HRT) with documented plasma follicle-stimulating hormone (FSH) level >35mLU/mL] for at least 1 year, must use one of the following birth control methods throughout the duration of the study: a) One of these highly effective contraception methods: • Intrauterine device (IUD); • Hormonal, for at least 3 months. (Pills, injections, implants, transdermal patch, vaginal ring); • Abstinence OR b) Double-barrier methods (male and female) of contraception listed below: • Combined use of male and female condom; • Male condom and female occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/

	cream/suppository; or • Male condom and female contraceptive sponge with spermicide In addition, Patients entering the trial that are on hormonal contraceptives must have been on this method for at least 3 consecutive months (90 days) prior to Baseline and agree to continue the same hormonal contraceptive or pill for the duration of the trial. Patients who have 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 Baseline and have undergone an Essure confirmation test to ensure its efficacy. A sterile/vasectomized sexual partner alone is not considered an adequate form of birth control. In this case an additional contraceptive method is required. 8. Male Patients must be clean-shaven or have a cut beard/facial hair that does not interfere with study assessment, and they should also agree to remain so during the study visits. 9. Use of multivitamins at recommended daily doses is acceptable and the patient agrees not to change dose during study participation. 10. Premenarchal females and FOCBP must have a negative urine pregnancy test at the screening and baseline visits.
Patient Exclusion Criteria:	The presence of any of the following will exclude the potential Patients from entry into the study: 1. More than two acne nodules or cysts (defined as an inflammatory lesion greater than or equal to 5 mm in diameter). 2. Acne conglobata, acne fulminans, secondary acne (chloracne, drug-induced acne, etc.) 3. History of blood dyscrasia (e.g., leukemia, haemophilia, sickle cell anemia, multiple myeloma, etc.) 4. Underlying disease that requires the use of interfering topical or systemic therapy. 5. Other dermatological conditions that require the use of interfering topical or systemic therapy or that might interfere with study assessments such as, but not limited to, atopic dermatitis, perioral dermatitis, or rosacea. 6. Beard, facial hair, or tattoo that may interfere with study assessments. 7. Use of tanning booths or tanning lamps within one week prior to Baseline and an unwillingness to refrain from use during the study. 8. Use of hormonal contraceptives, unless Patient is on a stable dose for at least three consecutive months prior to enrollment and agrees not to change or discontinue type of hormonal contraceptive use during study participation. 9. Use of hormonal contraceptives solely for the control of acne. 10. Use of systemic Isotretinoin and/or Anti- androgens in the past 6 months.

11. Use of prohibited medications prior to the study and unwillingness to refrain from use during the study.
12. Does not meet one or more specified washout period prior to Baseline for TOPICAL treatments on the face as follows:

Topical Medication/Therapy	Washout Period
Hyaluronic Acid and Retinol	1 day
Antimicrobial Soaps	1 week
Phototherapy devices for acne (e.g., ClearLight™), adhesive cleansing strips (e.g., Ponds, Biore) as well as, use of tanning booths or tanning lamps.	1 week
OTC topical products containing salicylic acid and BPO (e.g. Clearasil, Clean & Clear)	1 week
Astringents (e.g., Witch hazel, Noxzema), abrasives (e.g., Clarisonic brushes, facial scrub products), and preparations that contain spices or lime or lemon	1 week
Topical medicated cleansers with sulfur or triclosan	1 week
Potentially irritating OTC acne products: Alpha-hydroxy-Acid, and Glycolic Acid	1 week
Essential Oils (used specifically for acne, e.g., tree tea oil, oregano, lavender, etc.)	1 week
Azelaic Acid	2 weeks
Topical Corticosteroids in treatment area (inhaled and intranasal are allowed), topical vasoconstrictors and topical non-steroidal anti-inflammatory drugs, topical antibiotics (including antimicrobials like benzoyl peroxide containing products, [e.g., benzamycin], zinc and sulfur)	2 weeks
Other topical acne procedures (including photodynamic therapy or laser, microdermabrasion) as well cosmetic procedures (i.e., facials, peels, comedo extraction, facial threading, use of Nair on the face	2 weeks
Topical retinoids (e.g., tretinoin, Differin, Adapalene)	4 weeks

13. Does not meet one or more specified washout period prior to Baseline for SYSTEMIC medications as follows:

Systemic Medications	Washout Period
Corticosteroids (includes intramuscular)	4 weeks

[1]Antibiotics	4 weeks
Testosterone (All forms includes injections)	4 weeks
Ostarine (All forms, includes oral)	4 weeks
Lithium (e.g., Lithium Orotate, Lithium Carbonate)	4 weeks
Hormonal contraceptives used for less than three consecutive months prior to enrollment or used solely for acne control.	3 months[2]
Isotretinoin and Anti-androgens	6 months

14. Known sensitivities to the study drug ingredients. Allergy to benzoyl peroxide, tretinoin, parabens and glycerin or other ingredients listed in the Investigator Brochure.
15. Use of testosterone and Ostarine within four (4) weeks prior to Baseline and an unwillingness to refrain from use during the study.
16. Use of Lithium supplements or prescription (e.g., Lithium Orotate and Lithium Carbonate) within four (4) weeks prior to Baseline and an unwillingness to refrain from use during the study.
17. Clinically significant abnormal findings or conditions (other than acne), which might, in the opinion of the Investigator, interfere with study evaluations or pose a risk to Patient safety during the study.
18. Female Patients who are pregnant and/or nursing or planning to become pregnant during the course of the trial. Patients who test positive for pregnancy after start of test treatment will be discontinued from test treatment but will be followed for safety purposes.
19. Participation in another investigational drug or device research study within 30 days of enrollment or five half-lives of the drug, whichever is longer.
20. Previous enrollment in this study or current enrollment in this study at another participating site.
21. Current or history of facial skin cancer.
22. Patient is an employee or family member of the study Investigator or other study staff having direct involvement in the study.
23. Patients living (e.g., siblings, spouses, relatives) in the same household cannot be enrolled in the study at the same time.
24. Female Patients with a history of polycystic ovarian disease
25. Topical and oral treatment for acne other than the face (e.g., chest or back) is not allowed during the study.

[1] Upon randomization one course of penicillin and its derivatives (e.g. amoxicillin) and cephalosporins are allowed for a duration of 10 days or less, however not during the two (2) week period just prior to week 12 visit.

[2] If a Patient is on hormonal contraceptives for less than 3 months, she should continue using the same hormonal contraceptives and she can be considered to enter the study after completing 3 months of use.

Primary Efficacy Endpoints:	• Proportion of Patients with an assessment of clear or almost clear and with at least a 2-grade improvement in IGA from baseline at Week 12. • Absolute change from Baseline in lesion count on the face at Week 12 (separately for inflammatory and non-inflammatory lesions).
Secondary Efficacy Endpoints:	The secondary efficacy endpoints will be the following: • Percent change from Baseline, in non-inflammatory lesion count at Week 12. • Percent change from Baseline, in inflammatory lesion count at Week 12. • Proportion of Patients in the E-BPO/E-ATRA cream arm compared to vehicle control achieving at least a 4-point reduction on Item 1 (pimples) of the PRE-FACE from Baseline to Week 12. • Proportion of Patients in the E-BPO/E-ATRA Cream arm compared to vehicle control achieving at least a 4-point reduction on Item 5 (embarrassment) of the PRE-FACE from Baseline to Week 12. • Absolute change from Baseline, in non-inflammatory lesion count at Week 8 • Absolute change from Baseline, in inflammatory lesion count at Week 8. • Absolute change from Baseline, in non-inflammatory lesion count at Week 4. • Absolute change from Baseline, in inflammatory lesion count at Week 4.
Supportive Efficacy Endpoints:	• Proportion of Patients with an assessment of clear or almost clear and with at least a 2-grade improvement from Baseline in IGA, at Weeks 2, 4 and 8. • Absolute change from Baseline in inflammatory and non-inflammatory lesion counts from Baseline to weeks 2, 4 and 8. • PRE-FACE ASD: Mean absolute change in PRE-FACE ASD scores from Baseline to Weeks 2, 4, and 8. • PRE-FACE AID: Mean absolute change in PRE-FACE AID scores from Baseline to Weeks 2, 4, and 8. • Proportion of Patients in treatment relative to control who report at least "minimally improved" as measured by the PGI-C at Week 12. • Patient Global Impress of Symptom Severity (PGI-S) at Week 12. • Patient Global Impression of Treatment Satisfaction (PGI-TS) at Week 12.

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.
Exploratory Endpoint:	• The mean change in Acne-specific Quality of Life questionnaire (Acne-QoL) domain scores from Baseline to Week 12.
Safety:	The incidence of all AEs reported during the study will be summarized by treatment group. Safety of the study product with will be evaluated by comparing the nature, severity and frequency of their AE profiles. Safety variables include Investigator Cutaneous Safety Assessment score, treatment-emergent AEs (TEAEs), SAEs, treatment related AEs, AEs leading to study discontinuation, concomitant medications.
Statistical Method:	**General Statistical Methods** All statistical processing will be performed using SAS® version 9.3 or later unless otherwise stated. Statistical significance will be based on two-tailed tests of the null hypothesis resulting in p-values of 0.05 or less. **Analysis Populations** The intent-to-treat (ITT) population will consist of all randomized Patients who were dispensed study product. The safety population will be comprised of all randomized Patients who are presumed to have used the study product at least once and who provide at least one post-baseline safety evaluation. Patients will be considered per protocol (PP) if they complete the 12-week evaluation without noteworthy study protocol violations (i.e., any Patient or Investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy). Patients that discontinue from the study due to an AE related to study product or documented lack of treatment effect will be included in the PP population. Data for these Patients will not be imputed by multiple imputation but rather their data will be imputed with values consistent with their status as treatment failures. Prior to breaking the blind, other additional criteria may be added to the list to accommodate for unforeseen events that occurred during the conduct of the trial that result in noteworthy study protocol violations. **Evaluations and Analyses** The co-primary efficacy analyses will be to compare Product S6G5T-3 with vehicle for (1) success rate at Week 12 (defined as 'clear' or 'almost clear' [at least a 2-grade improvement in the IGA]) and (2) absolute change from baseline in lesion counts at Week 12 based on the intent-to-treat [ITT] population (separately for inflammatory and non-inflammatory lesions). **Statistical Hypothesis Testing** Tests of superiority for the absolute change from Baseline in inflammatory lesions or non-inflammatory will be based on either parametric or non-

	parametric methods consistent with the statistical assumptions required to support the analyses. Specifically, the tests of superiority will be based on an ANCOVA with factors of treatment and analysis center and the respective Baseline lesion count as a covariate or on ranked data submitted to an ANCOVA with factors of treatment and analysis center and the respective Baseline lesion count as a covariate. If the treatment-by-analysis center interaction effect is significant at an alpha less than 0.10, then the effect will be included in the model; otherwise it will be removed. Following imputation of missing values, a skewness test, based on the methods presented by J.H. Zar (1984), will be applied to the residuals resulting from an ANCOVA. A two-sided p-value for the skewness test significant at 0.01 will imply the use of the non-parametric method. If a parametric analysis is indicated, the results of the parametric analysis will be considered the primary analysis. Should a non-parametric analysis be indicated, the absolute or percent changes in inflammatory lesions will be rank transformed prior to submitting them to the ANCOVA. Results of the rank-transformed analyses then will be considered the primary analysis; however, results of the non-ranked transformed analyses will also be presented The IGA will be dichotomized into "success" and "failure" with a Patient considered a success for those visits if the IGA is at least 2 grades less than Baseline and "Clear" or "Almost Clear". The analysis of the dichotomized IGA will be based on a logistic regression test with factors of treatment group and analysis center. **Missing Efficacy Data Imputations** Missing Week 12 data will be estimated by multiple imputation and subsequently analyzed. Missing lesion count data will be derived for the analysis using the method of Markov Chain Monte Carlo (MCMC) multiple imputation. Imputation will be conducted independently for each treatment group. **Sensitivity Efficacy Analyses** Sensitivity analyses for the primary efficacy endpoints will use 3 methods. The first method will use a repeated measures ANCOVA, with treatment, analysis center, and visit (i.e., Week 2, Week 4 and Week 8) as independent factors and a covariate of baseline. In this analysis, data from all post-Baseline visits will be included with no imputation for missing data. The second sensitivity analyses will use the model based multiple imputation method to impute missing data for the absolute change at Week 12. The third sensitivity analysis will involve a tipping point analysis. Statistical analysis plan (SAP), describing all statistical analyses will be provided as a separate document.

5 LIST OF ABBREVIATIONS AND TERMS

AE(s)	Adverse Event(s)
ANCOVA	Analysis of Covariance
ATRA	All Trans Retinoic Acids: Tretinoin
BPO	Benzoyl Peroxide
°C / °F	Degrees Centigrade / Degrees Fahrenheit
CFR	Code of Federal Regulations
ClinRo	Clinician Reported Outcome
CRA	Clinical Research Associate
CRO	Contract Research Organization
E-ATRA	Encapsulated All Trans Retinoic Acid: Encapsulated tretinoin
E-BPO	Encapsulated Benzoyl Peroxide
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
G	Grams
cGCP	current Good Clinical Practice
H	Hour(s)
hCG	Human Chorionic Gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	Health related Quality of Life
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IGA	Investigator's Global Assessment
IND	Investigational New Drug
IRAE	Immediately Reportable Adverse Event
IRB	Institutional Review Board
ITT	Intent To Treat
IWRS	Interactive Web Response System
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minutes
Mg	Milligram
NRS	Numeric Rating Scale
OTC	Over The Counter
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Symptom Severity
PGI-SE	Patient Global Impression of treatment Side-Effects
PGI-TS	Patient Global Impression of Treatment Satisfaction
PI	Principal Investigator
PRE-FACE	Patient-Reported Evaluation of Facial Acne
PRO	Patient Reported Outcome
PP	Per Protocol
Qd	Once a Day
QoL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
Sub-I	Sub-Investigator
TEAE	Treatment-Emergent Adverse Event

VRS	Verbal rating scale

6 INTRODUCTION AND BACKGROUND

Acne vulgaris is a common condition of the pilosebaceous units of the skin (hair follicles and oil glands). Acne is the most common skin disorder in the United States, affecting 40-50 million Americans. Acne usually begins in puberty, but the condition is not restricted to any age group.

Approximately 85% of people between the ages of 12 and 24 experience at least minor, most often on the face, chest, and back (Bhate, 2013). Acne is caused by four major factors:

1. Production of oil by enlarged oil glands in the skin.
2. Blockage of the hair follicles that release oil.
3. Growth of bacteria, called *Propionibacterium acnes*, within the hair follicles.
4. Inflammatory/immune response to *P. acnes*

The pathophysiologic features of acne suggest that combination therapy should be utilized as early as possible to simultaneously attack the multiple pathogenic factors of the condition (Gollnick 2003). Antimicrobials have been a mainstay of acne treatment for many years, having multiple mechanisms of action. The most important may be the ability of antibiotics to decrease the number of *P. acnes* in and around the follicle. They have a bacteriostatic effect on *P. acnes*, which prevents the bacteria from producing pro-inflammatory molecules (Leyden 2001).

In clinical practice, it is common for physicians to prescribe multiple topical products for acne. Topical products are applied one or two times a day by the Patient. However, many of these compounds are irritating with resultant development of facial erythema and discontinuation of the products or noncompliance with therapy. Benzoyl peroxide (BPO) and tretinoin (ATRA) are two active ingredients with different pharmacological actions that are commonly used for the treatment of acne.

Topical retinoids are keratinization inhibitors. They work by decreasing the cohesiveness of follicular epithelial cells. This, results in an inhibition in the formation of microcomedones, preventing the formation of mature comedones and inflammatory lesions (Gollnick 2003). Use of retinoids promotes the normal desquamation of follicular epithelium. The action of the retinoid may enhance the penetration of other topical compounds used to treat acne.

Benzoyl peroxide (BPO) is a commonly used topical antibacterial agent for acne available either by prescription or over the counter (OTC). BPO has been found to be lethal to *P. acnes* as well as other bacteria that may reside on the skin. So far there has been no indication of any bacteria developing a resistance to BPO. It has also been demonstrated that BPO has keratolytic activity contributing to its efficacy in treating comedonal acne (Tanghetti 2008). BPO reduces the cohesiveness of the cells of the stratum corneum, thus improving topical drug delivery through the epidermal barrier.

Silica microcapsule systems have been developed to overcome many of the limitations

(such as degradation and irritation) of standard pharmaceutical formulations involving multiple active ingredients. The encapsulation of active ingredients in silica microcapsules serves to protect components in the formulation from interacting with one another and, as a consequence, increases overall formulation stability. Silica is chemically inert, photochemically and physically stable, and safe for topical use. Sol-Gel's silica encapsulated products meet the criteria for categorical exclusion defined in 21 CFR 25.31(e), and that to the knowledge of Sol-Gel, no extraordinary circumstances exist as defined in 21 CFR 25.21. Thus, no environmental assessment is required according to 21 CFR 25.20(l). For the case of E-BPO/E-ATRA, microencapsulation of both BPO and tretinoin protects the tretinoin from oxidative decomposition by BPO, thereby enhancing the stability for this novel combination product and ensuring a suitable clinical and commercial shelf life. The encapsulation may also contribute to decreased skin irritation as evidenced in the 14-day minipig irritation study referenced in the nonclinical section of the Investigator's Brochure.

Combination topical therapy is the recommended standard of care for the management of Patients with acne (Gollnick 2003). Combination therapy targets multiple pathogenic factors: abnormal follicular keratinization, P. acnes proliferation and inflammation. Combining the separate product applications into a single delivery system would provide the Patient with the convenience of a single product, thus improving Patient adherence and improving treatment outcomes.

[redacted]

[redacted]

7 OBJECTIVES

The primary objectives of this pivotal study are:

1. To assess the efficacy of S6G5T-3 compared to its Vehicle when applied once daily for 12 weeks in Patients with acne vulgaris.
2. To assess the safety of S6G5T-3 when applied once daily for 12 weeks in Patients with acne vulgaris.

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

- Proportion of Patients with an assessment of clear or almost clear and with at least a 2-grade improvement in IGA from baseline at Week 12.
- Absolute change from Baseline in lesion count on the face at Week 12 (separately for inflammatory and non-inflammatory lesions).

The secondary objective of this pivotal study is:

To demonstrate statistical superiority in efficacy of Products S6G5T-3 as compared to the vehicle regarding percent change from baseline.

The secondary efficacy endpoints will be the following:

- Percent change from Baseline, in non-inflammatory lesion count at Week 12.
- Percent change from Baseline, in inflammatory lesion count at Week 12.
- Proportion of Patients in the E-BPO/E-ATRA cream arm compared to vehicle control achieving at least a 4-point reduction on Item 1 (pimples) of the PRE-FACE from Baseline to Week 12.
- Proportion of Patients in the E-BPO/E-ATRA Cream arm compared to vehicle control achieving at least a 4-point reduction on Item 5 (embarrassment) of the PRE-FACE from Baseline to Week 12.
- Absolute change from Baseline, in non-inflammatory lesion count at Week 8
- Absolute change from Baseline, in inflammatory lesion count at Week 8.
- Absolute change from Baseline, in non-inflammatory lesion count at Week 4.
- Absolute change from Baseline, in inflammatory lesion count at Week 4.

The supportive objective of this pivotal study is:

To determine the time required to observe improvement in the efficacy parameters associated with clearance of acne for Products S6G5T-3 compared to vehicle.

Supportive efficacy endpoints include the following:

- Proportion of Patients with an assessment of clear or almost clear and with at least a 2-grade improvement in IGA from Baseline, at Weeks 2, 4 and 8.
- Absolute change from Baseline in inflammatory and non-inflammatory lesion counts from Baseline to weeks 2, 4 and 8.
- PRE-FACE ASD: Mean absolute change in PRE-FACE ASD scores from Baseline to Weeks 2, 4, and 8.
- PRE-FACE AID: Mean absolute change in PRE-FACE AID scores from Baseline to Weeks 2, 4, and 8.
- Proportion of Patients in treatment relative to control who report at least “minimally improved” as measured by the PGI-C at Week 12.
- Patient Global Impress of Symptom Severity (PGI-S) at Week 12.

- Patient Global Impression of Treatment Satisfaction (PGI-TS) at Week 12.

The safety objectives of this pivotal study are:

To determine the nature, severity and frequency of the AEs rate and the local cutaneous reaction and tolerability of Products S6G5T-3 compared to the vehicle.

The safety endpoints to be assessed include the following:

- The frequency of both local and systemic AEs
- Investigator Cutaneous Reaction (erythema, dryness, pigmentation and scaling) and Local Tolerability Assessment (itching burning and stinging) at Baseline and at all study visits.

8 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 study 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.

9 INSTITUTIONAL REVIEW BOARD (IRB) AND INFORMED CONSENT

Before study initiation, this protocol, the investigational brochure for Encapsulated Benzoyl Peroxide 3%/Encapsulated All-Trans-Retinoic Acids 0.1% Cream (E-BPO/E-ATRA 3%/0.1%) in the treatment of acne vulgaris, the ICF, 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 Contract Research Organization (CRO) designee.

The IRB-approved ICF must include all elements required by the Food and Drug Administration (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 ICF. 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 ICF, 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.

10 OVERALL STUDY DESIGN

This study will be a randomized, double-blind, multicenter, parallel group, active- and vehicle-controlled pivotal study to asses efficacy, and safety of Products S6G5T-3 and its vehicle for the treatment of acne vulgaris for 12 weeks. Approximately 420 Patients with moderate to severe acne vulgaris (rated 3 or 4 on the 5-point IGA) will be enrolled at up to 25 sites. Patients in this randomized, double-blind, vehicle-controlled, parallel-group multi-center study will be randomly assigned in a 2:1 ratio to Encapsulated Benzoyl Peroxide 3%/Encapsulated All-Trans-Retinoic Acids 0.1% (E-BPO/E-ATRA) Cream or Vehicle Cream respectively. Patients with severe acne vulgaris who are appropriate for systemic treatment need to be counseled regarding their treatment options by the Principal Investigator (PI).

The overall schedule of study visits includes:

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

Treatment efficacy will be evaluated using both clinician reported outcome (ClinRO) and Patient-reported outcome (PRO) questionnaires. Clinician reported efficacy assessments will include facial inflammatory and non-inflammatory lesion counts and an IGA which asks assessors to rate Patient's acne from 0 (Clear) to 4 (Severe). Patient reported efficacy assessments include the Patient-Reported Evaluation of Facial Acne (PRE-FACE), the Patient Global Impression of Symptom Severity (PGI-S), the Patient Global Impression of Change (PGI-C), and the Patient Global Impression of Treatments Satisfaction (PGI-TS).

Safety will be assessed at all visits and will include monitoring local and systemic AEs; the Investigator Cutaneous Safety Assessment rating of pigmentation, erythema, dryness and scaling on a scale ranging from 0 (None) to 3 (Severe) and the Patient assessment of Local Tolerability Assessment rating itching, burning and stinging on a scale ranging from 0 (None) to 3 (Severe). A Patient Global Impression of Treatment Side Effects (PGI-SE) will also be administered as part of the study design.

Clinician reported outcomes will be collected at study Visit 1, 2, 3, 4, 5 and 6. Patient-reported outcomes will be collected at study visit 2, 3, 4, 5, and 6 (with the exception of the PGI-C, PGI-TS and PGI-SE) which are not collected at Visit 1 or Visit 2). AEs and concomitant medications will be assessed throughout the treatment period. A urine pregnancy test is required at Visit 1, 2, 3, 4, 5 and 6 for all females of child-bearing potential and premenarchal.

11 STUDY POPULATION

11.1 Randomization and Blinding

It is planned that approximately 420 Patients, who meet the inclusion/exclusion criteria, will be enrolled in this study at up to 25 U.S. study sites. Patients will be at least 9 years of age and older, of either gender.

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

- E-BPO/E-ATRA 3%/0.1% Cream (Product S6G5T-3) (280 Patients)
- Vehicle Cream (Product S6G5T-8) (140 Patients)

Each Patient who signs an informed consent, meets inclusion/exclusion criteria, and successfully completes the screening procedures will be enrolled in the study. The Patient randomization schedule will be a permuted block design stratified by investigational site. Blocks will be composed of 3 treatment assignments in a ratio of 2:1 Product S6G5T-3 and vehicle respectively. Complete blocks from the randomization schedule will be allocated to investigational sites as they randomize Patients to maintain the randomization ratio of 2:1 Product S6G5T-3 and vehicle respectively.

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

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

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

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

11.2 Inclusion Criteria

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

1. Patient must consent to participate, verified by signing an approved written Informed Consent Form (ICF). For Patients under the age of consent, both a signed assent form and a signed ICF from the parent/guardian are required in accordance with local and federal regulations.
2. Male and female 9 years of age and older.
3. Willingness and capacity for protocol compliance (for Patients under the age of consent, the parent/guardian must be willing and able to comply with study requirements).
4. Have a diagnosis of facial acne with ≥30 and ≤150 non-inflammatory lesions and ≥20 and ≤100 inflammatory lesions including the nose.
5. Have a score of "3" or "4" (Moderate or Severe) on the IGA scale.
6. Have two (2) or fewer cysts or nodules (defined as an inflammatory lesion greater than or equal to 5 mm in diameter).
7. All females of child-bearing potential and premenarchal, excluding women who are surgically sterile (including Essure procedure, tubal ligation, bilateral oophorectomy or hysterectomy) or post-menopausal: [defined as amenorrhea >12 consecutive months; or women on hormone replacement therapy (HRT) with documented plasma follicle-stimulating hormone (FSH) level >35mLU/mL] for at least 1 year, must use one of the following birth control methods throughout the duration of the study:
   c) One of these highly effective contraception methods:
      - Intrauterine device (IUD);
      - Hormonal, for at least 3 months. (Pills, injections, implants, transdermal patch, vaginal ring);
      - Abstinence

   OR

   d) Double-barrier methods (male and female) of contraception listed below:
      - Combined use of male and female condom;
      - Male condom and female occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/ cream/suppository; or
      - Male condom and female contraceptive sponge with spermicide

   In addition, Patients entering the trial that are on hormonal contraceptives must have been on this method for at least 3 consecutive months (90 days) prior to Baseline and agree to continue the same hormonal contraceptive for the duration of the trial. Patients who have 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 Baseline and have undergone an Essure confirmation test to ensure its efficacy. A sterile/vasectomized sexual partner alone is not considered an adequate form of birth control. In this case an additional contraceptive method is required.
8. Male Patients must be clean-shaven or have a cut beard/facial hair that does not interfere with study assessment, and they should also agree to remain so during the study visits.
9. Use of multivitamins at recommended daily doses is acceptable and the patient agrees not to change dose during study participation.

10. Premenarchal females and FOCBP must have a negative urine pregnancy test at the screening and baseline visits.

11.3 Exclusion Criteria

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

1. More than two acne nodules or cysts (defined as an inflammatory lesion greater than or equal to 5 mm in diameter).
2. Acne conglobata, acne fulminans, secondary acne (chloracne, drug-induced acne, etc.)
3. History of blood dyscrasia (e.g., leukemia, haemophilia, sickle cell anemia, multiple myeloma, etc.)
4. Underlying disease that requires the use of interfering topical or systemic therapy.
5. Other dermatological conditions that require the use of interfering topical or systemic therapy or that might interfere with study assessments such as, but not limited to, atopic dermatitis, perioral dermatitis, or rosacea.
6. Beard, facial hair, or tattoo that may interfere with study assessments.
7. Use of tanning booths or tanning lamps within one week prior to Baseline and an unwillingness to refrain from use during the study.
8. Use of hormonal contraceptives, unless Patient is on a stable dose for at least three consecutive months prior to enrollment and agrees not to change or discontinue type of hormonal contraceptive use during study participation.
9. Use of hormonal contraceptives solely for the control of acne.
10. Use of Isotretinoin and/or Anti- androgens in the past 6 months.
11. Use of prohibited medications prior to the study and unwillingness to refrain from use during the study.
12. Does not meet one or more specified washout period prior to Baseline for TOPICAL treatments on the face as follows:

Table 1: prohibited medication and washout periods

Topical Medication/Therapy	Washout Period
Hyaluronic Acid and Retinol	1 day
Antimicrobial Soaps	1 week
Phototherapy devices for acne (e.g., ClearLight™), adhesive cleansing strips (e.g., Ponds, Biore) as well as, use of tanning booths or tanning lamps.	1 week
OTC topical products containing salicylic acid and BPO (e.g. Clearasil, Clean & Clear)	1 week
Astringents (e.g., Witch hazel, Noxzema), abrasives (e.g., Clarisonic brushes, facial scrub products), and preparations that contain spices or lime or lemon	1 week
Topical medicated cleansers with sulfur or triclosan	1 week
Potentially irritating OTC acne products: Alpha-hydroxy-Acid, and Glycolic Acid	1 week

Essential Oils (used specifically for acne, e.g., tree tea oil, oregano, lavender, etc.)	1 week
Azelaic Acid	2 weeks
Topical Corticosteroids in treatment area (inhaled and intranasal are allowed), topical vasoconstrictors and topical non-steroidal anti-inflammatory drugs, topical antibiotics (including antimicrobials like benzoyl peroxide containing products, [e.g., benzamycin], zinc and sulfur)	2 weeks
Other topical acne procedures (including photodynamic therapy or laser, microdermabrasion) as well cosmetic procedures (i.e., facials, peels, comedo extraction, facial threading, use of Nair on the face	2 weeks
Topical retinoids (e.g., tretinoin, Differin, Adapalene)	4 weeks

13. Does not meet one or more specified washout period prior to Baseline for SYSTEMIC medications as follows:

Systemic Medications	Washout Period
Corticosteroids (includes intramuscular)	4 weeks
[1]Antibiotics	4 weeks
Testosterone (All forms includes injections)	4 weeks
Ostarine (All forms, includes oral)	4 weeks
Lithium (e.g., Lithium Orotate, Lithium Carbonate)	4 weeks
Hormonal contraceptives used for less than three consecutive months prior to enrollment or used solely for acne control.	3 months[2]
Isotretinoin and Anti-androgens	6 months

14. Known sensitivities to the study drug ingredients. Allergy to benzoyl peroxide, tretinoin, parabens and glycerin or other ingredients listed in the Investigator Brochure.
15. Use of testosterone and Ostarine within four (4) weeks prior to Baseline and an unwillingness to refrain from use during the study.
16. Use of Lithium supplements or prescription (e.g., Lithium Orotate and Lithium Carbonate) within four (4) weeks prior to Baseline and an unwillingness to refrain from use during the study.
17. Clinically significant abnormal findings or conditions (other than acne), which might, in the opinion of the Investigator, interfere with study evaluations or pose a risk to Patient safety during the study.
18. Female Patients who are pregnant and/or nursing or planning to become pregnant during the course of the trial. Patients who test positive for pregnancy after start of test treatment will be discontinued from test treatment but will be followed for safety purposes.
19. Participation in another investigational drug or device research study within 30 days of enrollment or five half-lives of the drug, whichever is longer.

[1] Upon randomization one course of penicillin and its derivatives (e.g. amoxicillin) and cephalosporins are allowed for a duration of 10 days or less, however not during the two (2) week period just prior to week 12 visit.

[2] If a Patient is on hormonal contraceptives for less than 3 months, she should continue using the same hormonal contraceptives and she can be considered to enter the study after completing 3 months of use.

20. Previous enrollment in this study or current enrollment in this study at another participating site.
21. Current or history of facial skin cancer.
22. Patient is an employee or family member of the study Investigator or other study staff having direct involvement in the study.
23. Patients living (e.g., siblings, spouses, relatives) in the same household cannot be enrolled in the study at the same time.
24. Female Patients with a history of polycystic ovarian disease
25. Topical and oral treatment for acne other than the face (e.g., chest or back) is not allowed during the study.

11.4 Prohibited, Previous and Concomitant Medications/ Therapies

Any previous acne therapies must be stopped for the appropriate washout period as specified below and as noted in the exclusion criteria, and are excluded as concomitant medications / therapies throughout the trial unless otherwise specified below:

- Topical Hyaluronic Acid and Retinol within 1 day of Baseline.
- Antimicrobial Soaps within 1 week of Baseline.
- Phototherapy devices for acne (e.g., ClearLight™), adhesive cleansing strips (e.g., Ponds, Biore) as well as use of Nair on the face, use of tanning booths or tanning lamps), within 1 week of Baseline.
- OTC topical products containing salicylic acid and BPO (e.g., Clearasil, Clean & Clear) within 1 week of Baseline.
- Astringents (e.g., witch hazel, Noxzema), abrasives (e.g., Clarisonic brushes, facial scrub products), and preparations that contain spices or lime or lemon within 1 week of Baseline.
- Use of medicated cleansers on the face (e.g., sulfur or triclosan) within 1 week of Baseline.
- Topical alpha-hydroxy-Acid and glycolic acid within 1 week of Baseline.
- Topical essential oils (used specifically for acne, e.g., tree tea oil, oregano, lavender, etc.) within 1 week of Baseline.
- Topical azelaic Acid within 2 weeks of Baseline.
- Topical corticosteroids (inhaled and intranasal are allowed), topical vasoconstrictors and topical non-steroidal anti-inflammatory drugs; topical antibiotics (including antibacterial like benzoyl peroxide containing products, [e.g., benzamycin], zinc and sulfur) – within 2 weeks of Baseline.
- Other topical acne procedures (including photodynamic therapy or laser, microdermabrasion) as well as cosmetic procedures (i.e., facials, peels, comedo extraction, facial threading, within 2 weeks of Baseline
- Topical retinoids (e.g., Differin, Adapalene)– 4 weeks prior to Baseline.
- Systemic corticosteroids (includes intramuscular) within 4 weeks of Baseline.
- Systemic antibiotics 4 weeks prior to baseline. Upon randomization one course of penicillin and its derivatives (e.g. amoxicillin) and cephalosporins are allowed for a duration of 10 days or less, however not during the two (2) week period just prior to week 12 visit.
- Systemic testosterone (all forms includes injections) within 4 weeks of Baseline
- Systemic Ostarine (all forms, includes oral) within 4 weeks of Baseline.
- Systemic Lithium (e.g., Lithium Orotate, Lithium Carbonate) within 4 weeks of

Baseline.
- Systemic hormonal contraceptives used for less than three consecutive months prior to Baseline or used solely for acne control within 3 months of Baseline.
- Systemic Isotretinoin and Anti-androgens) within 6 months of Baseline.

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

No medicated cleansers or moisturizers are allowed on the face. Only the sponsor-provided cleanser and moisturizer/sunscreen or a study-approved cleanser or moisturizer/sunscreen will be allowed to be used on the face during the study. Study product shall be applied to clean skin and no cleanser should be applied to the face within two (2) hours after study product application. Approved moisturizer/sunscreen may be applied after at least 30 minutes following 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 Baseline and must agree to not change make-up brand/type or frequency of use throughout the study. Patients should not apply the moisturizer or sunscreen or combination of them or wear make-up during study visits as it may interfere with the evaluator's assessments.

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

Therapies (medication and non-medication therapies) not restricted by the protocol may be used during the study for the treatment or prevention of disease or to maintain good health. Vitamins and mineral supplements are permitted at dosages considered by the Investigator as reasonable for maintaining good health. Non-prohibited chronic therapies being used at Baseline 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 Medications form at each visit. The reason for any change in concomitant medications/therapies should be reported as, or in conjunction with, an AE except as noted below:

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

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.

11.5 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 (suggest before going to bed) to avoid spreading it on other areas of the face (e.g., eyes, ears, neck, etc.) and bedding.
5. The study product should be spread smoothly and 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. 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. Make-up should not be changed during the study.
8. Patients should not apply moisturizers, make-up, creams, lotions, powders or any topical product they do not routinely use on their face.
9. Patients should not cover the treated area with a bandage (occlusive dressing) or other types of dressing after applying the study product.
10. Patients should limit sun exposure, including sunlamps (non-prescription UV light sources); avoid tanning beds/booths/parlors and sauna while on the study.
11. Patients should use moisturizer with SPF supplied by the Sponsor or from study-approved products and protective apparel (e.g. wide- brimmed hat) when outdoors. Patients should wait at least 30 minutes after study product is applied on the face before applying an approved sunscreen. Weather extremes, such as wind or cold, may be irritating to Patient.
12. UVA/UVB treatments to the face are also prohibited.
13. 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 Investigator or Sub-Investigator (Sub-I).
14. Patients should consult the Investigator with any questions regarding concomitant medications/therapies.
15. Abrasive cleansers or washes, alcoholic toners, astringents are prohibited throughout the study.
16. "Waxing" as a depilatory method should be avoided on skin treated with study product.
17. Patients should be informed that local skin reactions [dryness, burning, stinging, pruritus (itching), scaling/peeling] may occur.

12 STUDY PROCEDURES

12.1 Study Patient Identification

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

12.2 Screen Failure and Discontinuation Criteria

A screen failure is a Patient who is not randomized/enrolled in the study due to ineligibility, after signing an ICF, and would not have received study product. The ICF 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 or designee's approval.

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

- Investigator opinion that it is not in the Patient's best interest to continue.
- Patient Request/Withdraw Consent – Whenever the Patient decides it is in his/her best interest to withdraw.
- Lack of Efficacy/Worsening of Condition.
- AE – 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 efforts 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.

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

In the case of Patients who discontinue due to an AE, 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.

12.3 Patient Screening and Enrollment

The study personnel will review the IRB-approved ICF, and assent as applicable, with each Patient and give the Patient an opportunity to have all questions answered before proceeding. The ICF must be signed by each Patient before the Patient is enrolled into

the study. A copy of the signed ICF 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 screen-failed, then re-consented as a "new" Patient before any further study procedures can begin.

12.4 Assignment of Randomization

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

The first supplied pump in each kit is marked A (e.g. number of pump within a kit is 1234A). At Week 4 the Patient will return the pump and will be dispensed with the next pump which is marked with same number followed by B. At Week 8, the Patient will return the pump and will be dispensed with a pump marked with same number followed by C. Pump marked as D may be dispensed to Patients who lost/damage/ran-out of study product.

12.5 Demographics/Medical History

A demographic profile and complete medical history will be recorded prior to randomizing and starting study product. Medical histories having resolved 2 or more years before Baseline need not be collected unless considered relevant by the Investigator.

12.6 Concomitant Medications

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

12.7 Physical Examination

The Investigator, Sub-I or appropriately delegated and qualified designee will perform a brief physical examination, prior to the Patient starting study product as well as at the End of Study (Visit 6) Week 12/Early Termination Visit. The exam will include heart, lung, abdomen evaluation as well as recording height and weight.

12.8 Vital Signs

Vital signs are performed at the time of the physical examination and include sitting blood pressure, temperature, heart rate and respiratory rate.

12.9 Urine Pregnancy Test

All Females of child-bearing potential and premenarchal (excluding women who are surgically sterile or post-menopausal [defined as amenorrhea >12 consecutive months; or women on hormone replacement therapy (HRT) with documented plasma follicle-stimulating hormone (FSH) level >35mLU/mL] for at least 1 year), 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 may 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 be conducted at every visit, starting from Screening and until Week 12/ End of Study or Early Termination Visit. If more than 2 weeks washout period is needed between Screening to Baseline visit, urine pregnancy test should be repeated at the Baseline visit. For this study, the following are considered acceptable methods of birth control: Intrauterine device (IUD); Hormonal, for at least 3 months. (Pills, injections, implants, transdermal patch, vaginal ring); Abstinence. Double-barrier methods (male and female) of the following contraception: Combined use of male and female condom; Male condom and female occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/ cream/suppository; Male condom and female contraceptive sponge with spermicide.

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/vasectomized sexual partner alone is not considered an adequate form of birth control. In this case an additional contraceptive method is required.

12.10 Study Flow Chart

Procedures	Visit 1[1]	Visit 2[2]	Visit 3[2]	Visit 4[2]	Visit 5[2]	Visit 6[3] (EOS[4]/ ET[5])
Name of Visit	Screening	Baseline Day 1	Week 2 Day 15	Week 4 Day 29	Week 8 Day 57	Week 12 Day 85
Visit Window	Day -35 to Day 0		±3 days	±3 days	±3 days	±4 days
Informed Consent/Assent	X					
Demographics	X					
Medical History/ Previous Therapies	X	X				
Brief Physical Examination & Vital signs		X				X
Inclusion/Exclusion Criteria	X	X				
Urine Pregnancy Test[6]	X	X[7]	X	X	X	X
Complete PRE-FACE and PGI-S[8,]	X	X	X	X	X	X
Complete PGI-C, PGI-TS and PGI-SE[9]			X	X	X	X
Complete Acne-QoL questionnaire[10]		X				X
IGA	X	X	X	X	X	X
Lesion Counts	X	X	X	X	X	X
Assessment of Eligibility		X				
Randomization		X				
Cutaneous Safety Assessment and Local Tolerability Assessments		X	X	X	X	X
Administer/ Review Patient Instructions		X	X	X	X	
Weigh Study Product		X		X	X	X
Dispense Study Product		X[11]		X	X	
Dispense Cleanser & Moisturizer		X[12]				
Diary Card dispensed		X		X	X	
Study Product collected				X	X	X
Diary Card collected				X	X	X
Patient Compliance Reviewed (Diary)			X	X	X	X
Prior and Concomitant Therapy and Medication Reviewed	X	X	X	X	X	X
Assessment of Adverse Events	X[13]	X	X	X	X	X
Photography (select site(s))		X	X	X	X	X

[1] If no washout is needed, Visits 1 and 2 may occur on the same day. If a washout is needed, visit 2 must occur within 35 days of Visit 1.
[2] All visit dates are in reference to Baseline, e.g., Visit 5 occurs 8 weeks ± 3 days after Baseline Visit.
[3] Week 12/ End of Study procedures should be completed for Patients who terminate early.
[4] EOS – End of Study
[5] ET – Early Termination
[6] All females of child-bearing potential and premenarchal must undergo Urine Pregnancy Tests, at every visit.
[7] Urine Pregnancy test should be repeated if more than 2 weeks washout is needed.
[8] Questionnaires are to be completed by all patients prior to any treatment related assessments. In case Screening Visit and Baseline occur at the same day, the PRO questionnaires should be completed prior to screening procedures.
[9] Questionnaires are to be completed by all patients prior to any treatment related assessments.
[10] Questionnaires are to be completed by all patients prior to any treatment related assessments. In case Screening Visit and Baseline occur at the same day, the QoL questionnaires should be completed prior to screening procedures.
[11] Dispense one pump of study product at the Baseline Visit and dispense additional pump at Visit 4 and 5.
[12] The Patients will use only products which were supplied by the Sponsor or approved by the Investigator.
[13] Adverse events after ICF is signed will be collected.

12.11 Screening Visit (Visit 1)

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

- Obtain a signed and dated, written ICF for all Patients prior to any study related procedures.
- Confirm the Patient meets the inclusion/exclusion criteria as outlined in sections 11.211.2 and 11.3
- Record any AEs.
- Perform a Urine Pregnancy Test for all females of child-bearing potential and premenarchal (see section 12.9); 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 the Concomitant Medications form as outlined in section 11.4.
- Ask the Patient to complete PRE-FACE questionnaires (see APPENDIX 2: PRO – PRE-FACE - Signs/Symptoms and APPENDIX 3: PRO – PRE-FACE - Impacts). Patient will also complete the PGI-S questionnaire (see APPENDIX 4: PRO – PGI-S). PRE-FACE and PGI-S questionnaires are to be completed prior to Investigator's assessment of signs of acne as described in section 12.20. In case Screening Visit and Baseline are on the same day, the PRO questionnaires should be completed prior to screening procedures.
- Ask the Patient to complete the QoL Questionnaire (see APPENDIX 9: ACNE-SPECIFIC Qol QUESTIONNAIRE) only if the Screening and Baseline visits are expected to occur on the same day (no washout is required), in which case the QOL should be completed prior to Investigator's assessment of signs of acne as described in section 12.18 other screening procedures.
- Perform IGA to determine eligibility (See section 12.18)
- Perform facial inflammatory and non-inflammatory lesion counts to determine eligibility (Section 12.19).
- Determine if Patient requires washout and schedule Baseline Visit.

12.12 Baseline Visit (Visit 2, Day 1)

The following procedures will be conducted at this visit:

- Confirm the Patient meets the inclusion/exclusion criteria.
- Assess eligibility.
- Update since Screening Visit the medical history for the Patient.
- Perform brief physical examination and vital signs measurement as described in section 12.7and 12.812.8.
- Perform a Urine Pregnancy Test for all females of child-bearing potential and premenarchal (see section 12.912.9); the results must be negative for the Patient to be enrolled.
- Update since Screening the Patient's concomitant medications and/or therapies on Concomitant Medications form as outlined in section 11.4.
- Ask the Patient to complete PRE-FACE questionnaires (see APPENDIX 2: PRO – PRE-FACE - Signs/Symptoms and APPENDIX 3: PRO – PRE-FACE - Impacts). Patient

will also complete the PGI-S questionnaire (see APPENDIX 4: PRO – PGI-S). PRE-FACE and PGI-S questionnaires are to be completed prior to Investigator's assessment of signs of acne as described in section 12.20. In case Screening Visit and Baseline are at the same day, the PRO questionnaires should be completed prior to screening procedures.

- Ask the Patient to complete Acne-QoL questionnaire (see APPENDIX 9: ACNE-SPECIFIC Qol QUESTIONNAIRE).
- Perform the efficacy evaluations including the Investigator's Global Assessment, inflammatory and non-inflammatory lesion counts described in sections 12.18 & 12.19. Every effort shall be made to have the same Investigator perform the Baseline and Visit 6/Week 12/ End of Study or Early Termination evaluations for the same Patient.
- Perform Cutaneous Reaction Assessment and Local Tolerability Assessment as described in section 14.1 & 14.2.
- Take standardized photography of the face (at selected sites, see separate photographic manual for instructions) as described in section 13.
- Instruct the Patient on the study product application as described in section 16.5.
- Dispense the Patient Instruction Sheet and Diary Card to the Patient (see APPENDIX 1: PATIENT INSTRUCTIONS SHEET).
- Record any AEs.
- Instruct the Patient that throughout the study overexposure of the face to sunlight should be avoided. Instruct the Patient to use the sponsor-provided or study-approved cleanser and moisturizer/sunscreen; any exposure to tanning beds must be avoided during the study.
- Perform randomization via IWRS after inclusion/exclusion criteria are confirmed as met.
- Weigh and dispense study drug in a cool pack bag if needed.
- Instruct the Patient on the study product application as described in APPENDIX 1: PATIENT INSTRUCTIONS SHEET. Pump usage will be demonstrated by the site personnel at the clinic, using a demonstration (dummy) pump, to help assure the Patient understands the procedure.
- Dispensing Cleanser and Moisturizer with Sunscreen
- Remind Patient to not wear make-up to all subsequent visits.
- Schedule the next study visit.

12.13 On-treatment (Visit 3) – Week 2, Day 15 (± 3 days)

The following procedures will be conducted at this visit:

- Ask the Patient to complete the following questionnaires: PRE-FACE (see APPENDIX 2: PRO – PRE-FACE - Signs/Symptoms and APPENDIX 3: PRO – PRE-FACE - Impacts), PGI-S (see APPENDIX 4: PRO – PGI-S), PGI-C (see APPENDIX 5: PRO – PGI-C), PGI-TS (see APPENDIX 6: PRO – PGI-TS) and PGI-SE (see APPENDIX 7: PRO – PGI-SE). All of the questionnaires should be completed prior to Investigator's assessment of signs of acne as described in section 12.20.
- Observe and query the Patient in a non-directive fashion about any AEs since the previous study visit.
- Query the Patient about any changes in concomitant therapies and medication since the previous study visit.

- Perform a Urine Pregnancy Test for all females of child-bearing potential and premenarchal (see section 12.9).
- Perform the efficacy evaluations including the Investigator's Global Assessment, inflammatory and non-inflammatory lesion counts described in sections 12.18 - 12.19.
- Perform Cutaneous Reaction Assessment and Local Tolerability Assessment as described in section 14.1 & 14.2.
- Take standardized photography of face (at selected sites, see separate photographic manual for instructions) as described in section 13.
- Review the Patient's compliance with the study requirements (review Patient diary). The Patient Diary Card will Not be collected at this visit.
- Record number of missed doses on the appropriate eCRF page.
- Review the study product application instructions with the Patient.
- Schedule/confirm the next study visit.

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

The following procedures will be conducted at these visits:

- Ask the Patient to complete the following questionnaires: PRE-FACE (see APPENDIX 2: PRO – PRE-FACE - Signs/Symptoms and APPENDIX 3: PRO – PRE-FACE - Impacts), PGI-S (see APPENDIX 4: PRO – PGI-S), PGI-C (see APPENDIX 5: PRO – PGI-C), PGI-TS (see APPENDIX 6: PRO – PGI-TS) and PGI-SE (see APPENDIX 7: PRO – PGI-SE). All the questionnaires should be completed prior to Investigator's assessment of acne as described in section 12.20.
- Observe and query the Patient in a non-directive fashion about any AEs since the previous study visit.
- Query the Patient about any changes in concomitant therapies and medication since the previous study visit.
- Perform a Urine Pregnancy Test for all females of child-bearing potential and premenarchal (see section 12.9).
- Perform efficacy evaluations: IGA, inflammatory and non-inflammatory lesion counts described in sections 12.18 & 12.19.
- Perform Cutaneous Reaction Assessment and Local Tolerability Assessment as described in section 14.1 - 14.2.
- Take standardized photography of face (at selected sites, see separate photographic manual for instructions) as described in section 13.
- Review the Patient's compliance with the study requirements; collect and review the Patient Diary Card.
- Dispense a Diary Card to the Patient
- Record number of missed doses on the appropriate eCRF page.
- Review the study product application instructions with the Patient.
- Collect and weigh returned study product pump.
- Weigh and dispense the next pump of study product.
- Schedule/confirm the next study visit.

12.15 End of Study (Visit 6) – Week 12, Day 85 (± 4 days) or Early Termination

The following procedures will be conducted at this visit:

- Ask the Patient to complete the following questionnaires: PRE-FACE (see APPENDIX 2: PRO – PRE-FACE - Signs/Symptoms and APPENDIX 3: PRO – PRE-FACE - Impacts), PGI-S (see APPENDIX 4: PRO – PGI-S), PGI-C (see APPENDIX 5: PRO – PGI-C), PGI-TS (see APPENDIX 6: PRO – PGI-TS) and PGI-SE (see APPENDIX 7: PRO – PGI-SE). All the questionnaires should be completed prior to Investigator's assessment of signs of acne, as described in section 12.18.
- Ask the Patient to complete Acne-QoL questionnaire (see APPENDIX 9: ACNE-SPECIFIC Qol QUESTIONNAIRE)
- Observe and query the Patient in a non-directive fashion about any AEs since the previous study visit.
- Query the Patient about any changes in concomitant therapies and medication since the previous study visit.
- Perform physical examination as described in section 12.7.
- Assess vital signs as described in section 12.8.
- Perform efficacy evaluations: IGA, inflammatory and non-inflammatory lesion counts described in sections 12.18 - 12.19. The evaluator who performed the Baseline evaluations should perform all subsequent evaluations for a Patient. When this is not possible, it is recommended that another delegated evaluator with overlapping experience with the Patient may perform the evaluations.
- Perform Cutaneous Reaction Assessment and Local Tolerability Assessment as described in section 14.1- 14.2.
- Take standardized photography of face (at selected sites, see separate photographic manual for instructions) as described in section 13.
- Review the Patient's compliance with the study requirements; collect and review the Patient Diary Card.
- Record number of missed doses and report the last date the Patient applied the study product.
- Perform a Urine Pregnancy Test for all females of child-bearing potential and premenarchal (see section 12.9).
- Collect and weigh the study product.

12.16 Unscheduled Visit

An unscheduled visit may occur at any time during the study at the Patient's request or as deemed necessary by the Investigator for any reason. For example: dispensing new pump/kit or in order to report any discomfort following the usage of the study drug. At a minimum, concomitant medications, AEs and the date and reason for the unscheduled visit will be recorded. Other procedures to be performed during an unscheduled visit, will be according to the discretion of the Investigator.

12.17 Clinical Outcome Assessments

Consistent with recommendations from the FDA "Guidance for Industry, Acne Vulgaris: Establishing Effectiveness of Drugs Intended for Treatment Guidance for

Industry." (May2018), the determination of efficacy will be based on evaluations of the IGA and inflammatory and non-inflammatory absolute lesion counts, on the face at Week 12/ End of Study or Early Termination. Additionally, Patient reports of symptoms and disease impacts will be collected as secondary efficacy assessments. The Cutaneous Safety Assessment or Erythema and Scaling, evaluated by the Investigators, provides a reliable assessment of local effects, while the local tolerance measures of itching, burning and stinging sensation are designed to provide Patient-reported outcomes that will support recommendations for use and expected reactions. The additional safety measures, including AEs reporting, Urine Pregnancy Tests for females, and Concomitant Medications are standard, accepted measures in clinical research.

Evaluators must be a physician or have appropriate documented experience and training. Every effort will be made to ensure appropriate training is provided to the Investigators for consistent diagnosis and evaluation of Acne Vulgaris.

For consistency of evaluations, the same designated evaluator who performs the Baseline assessments shall perform the assessments at Week 12/ End of Study or Early Termination. When this becomes impossible, another delegated evaluator may perform the assessments.

12.18 Investigator Global Assessment (IGA)

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

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

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

Table 2: Investigator Global Assessment (IGA) Scale

Grade	Description
0 – Clear	Normal, clear skin with no evidence of acne vulgaris
1 – Almost Clear	Rare non-inflammatory lesions present, with rare non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red)
2 – Mild	Some non-inflammatory lesions are present, with few inflammatory lesions (papules/pustules only; no nodulo-cystic lesions)
3 – Moderate	Multiple Non-inflammatory lesions and, inflammatory lesions are evident: several to many comedones and papules/pustules, and there may or may not be one small nodulo-cystic lesion
4 – Severe	Inflammatory lesions are more apparent, many comedones and papules/pustules, there may or may not be a few nodulo-cystic lesions

12.19 Inflammatory and Non-Inflammatory Lesion Counts

Lesions count will be performed at visits: Screening, Baseline, Weeks 2, 4, 8 and 12/ End of Study or Early Termination.

At Screening/Baseline, Patients must have at least 20 and no more than 100 inflammatory lesions (papules, pustules) and at least 30 and no more than 150 non-inflammatory (open and closed comedones) lesions on the face, including the nose.

Patients must have two (2) or fewer cysts or nodules.

12.19.1 Inflammatory Lesion Definitions:

Papule – A small, solid elevation less than 5 mm in diameter. Most of the lesion is above the surface of the skin.

Pustule – A small circumscribed elevation less than 5 mm in diameter that contains yellow-white exudate.

Nodule - An inflammatory lesion greater than or equal to 5 mm in diameter.

Cyst – An inflammatory lesion that contains yellow-white exudate that is greater than or equal to 5mm in diameter.

12.19.2 Non-Inflammatory Lesion Definitions:

Open Comedone - (Black head) A lesion in which the follicle opening is widely dilated with the contents protruding out onto the surface of the skin, with compacted melanin cells giving the plug a black appearance.

Closed Comedone - (White head) A lesion in which the follicle opening is closed, but the sebaceous gland is enlarged by the pressure of the sebum buildup, which in turn cause the skin around the follicle to thin and become elevated with a white appearance.

12.20 Patient-Reported Outcomes (PRO)

There are five PRO questionnaires to be administered in the study and each is summarized below. Each will be administered to all Patients, from the age of 9 years old, during the designated study visits with instructions from the Study Staff that they be completed:

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

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

The Patient-Reported Evaluation of Facial Acne (PRE-FACE): The PRE-FACE, which can be completed in less than 2 minutes, is a seven item PRO questionnaire that assesses acne vulgaris-related signs, symptoms and impacts. The four-item acne sign and symptom domain (ASD) assesses the severity of acne vulgaris-related pimples, whiteheads, blackheads, and redness, at their worst, in the 24 hours prior to

administration on an 11-point numeric rating scale (NRS) ranging from 0 ("no [Concept] at all") to 10 ("[Concept] as bad as you can imagine"). The three-item acne impact domain (AID) assesses acne vulgaris-related embarrassment, self-consciousness, and sadness in the seven days prior to administration on an 11-point NRS ranging from 0 ("not [Concept] at all) to 10 ("extremely [Concept]"). The PRE-FACE will be administered at study visits 2-6, including Screening, Baseline, and at Weeks 2, 4, 8, and 12/ End of Study or Early Termination.

Patient Global Impression of symptom Severity (PGI-S): The PGI-S (presented in appendix 4) is a single-item global self-assessment of the current severity of Patients' acne vulgaris symptoms rated on a five-point verbal response scale ranging from 0 (None: No pimples, clear skin) to 4 (Very severe: Large amount of pimples, no clear skin), where higher scores indicate greater severity of acne vulgaris symptoms. The PGI-S will be administered at study visits 2-6, including Screening, Baseline, and at Weeks 2, 4, 8, and 12/ End of Study or Early Termination. While PGI-S results can inform treatment efficacy, a main use for the tool in this study is to support supplementary anchor-based analysis. Anchor-based analysis use an external criterion (in this case, the PGI-S) to categorize Patients into groups each reflecting an *a priori* determined change grouping (e.g., no change, large positive change, or large negative change) to inform conclusions about the meaning of observed within person change on other measures.

Patient Global Impression of Change (PGI-C): The PGI-C is a single item questionnaire that asks respondents to describe the change they have noticed in their acne symptoms since the start of the study on a 7-point VRS ranging from "Very much improved" to "Very much worse". Patients are encouraged to look in a mirror to help with their response and the questionnaire can be completed in less than 30 seconds. The PGI-C is administered via pen-and-paper at the site visits at Week 2, Week 4, Week 8 and Week 12/ End of Study or Early Termination. Similar to the PGI-S described above, the PGI-C data collected in this study to support supplementary anchor-based analysis.

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

Patient Global Impression of treatment Side Effects (PGI-SE): The PGI-SE is a single item questionnaire that asks respondents to describe how bothered they are "right now" with the acne treatment administered as part of the study on a 5-point VRS ranging from "I am not bothered" to "I am very bothered". The questionnaire can be completed in less than 30 seconds and is administered via pen-and-paper at the site visits at Week 2, Week 4, Week 8 and Week 12/ End of Study or Early

Termination. Though data generated from the PGI-SE can be used for other purposes, its primary purpose is to support anchor-based analyses that will inform how researchers may interpret the meaning of change in the primary and secondary assessments.

12.21 Acne-Specific Quality of Life Questionnaire (Acne-QoL)

The Acne-specific Quality of Life questionnaire (Acne-QoL) is a health-related quality of life instrument developed by MERCK & CO., INC. for use in clinical trials to assess the impact of therapy on quality of life among patients with facial acne.

The Acne-QoL questionnaire consists of 19 questions. Each will be administered to all Patients, aged 9 and older, during the designated study visits. Study Staff will instruct the patients to complete the questionnaire:

- 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.

The Acne-QoL is self-administrated (i.e. the patient is able to complete the questionnaire without assistance) and should take approximately 10 minutes or less to complete. The questionnaire is administered via pen-and-paper (using a black ballpoint pen) during the site visits at Baseline visit and Week 12/ End of Study or Early Termination.

In the event the Patient skips any questionnaire item(s); the Study Staff will ask the Patient to complete all of the questions. The Acne-QoL questionnaire data will be entered into the eCRF, and a copy will be placed with the remaining Patient's source documents at the site according to the ICH-GCP guideline.

The questions in the Acne-QoL questionnaire are organized in four domains which address the impact of facial acne on health-related quality of life (HRQoL): Self Perception, Role-Social, Role-Emotional and Acne Symptoms. The items included within each domain are those which facial acne sufferers consider important, which can distinguish between acne severity groups and were responsive to changes in acne severity over time following treatment in an uncontrolled study. For all domain scores, the responses to items comprising the domain are summed, and no weighting scheme is used.

Self-Perception: The Self Perceptions domain of the Acne-QoL is comprised of 5 questions. In each question, the respondent is asked for the extent to which their facial acne has affected a particular area of their self-perception over the past week. Items such as feeling self-conscious, feeling unattractive, dissatisfaction with self-appearance are included in the domain. The response options are on a 0-6 scale (extremely, very much, quite a bit, a good bit, somewhat, a little bit, not at all). The range of possible scores is 0 to 30.

Role-social: The Role-social domain of the Acne-QoL is comprised of 4 questions which attempt to assess the impact of facial acne on a respondent's intersocial relationships. For example, questions related to going out in public, meeting new

people, and socializing are included. The response options are on 0-6 scale (extremely, very much, quite a bit, a good bit, somewhat, a little bit, not at all). The range of possible scores is 0 to 24.

Role-emotional: The Role-emotional domain is focused on the emotional effect or impact of facial acne. The domain includes questions about the respondent's annoyance at having to spend time cleaning and treating their face, their worry or concern that medications were working fast enough, the bothersomeness of needing to always have cover-up available, etc. The response options are on a 0-6 scale exactly as the same as that for the Self-Perceptions and Role-Social domains, ranging from "extremely" to "not at all". The range of possible scores is 0-30.

Acne Symptoms: The final domain of the Acne-QoL is aimed at assessing the physical symptoms experienced by facial acne sufferers, which acne patients rated as frequent and important. The response options for this domain are on a 0-6 scale (extensive, a whole lot, a lot, a moderate amount, some, very few, none) and differs from the above domains for several of the questions. Five questions comprise the Acne Symptoms domain covering symptoms such as the number of bumps on the face, the extent of scabbing from the acne, and the level of worry associated with scarring from the acne. Possible domain scores range from 0 to 30.

Within each domain, a minimum number of responses is required in order to score the domain. Overall domain scores will be calculated so long as at least 3 items are answered for each domain. If the minimum number of items have been answered but 1-2 questions have missing responses the mean value of the answered questions will be used to replace the missing values. If fewer than the minimum number of items have been answered, the domain score will not be calculated. Further details on calculation of the domain scores will be detailed in the Statistical Analysis Plan (SAP).

13 PHOTOGRAPHY

Standardized photography of facial acne at Baseline, and at the Weeks 2, 4, 8 and 12/End of Treatment Visit will be performed at select sites. These photographs will be optional for Patients at the selected sites and will not be used for efficacy assessment purposes. Participating Investigators shall refer to separate photographic manual for instructions.

14 SAFETY EVALUATIONS

Safety will be assessed by monitoring incidence of Cutaneous Reactions Assessments, Local Tolerability Assessments, and AEs reporting; at Baseline, at all treatment visits and end-of-treatment visit.

14.1 Cutaneous Reactions Assessments

The evaluator will assess local application site cutaneous reactions by rating the erythema, dryness, pigmentation and scaling at each study visits except Screening visit. The evaluator will determine the score for each of these variables by direct evaluation. The following definitions of terms will be applied to these evaluations.

Cutaneous Signs Evaluation will include assessments of erythema, scaling, dryness and pigmentation based on the following 4-point scale shown in table 3 below.

Table 3: Assessments of erythema, scaling, dryness and pigmentation

	Score	Rating	Definition
Erythema	0	None	No erythema
	1	Mild	Slight pinkness present
	2	Moderate	Definite redness, easily recognized
	3	Severe	Intense redness
Scaling	0	None	No scaling
	1	Mild	Barely perceptible shedding, noticeable only on light scratching or rubbing
	2	Moderate	Obvious but not profuse shedding
	3	Severe	Heavy scale production
Pigmentation	0	None	No disturbance of pigmentation
	1	Mild	Barely perceptible pigment change
	2	Moderate	Markedly darker or lighter
	3	Severe	Complete de-pigmentation or severe hyperpigmentation
Dryness	0	None	No dryness
	1	Mild	Slight but define roughness
	2	Moderate	Moderate roughness
	3	Severe	Marked roughness

Application site reactions (erythema, scaling, dryness and pigmentation) are not to be recorded as AEs 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.

14.2 Local Tolerability Assessments

The evaluator will assess local application site tolerability by rating the itching, burning and stinging at each study visits except 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 following definitions of terms will be applied to these evaluations:

Local Tolerability Assessment: The evaluations of itching, burning and stinging will be made by the Investigator at the time of the visit.

Table 4: Assessments of Itching, Burning and Stinging

	Score	Rating	Definition
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	0	None	No burning
	1	Mild	Slight burning sensation; not really bothersome
	2	Moderate	Definite warm, burning sensation that is somewhat bothersome
	3	Severe	Hot burning sensation that causes definite

			discomfort and may interrupt daily activities or sleep
Stinging	0	None	No stinging
	1	Mild	Slight stinging sensation; not really bothersome
	2	Moderate	Definite stinging sensation that is somewhat bothersome
	3	Severe	Severe stinging sensation that causes definite discomfort and may interrupt daily activities or sleep

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

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

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

15 ADVERSE EVENTS

When an AE occurs requiring an early termination from the study for a Patient, the Investigator or medical professional 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.

15.1 Definitions

An 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 AE 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 SAE is an AE 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 AEs 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 AEs (IRAE) is any SAE or any AE that necessitates discontinuation of study product, including pregnancy.

Unexpected AE 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

Intensity of AEs is 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.

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:

- Does not follow a reasonable temporal sequence from the time of study drug administration; and
- Was likely produced by other factors such as the subject's clinical state, therapeutic intervention, or concomitant therapy but for which relationship cannot be definitely ruled out.

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.

Action Taken with Study Treatment

The Investigator will describe the action taken with the study treatment in the appropriate section of the eCRF, as follows:

- Dose Increased
- Dose Not Changed
- Dose Reduced
- Drug Interrupted
- Drug Withdrawn
- Not Applicable
- Unknown

Action Taken to Treat Event

The Investigator will describe other action(s) taken in the appropriate section of the eCRF, as follows:

- None
- Concomitant Medication
- Procedure/Therapy
- Hospitalization/Prolonged Hospitalization
- Withdrawal from Study
- Other

15.2 Eliciting and Reporting of Adverse Events

The Investigator will periodically assess Patients for the occurrence of AEs. In order to avoid bias in eliciting AE, 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 AEs (as defined in Section 18.6), 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 AE, 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 AEs must be reported to the CRO within 24 hours of when the Investigator first learns of the occurrence of the event.

AEs will be documented in the source document and recorded in a timely manner on eCRFs. AEs 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.

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

The following data should be documented for each AE:

- Description of the symptom event

- Classification of “serious” or “not serious”
- Severity
- Date of first occurrence and date of resolution (if applicable)
- Action(s) taken
- Causal relationship
- Outcome of event (Recovered/Resolved, Recovered/Resolved with Sequelae, Not Recovered/Not Resolved, Unknown, Fatal [with date and cause reported])

15.3 Expedited Reporting Responsibilities of the Study Center

For any SAE, 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 SAEs are described below. Adequate information must be collected with supporting documentation to complete a standard report for submission to Sol-Gel. The AE 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 study product-related AE(s) or SAE(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 AE. The Investigator should continue to report any significant follow-up information to the sponsor up to the point that the event has resolved. Any SAE 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 SAE, the Investigator (or the Study Coordinator) will promptly report any SAE 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.

15.4 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

15.5 SAE & AEs Requiring Discontinuation of Study Drug, including Pregnancies

Any SAE, should be collected following signing the ICF including any protocol required run-in period, 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 should be reported to the Sponsor or its designee immediately and within 1 working day.

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

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

15.6 Pregnancy

At the time, Investigator or site personnel becomes aware that a study Patient became pregnant following study participation, the 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) 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 no more than 30 days within completion of the pregnancy.

Upon delivery, miscarriage or abortion, the 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 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.

15.7 Post Study Adverse Events

15.7.1 Non-serious Adverse Events

AEs 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.

15.7.2 Serious Adverse Events

SAEs 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 SAEs, or any new SAEs 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 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 SAE 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 and captured in the eCRF.

16 STUDY PRODUCTS / CLINICAL SUPPLIES

16.1 Method of Treatment Assignment

Patients who satisfy all of the inclusion and none of the exclusion criteria will be randomized to one of two treatment arms. Randomization will be performed in the IWRS according to a computer-generated randomization schedule. The randomization schedule will be generated by the unblinded statistician and uploaded to the IWRS. The randomization schedule will be maintained securely within the IWRS. Patients will be randomized to Encapsulated Benzoyl Peroxide 3%/Encapsulated All-Trans-Retinoic Acids 0.1% Cream or Vehicle Cream, once daily on a 2:1 basis for twelve (12) weeks.

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

16.2 Formulations

Study Product name:	Encapsulated Benzoyl Peroxide (E-BPO) and Encapsulated Tretinoin (E-ATRA) Cream, 3%/0.1% (E-BPO/E-ATRA 3%/0.1%) Encapsulated
Sponsor name:	**S6G5T-3**
Active ingredients:	Benzoyl peroxide & all trans retinoic acid
Inactive ingredients:	See list below

Placebo Product:	Vehicle Cream (for study product)
Sponsor name:	**S6G5T-8**
Active ingredients:	None
Inactive ingredients:	See list below

The inactive ingredients include: Polyquarternium-7, Hydrochloric Acid, (S)-Lactic Acid, silicon Dioxide, Sodium Hydroxide, Cetrimonium Chloride, Squalane, Butylated Hydroxytoluene, Beeswax, Macrogol Stearate Type I, Cetyl Alcohol, Cyclomethicone 5, Mono– and di– Glycerides, Anhydrous Citric Acid, Edetate Disodium, Glycerin, Imidurea, Carbomer 980, Methylparaben (only in vehicle), Tartrazine (only in vehicle) & Purified Water.

16.3 Study Products Packaging and Labeling

The study product (Encapsulated Benzoyl Peroxide 3%/Encapsulated All-Trans-Retinoic Acids 0.1% Cream), S6G5T-3, and placebo for the study product (vehicle cream), S6G5T-8, will be packaged and labeled in 52 gr. pump. During the 12 weeks of treatment, a double-blind technique will be used. In order to maintain the blind, the study product and vehicle will be supplied in identically-appearing labeled pump cartons. Neither the Patient nor the investigational staff (Sponsor, Investigator, and evaluators) will know which treatment a Patient is receiving.

The study products will be shipped to sites under refrigerating conditions in the rage of 2-8°C (36-46°F) in blocks of three (3) products to keep ratio 2:1 between study product and vehicle. The study products will be labelled as follows:

- Protocol number
- Patient number
- Patient initials
- Dispenser initials
- Dispense date

- Contains: Study Product (Encapsulated Benzoyl Peroxide 3%/Encapsulated All-Trans-Retinoic Acid 0.1% Cream or its Vehicle Cream(
- Directions for use: Apply as directed, for topical use only
- Patient: store at room temperature at or below 25°C (77°F). Do not freeze.
- Keep container tightly closed
- Keep out of reach of children
- Sponsor information
- Investigational drug warning. "Caution: New Drug - Limited by Federal Law to Investigational Use

Each Study Product Kit Box label, will contain four (4) 52 gr. each, pumps that will carry a one-part tear-off label that must remain attached to the box. Both label parts will show an identical information label and have spaces to enter the Patient's initials, date dispensed, dispenser's initials and each label shows:

- Protocol number
- Patient number
- Patient initials
- Dispenser initials
- Dispense date
- Contains: 4 pumps, 52 gr. each, of Study Product (Encapsulated Benzoyl Peroxide 3%/Encapsulated All-Trans-Retinoic Acids 0.1% Cream or its Vehicle Cream)
- Directions for use: Apply as directed, for topical use only
- Pharmacist of site staff: Prior to dispensing: Store in a refrigerator 2°C to 8°C (36°F to 46°F). Excursions permitted down to 0°C (32°F) and up to 25°C (77°F). Do not freeze.
- Keep out of reach of children
- Investigational drug warning. "Caution: New Drug - Limited by Federal Law to Investigational Use only"
- Sponsor information

16.4 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 assigned by IWRS at Baseline. IP will be dispensed at Baseline, Week 4 and Week 8 from the assigned kit. IP will be returned at Week 4, Week 8 and Week 12/ End of Study or Early Termination. IP weight will be documented in eCRF prior to dispensing and after return of each pump per flow chart (section 12.10).

Each Patient will be instructed on the importance of returning his or her study product at every designated visit (excluding on Visit3/ Week 2). 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 refrigerated (2°C to 8°C, 36°F to 46°F) at the site, excursions permitted down to 0°C (32°F) and up to 25°C (77°F) until it is dispensed to the Patient. After dispensing to the Patient, the pump should be stored at room temperature at or below 25°C (77°F) with. Do not freeze the product.

16.5 Dosing Instructions

Topical application of study product will be made to the face once daily, at home and prior to bedtime, after cleansing, for a period of twelve (12) weeks. Study product will be applied as a thin coating that is gently rubbed into 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 cleanse their face with the given cleanser or Sponsor's approved cleanser using only the hands and pat dry with a soft clean towel. After the face has dried completely, the Patient shall apply one "pea sized" amount on each area of the face (chin, left cheek, right cheek, nose and forehead). The Patient will need to spread the investigational product smoothly and evenly. The investigational product will not be used on the mouth, eyes, inside the nose and lips or any body part other than the face. 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. No time interval between dosing and meals or any other activity is specified. During the trial, Investigators should remind Patients to avoid exposure to sunlight and sunlamps and to wear sunscreen when sun exposure cannot be avoided.

Patients will be instructed to continue using the same supplied/approved facial cleanser and not to change products during the study. At each visit, Patients are to be asked if they have changed their cleansing routine. The supplied/approved cleanser and moisturizer/sunscreen should be applied according to the directions on the bottle.

If necessary and in the case where a sunscreen with a higher SPF is required, Patient can be instructed to use another moisturizer with sunscreen that includes a higher SPF (Sun Protection Factor). Such case will require Sponsor approval.

Facial makeup (non-medicated) may be applied according to the Patient's normal daily routine (but not prior to 30 minutes after study product application); however, Patients should be instructed not to apply the moisturizer or sunscreen or combination of them or wear make-up during study visits as it may interfere with the evaluator's assessments. No other products should be used on the face.

Pump usage will be demonstrated by the site personnel on a sample pump at the clinic to help assure the Patient understands the procedure. The Patient will be provided a set of instructions (Appendix 1) that includes study reminders and restrictions as described in this protocol. Patients will be instructed to bring the study product to every visit, excluding to Visit3/ Week 2. 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 like clothing and bed sheets.

16.6 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, pump only- without the cover (~ 80g) before dispensing and upon return and weights will be recorded on the appropriate source document and eCRF.

16.7 Return and Destruction of Study Product Supplies

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

16.8 Additional Supplies Provided by Sponsor

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

17 STATISTICAL CONSIDERATIONS

17.1 General Statistical Methods

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

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

Sensitivity analyses for the primary efficacy endpoints will use 3 methods. For the lesion count endpoint, the first method will use a repeated measures ANCOVA, with treatment, analysis center, and visit (i.e., Week 2, Week 4 and Week 8) as independent factors and a covariate of baseline. In this analysis, data from all post-baseline visits will be included with no imputation for missing data.

The second sensitivity analyses will use the model based multiple imputation method to impute missing data for the absolute change at Week 12.

The third sensitivity analysis will involve a tipping point analysis.

Similar methods for the dichotomized IGA will involve a repeated measures logistic regression model and a model based multiple imputation and tipping point analysis.

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

17.1.1 Patient Disposition

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

17.1.2 Demographics and Baseline Characteristics

Patient demographic and baseline characteristics will be summarized by treatment group for the ITT, PP, and safety populations. For continuous variables (e.g. age) comparisons among the two treatment groups will be conducted using a two-way analysis of variance (ANOVA) with factors of treatment group and analysis center (see section 17.4.5 for definition of "analysis center"). Ethnicity and race will be analyzed with a Cochran-Mantel-Haenszel test stratified by analysis center. Past and current medical conditions, as well as history of disease will be presented in a data listing.

17.1.3 Protocol Deviations

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

17.1.4 Analysis Populations

Approximately 420 male and female Patients at least 9 years of age with moderate or severe acne vulgaris with 3 or 4 [moderate to severe] on the IGA scale will be enrolled and randomized in the study with a 2:1 randomization ratio, it is anticipated that:

- 280 Patients will be randomized to receive S6G5T-3, Encapsulated Benzoyl Peroxide 3%/Encapsulated All-Trans-Retinoic Acid 0.1% Cream
- 140 Patients will be randomized to receive S6G5T-8, Vehicle Cream

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

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

- Failed any of the inclusion/exclusion criteria;
- Have taken any interfering concomitant medications;
- Did not attend the Week 12 Visit;
- Missed more than 1 post baseline study visit prior to Week 12;

- Have not been compliant with the dosing regimen (i.e., Patients may not miss more than five consecutive days of dosing and must take 80-120% of expected doses. The number of expected doses will be determined for each Patient based on the length of their participation in the study);
- Out of visit window (± 4 days) at the 12-week Visit.

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

17.2 Study product Evaluations and Analyses

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

The IGA will be recorded for each Patient. The IGA will be dichotomized into "success" and "failure" at Weeks 2, 4, 8, and 12 with a Patient considered a success for those visits if the IGA is at least 2 grades less than baseline and are Clear or Almost Clear.

Patients will be asked to complete PRO questionnaires at appropriate time points.

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

17.3 Assessment of Efficacy

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

17.3.1 Primary Efficacy

There are two co-primary efficacy endpoints:

- Proportion of Patients with an assessment of clear or almost clear and with at least a 2-grade improvement in IGA from baseline at Week 12.
- Absolute change from Baseline in lesion count on the face at Week 12 (separately for inflammatory and non-inflammatory lesions).

17.3.2 Secondary Efficacy

The secondary efficacy endpoints will be the following:

- Percent change from Baseline, in non-inflammatory lesion count at Week 12.
- Percent change from Baseline, in inflammatory lesion count at Week 12.
- Proportion of patients in the E-BPO/E-ATRA cream arm compared to vehicle control achieving at least a 4-point reduction on Item 1 (pimples) of the PRE-FACE from Baseline to Week 12.

- Proportion of patients in the E-BPO/E-ATRA Cream arm compared to vehicle control achieving at least a 4-point reduction on Item 5 (embarrassment) of the PRE-FACE from Baseline to Week 12.
- Absolute change from Baseline, in non-inflammatory lesion count at Week 8.
- Absolute change from Baseline, in inflammatory lesion count at Week 8.
- Absolute change from Baseline, in non-inflammatory lesion count at Week 4.
- Absolute change from Baseline, in inflammatory lesion count at Week 4.

17.3.3 Supportive Efficacy

Supportive efficacy endpoints include the following:

- Proportion of Patients with an assessment of clear or almost clear and with at least a 2-grade improvement in IGA at Weeks 2, 4 and 8.
- Absolute change from Baseline in inflammatory and non-inflammatory lesion counts from Baseline to weeks 2, 4 and 8.
- PRE-FACE ASD: Mean absolute change in PRE-FACE ASD scores from Baseline to Weeks 2, 4, and 8.
- PRE-FACE AID: Mean absolute change in PRE-FACE AID scores from Baseline to Weeks 2, 4, and 8.
- Proportion of Patients in treatment relative to control who report at least "minimally improved" as measured by the PGI-C at Week 12.
- Patient Global Impress of Symptom Severity (PGI-S) at Week 12.
- Patient Global Impression of Treatment Satisfaction (PGI-TS) at Week 12.

17.3.4 Exploratory Endpoint

The mean change in Acne-QoL domain scores from Baseline to Week 12.

17.4 Statistical Hypothesis Testing

17.4.1 Test of Superiority for Lesion Count Variables

This section provides the basic model and statistical approach which is used in combination with the multiple imputation procedures described in Section 18.4.6. Tests of superiority for the absolute change from Baseline in inflammatory lesions will be based on either parametric or non-parametric methods consistent with the statistical assumptions required to support the analyses. Specifically, the tests of superiority will be based on an ANCOVA with factors of treatment and analysis center and the respective Baseline lesion count as a covariate or on ranked data submitted to an ANCOVA with factors of treatment and analysis center and the respective Baseline lesion count as a covariate. If the treatment-by-analysis center interaction effect is significant at an alpha less than 0.10, then the effect will be included in the model; otherwise it will be removed.

A skewness test, based on the methods presented by J.H. Zar (1984), will be applied to the residuals resulting from an ANCOVA. A two-sided p-value for the skewness test significant at 0.01 will imply the use of the non-parametric method. If a parametric analysis is indicated, the results of the parametric analysis will be considered the primary analysis. Should a non-parametric analysis be indicated, the absolute or percent

changes in inflammatory lesions will be rank transformed prior to submitting them to the ANCOVA. Results of the rank-transformed analyses then will be considered the primary analysis; however, results of the non-ranked transformed analyses will also be presented.

17.4.2 Test of Superiority for IGA

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

17.4.3 Test of Superiority for Secondary Efficacy and Control of Multiplicity

Appropriate descriptive statistics will be computed for all Secondary Efficacy parameters. Additionally, all inferential testing of percent change in lesions will follow the methods for the primary lesion count analyses. Methods corresponding to the analysis of IGA will be used to compare the proportion of patients in the E-BPO/E-ATRA Cream arm versus vehicle control achieving at least a 4-point reduction in pimples or in embarrassment scores from Baseline to Week 12.

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

Evaluation of the secondary efficacy variables will use a gated sequential procedure starting with the comparisons of the first step and proceeding onto the next step and etc. This stepwise process will be conducted for testing the secondary efficacy endpoints in order to control for multiplicity. These tests will be performed for only the ITT population. The testing process will terminate whenever a statistical test for a step is not significant. All subsequent tests for the remaining steps will be considered not significant. The order of testing is:

Step Number	Secondary Endpoint
1	Percent change from Baseline, in non-inflammatory lesion count at Week 12.
2	Percent change from Baseline, in inflammatory lesion count at Week 12.
3	Proportion of patients in the E-BPO/E-ATRA cream arm compared to vehicle control achieving at least a 4-point reduction on Item 1 (pimples) of the PRE-FACE from Baseline to Week 12.
4	Proportion of patients in the E-BPO/E-ATRA Cream arm compared to vehicle control achieving at least a 4-point reduction on Item 5 (embarrassment) of the PRE-FACE from Baseline to Week 12.
5	Absolute change from Baseline, in non-inflammatory lesion count at Week 8
6	Absolute change from Baseline, in inflammatory lesion count at Week 8.
7	Absolute change from Baseline, in non-inflammatory lesion count at Week 4.

8	Absolute change from Baseline, in inflammatory lesion count at Week 4.

17.4.4 Supportive Efficacy Analyses

Appropriate descriptive statistics will be computed for all Supportive Efficacy parameters. Additionally, all inferential testing will follow the methods for the co-primary variables wherein the continuous variables will parallel the lesion count analyses and the discrete variables will follow the analysis of the IGA.

17.4.5 Pooling Analysis

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

Prior to investigating the treatment effect within the analysis centers, the treatment effect within investigational site will be investigated to determine if the site-to-site variability is such that it could mask the analysis center effects. Thus, prior to pooling, change from baseline in inflammatory lesions and non-inflammatory lesions will be analyzed with an ANCOVA (unranked or ranked) with factors of treatment group, investigational site, and treatment group by investigational site interaction, and the respective baseline lesion count variable as a covariate. The dichotomized primary endpoint will be analyzed with a logistic regression with factors of treatment group, investigational site, and the interaction term of treatment group by investigational site. If any of the analyses are not computationally feasible due to some investigational sites having very few Patients enrolled, the low-enrolling investigational sites will be excluded from the analysis.

The consistency of treatment response will be investigated across the analysis centers subsequent to combining the data as described above. Statistical tests will be conducted to identify if there are extreme analysis centers that could affect the interpretation of common statistical and clinical conclusions. An analysis center by treatment interaction will be included in the primary variable analyses to test for parallel treatment effect at an alpha level of 0.10. Change from baseline in inflammatory lesions will be analyzed with an ANCOVA (unranked or ranked) with factors of treatment, analysis center, and treatment by analysis center interaction and the respective baseline lesion count variable as a covariate. For the purpose of testing consistency of treatment response, the

dichotomized IGA will be analyzed with a logistic regression procedure with factors of treatment, analysis center, and treatment by analysis center interaction. Further examination will follow for any variables that have a significant ANCOVA or logistic regression interaction term. In the event that the ANCOVA or logistic regression interaction (referred to henceforth as the "appropriate test") p-value is less than or equal to 0.10, a sensitivity analysis that excludes analysis centers with the extreme efficacy result will be performed to determine the robustness of the treatment effect. On the other hand, if the outcome of the appropriate test has a p-value greater than 0.10, then the conclusions from the pooled data will be considered to be free of the impact of extreme analysis centers.

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

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

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

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

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

17.4.6 Missing Efficacy Data Imputations

17.4.6.1 Lesion Count and PRE-FACE Variable Missing Data Imputation

Missing Week 12 data will be estimated by multiple imputation and subsequently analyzed. Missing lesion count data will be derived for the analysis using the method of Markov Chain Monte Carlo (MCMC) multiple imputation. Imputation will be conducted independently for each treatment group.

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

1. Create a dataset of Patients, one for each treatment group, with observed values and those needing estimation by MCMC. The missing lesion count values in each dataset will be filled in using the MCMC method 5 times to generate 5 datasets. The resulting datasets for each treatment arm will be combined into one complete dataset for each imputation.
   Syntax:
   ```
   proc mi data=datain out=dataout seed=&seed. nimpute=5 <options>;
     where trtpn=(1, or 2);
     mcmc chain=multiple;
     var baseline week2 week4 week8 week12;
   run;
   ```
2. For each complete dataset, the variable of interest for baseline minus the Week 12 value will be computed. Each complete dataset will be analyzed as specified for the particular analysis.
3. The results from these analyses will be combined into a single inference using SAS PROC MIANALYZE.

The following 4 random seeds have been pre-specified by using a random number generator:

- Inflammatory Lesion Counts; S6G5T-3: Seed = 813883085
- Inflammatory Lesion Counts; S6G5T-8 Vehicle: Seed = 2010726808
- Non-inflammatory Lesion Counts; S6G5T-3: Seed = 1326750493
- Non-inflammatory Lesion Counts; S6G5T-8 Vehicle: Seed = 1498908882

17.4.6.2 IGA Missing Data Imputation

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

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

1. Create a dataset, one for each treatment group, of Patients with observed values and those needing estimation by MCMC. The missing IGA values in each dataset will be filled in using the MCMC method 5 times to generate 5 datasets. The resulting datasets for each treatment arm will be combined into one complete dataset by imputation.
   Syntax:
   ```
   proc mi data=datain out=dataout seed=&seed. nimpute=5 <options>;
     where trtpn=(1, or 2);
     mcmc chain=multiple;
     var baseline week2 week4 week8 week12;
   run;
   ```
2. For each complete dataset, the dichotomous success rate (clear or almost clear with a 2-point change from baseline) will be computed. The Week 12 estimated global values will be rounded to the nearest integer value prior to evaluating the success rate. Each complete dataset will be analyzed with a logistic regression with factors of treatment group and analysis center.

3. The results from these analyses will be combined into a single inference using SAS PROC MIANALYZE.

The following 4 random seeds have been pre-specified by using a random number generator:

- PRO Pimples Scores; S6G5T-3: Seed = 1597410322
- PRO Pimples Scores; S6G5T-3 Vehicle: Seed = 466920922
- PRO Embarrassment Scores; S6G5T-3: Seed = 288784276
- PRO Embarrassment Scores; S6G5T-3 Vehicle: Seed = 1746263137

17.4.7 Sensitivity Efficacy Analyses

17.4.7.1 Sensitivity analyses for absolute change in lesion count

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

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

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

The third sensitivity analysis will involve a tipping point analysis. Full details will be presented in the SAP.

17.4.7.2 Sensitivity analyses for IGA

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

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

1. Missing values will be filled in 5 times to generate 5 complete datasets. The imputation model used logistic regression with factors of treatment group and analysis center (i.e., the imputation model will be the same as the analysis model).

2. Each complete dataset will be analyzed with a logistic regression a factors of treatment group and analysis center.
3. Results from these analyses will be combined into a single inference.

The third sensitivity analysis will involve a tipping point analysis. Full details will be presented in the SAP.

17.4.8 Subgroup Analyses

Subset analyses will be conducted for the ITT populations for the subgroups baseline global severity, gender, age, ethnicity, race, and geographic region. Age will be dichotomized to less than the median age of Patients and greater than or equal to the median age of Patients. An additional analysis will include age with categories of less than 18 and 18 to less than the median age and greater than or equal to the median age. Subset analyses will be conducted on the variables absolute change from baseline in inflammatory lesions at Week 12 as well as the dichotomized global severity score at Week 12. These analyses will contain only descriptive statistics.

17.5 Assessment of Safety

Safety will be evaluated by tabulations of AEs, the Investigator Cutaneous Safety Assessment rating of pigmentation, erythema, dryness and scaling; and the Patient assessment of Local Tolerability rating itching, burning and stinging will be presented with descriptive statistics at Baseline and at Weeks 2, 4, 8, and 12 for each treatment group. Frequencies and percentages for each outcome category will be included in these statistics. Mean values will be presented graphically by week and treatment group.

17.6 Adverse Events

All AEs 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 (if applicable), 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 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.

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

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

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

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

SAEs will be tabulated by Patient within treatment groups.

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

17.6.1 Vital Sign Measurements

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

17.6.2 Concomitant Medications

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

17.7 Sample Size Determination

The following power calculations are based on the observed Week 12 results of the Phase 2 study, SGT-65-02. This study was a six-arm trial including S6G5T-3 and Vehicle Cream in the treatment of acne vulgaris. Estimates from the S6G5T-3 arm were used in the power assessments. The anticipated randomization ratio is 2:1 for S6G5T-3 and S6G5T-8 Vehicle Cream, respectively. The computations were performed with nQuery Advisor Version 7.0 using a two-sided test with a statistical significance value of 0.05.

A sample size of 274 in the S6G5T-3 and 137 in the Vehicle Cream group (total of 411) has 99% power to detect a statistically significant difference in inflammatory lesions. The estimated absolute change from baseline in treatment means were -16.7 and -12.2 for S6G5T-3 and Vehicle Cream, respectively, with a common standard deviation of 10.0.

A sample size of 146 in the S6G5T-3 and 73 in the Vehicle Cream group (total of 219) has 99% power to detect a statistically significant difference in non-inflammatory lesions. The estimated absolute change from baseline in treatment means were -23.7 and -13.7 for S6G5T-3 and Vehicle Cream, respectively, with a common standard deviation of 19.0.

A sample size of 231 in the S6G5T-3 and 116 in the Vehicle Cream has group (total of 346) has 99% power to detect a statistically significant difference the proportion of Patients who have at least a 2-grade reduction at Week 12 from baseline in IGA and are Clear or Almost Clear. The estimated percentages with a 2-grade reduction at Week 12 from baseline in the IGA and Clear or Almost Clear are 33.3% and 12.6% for S6G5T-3 and Vehicle Cream, respectively.

Therefore, a total of 420 Patients has adequate power to demonstrate statistical significance of S6GT5-3 over S6GT5-8 Vehicle Cream for the lesion count endpoints as well as dichotomized IGA.

18 ADMINISTRATIVE CONSIDERATIONS

18.1 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.

18.2 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.

18.3 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.

18.4 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 Acknowledgment' page from the Sponsor and IRB approved protocol.
- Documentation of IRB approval of the protocol, ICF, any other written information provided to Patients and any recruitment advertisements.
- A copy of the IRB approved ICF.
- 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.

18.5 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 ICF. The eCRFs will be monitored against source documents. If data in the eCRF is not duplicated in a source document, a source document should be created and maintained by the site to capture that information. Source documentation for Patients includes but is not limited to the physician's Patient records, diaries, photographs. All source documents will be maintained at the study site.

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

18.6 Reports to the IRB

Before study initiation, the Investigator must have written and dated approval from the IRB for the protocol, ICF, 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.

18.7 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.

18.8 Records Retention

The Investigator must maintain records of the study product disposition, copies of the CRFs 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.

19 REFERENCES

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20 APPENDIXES

APPENDIX 1: PATIENT INSTRUCTIONS 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:

- Apply the cream, once a day, every day, at home and prior to bedtime, for twelve (12) weeks.
- Wash your face gently with the mild cleanser provided by the doctor or with study approved cleanser and water. Rinse thoroughly and gently pat dry.
- After the face has dried completely, apply a pea sized amount of study product for each area of the face (chin, left cheek, right cheek, nose and forehead) as a thin layer, as instructed at your first study visit.
- Apply the cream on each area of the face as evenly as possible and gently rub into the skin. Each pea-size amount should be used to evenly cover the following parts on your face: chin, left cheek, right cheek, nose, left forehead and right forehead, excluding the mouth, eyes and lips. (excessive rubbing should be avoided).
- Do not apply the cream on the mouth, eyes, inside the nose and lips or any body part other than the face.
- Do NOT treat specific lesions but rather the whole area.
- Be sure to wash your hands before and after you apply the product. But do not wash your face for at least two (2) hours after you apply the study product.
- Wait for at least 30 minutes before applying the moisturizer/sunscreen provided by the doctor for this study.
- If applicable, wait at least 30 minutes before applying only non-medicated make-up.

ADDITIONAL REMINDERS:

- Store test product at room temperature (at or below 25°C/77°F). Do not freeze or expose to extreme temperature. Keep test product in an upright position.
- Avoid contact with the eyes, inside the nose, lips, mouth and all mucous membranes.
- Caution: This test product contains ingredient which may cause bleaching of colored fabric.
- The test product should be used only by the person for whom it was provided
- The test product should be kept out of the reach of children or others of limited capacity to read or understand these instructions.
- Containers of test product must be returned to the study staff, 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 Calendar provided to you; indicate reason for any missed dose on the diary calendar.

- Throughout the study, continue to use on your face only the same cleanser provided by the Investigator for this study.
- If you use a moisturizer and/or sunscreen, you must use the one provided by the doctor for this study. If necessary, after consultation with your site staff you might be permitted to use another moisturizer with sunscreen that includes a higher SPF (Sun Protection Factor) which will require the sponsor to preapprove its use.
- The pump you received has enough cream for full four (4) weeks of treatment. If you are running out of cream in the pump before your next visit, contact the study staff immediately. A new pump will be supplied, and you will be reinstructed on how to use it.
- **On the day of your study visit, do not apply study product, the moisturizer with sunscreen, or make-up and do not shave your face.**
- You must not use any other treatment for your acne while you are participating in this study.
- Avoid unnecessary sun exposure and tanning booths**.** When sun exposure cannot be avoided, use the provided moisturizer with sunscreen and wear a wide-brimmed hat.
- It is important to inform the study site about any medications (i.e., prescriptions, over-the-counter medications, street drugs, or herbal medications) that you have taken during the study.

Bring this sheet, your updated Diary Card, and your study product pump with you to every study visit. On Visit3/ Week 2 ONLY, Do Not bring the study product pump.

STUDY VISIT SCHEDULE:

VISIT 2: Baseline Day 1 Date: Time:
VISIT 3: Week 2, Day 15 Date: Time:
VISIT 4: Week 4, Day 29 Date: Time:
VISIT 5: Week 8, Day 57 Date: Time:
VISIT 6: Week 12/ End of Study or Early Termination, Day 85 Date: Time:

Thank you for following these instructions

APPENDIX 2: PRO – PRE-FACE - SIGNS/SYMPTOMS

APPENDIX 3: PRO – PRE-FACE - IMPACTS

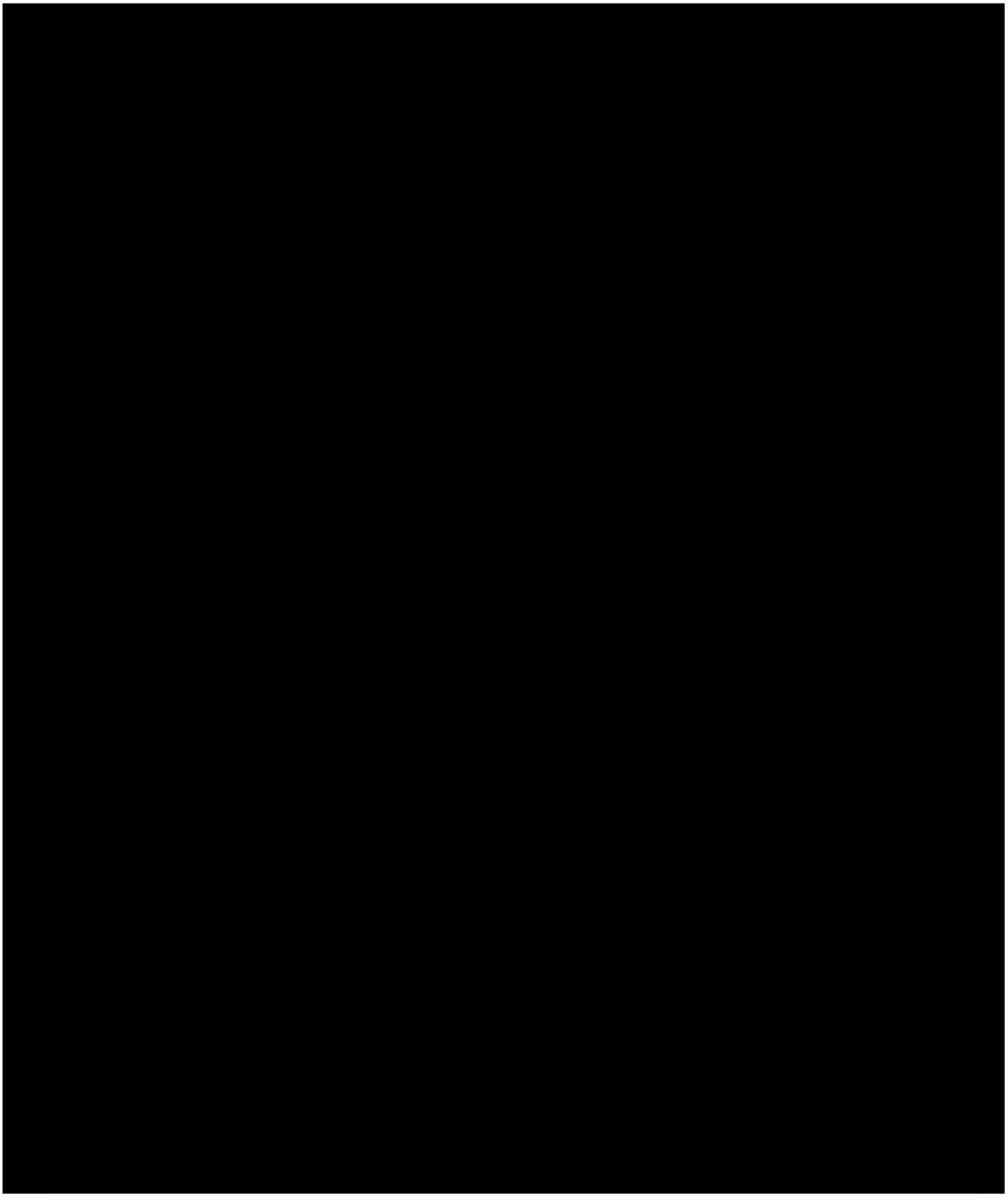
APPENDIX 4: PRO – PGI-S

APPENDIX 5: PRO – PGI-C

APPENDIX 6: PRO – PGI-TS

APPENDIX 7: PRO – PGI-SE

APPENDIX 8: ADMINISTRATION OF ACNE-QOL



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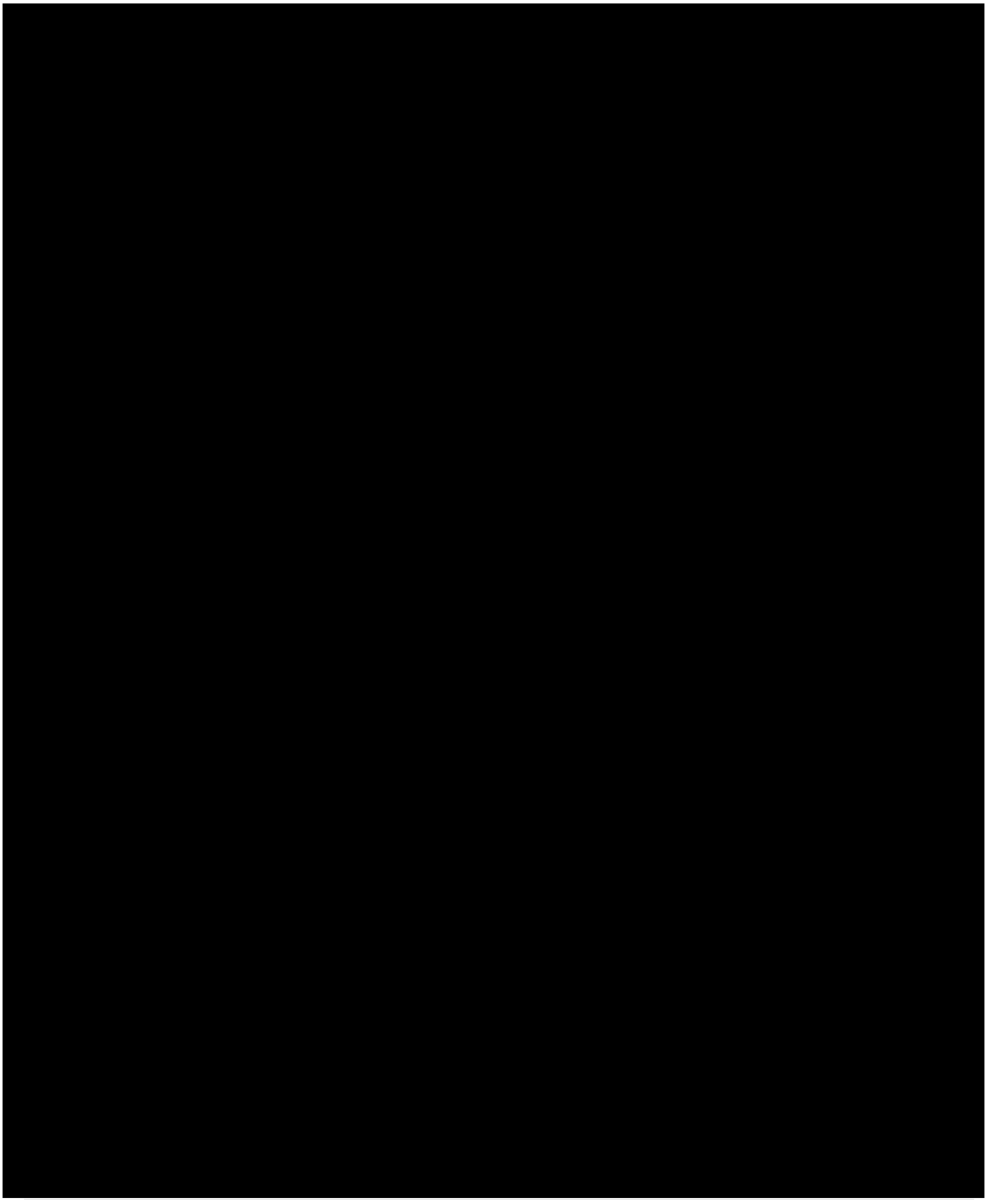
APPENDIX 9: ACNE-SPECIFIC QOL QUESTIONNAIRE



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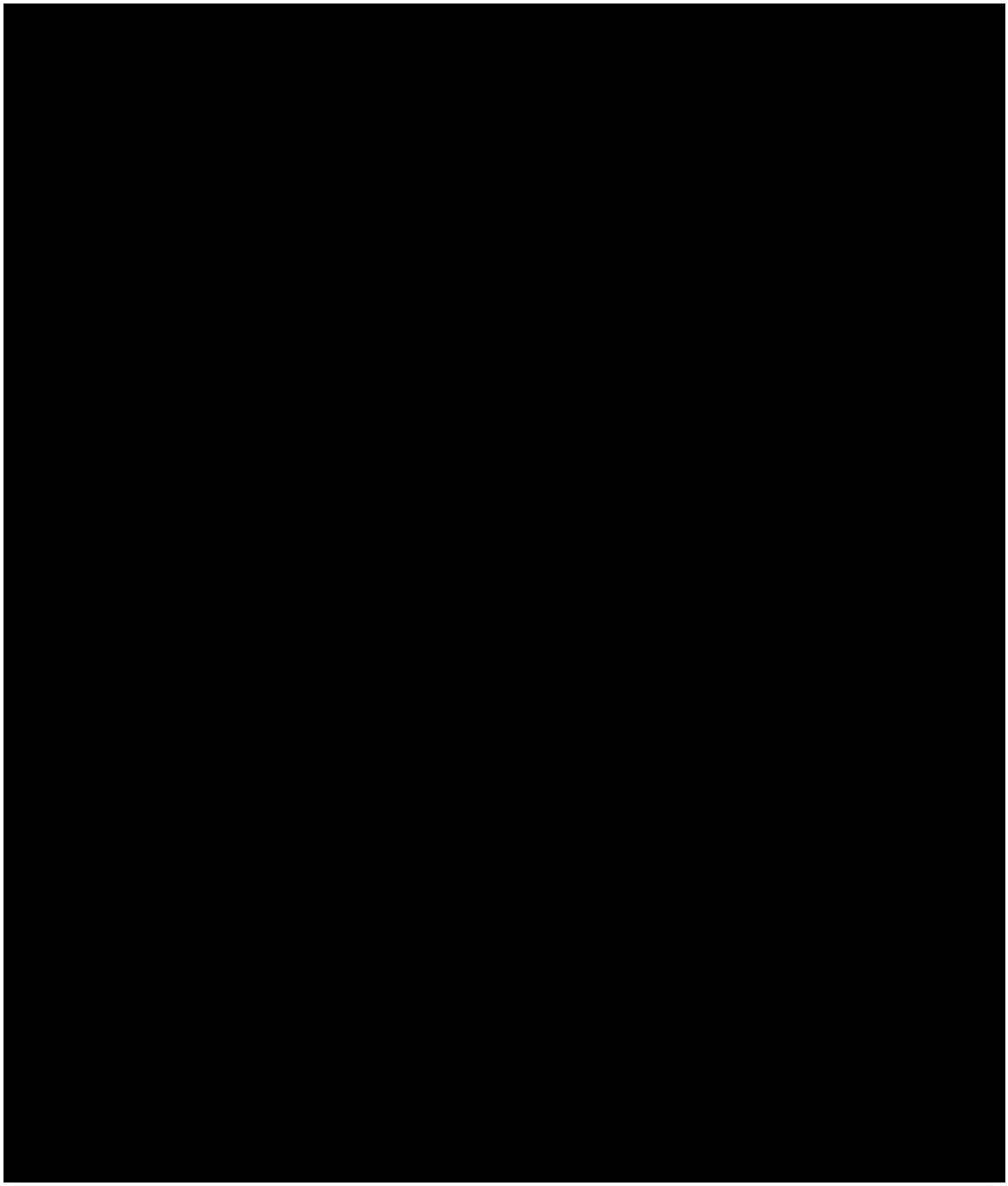

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