STUDY PROTOCOL

Protocol Title	**A pilot study on the use of Seysara for Rosacea**
Protocol Number	**SEY1901**
Protocol Date	**February 19, 2019**
Investigator/Sponsor	**Leon Kircik, MD** **Skin Sciences, PLLC** **Louisville, KY**

PROTOCOL SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the supplements, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and ICH-GCP guidelines.

Investigator

Printed Name	Signature	Date

1 GENERAL INFORMATION

1.1 Introduction

Acne rosacea is a chronic inflammatory disease with different components including inflammatory lesions, erythema, and telangiectasia. Although, we have several topical treatment options, the only FDA approved systemic medication is sub antimicrobial dose doxycycline (Oracea 40mg) however, all classes of tetracycline including antimicrobial dose doxycycline and minocycline are widely used treatment options for rosacea. We have done an investigator initiated study of Solodyne (weight based dose minocycline FDA approved for acne vulgaris)
Seysara has recently been approved as weight based dose tetracycline class drug for acne vulgaris. This pilot study will look into the efficacy and safety of Seysara in rosacea.

1.2 Study Population

One hundred (100) subjects with acne rosacea.

3 STUDY DESIGN

A prospective, parallel group, randomized, investigator-blinded, pilot clinical trial. One hundred (100) subjects will be randomized to either group A or B with 3:1 ratio:

Group A *N=70*	Seysara weight based dosing per label
Group B *N=30*	Multivitamin Centrum Adult

A pilot study on the use of Seysara for Rosacea. This will be a single blinded randomized multicenter study for 12 weeks. Visits will be: screening, baseline, week 4, week 8, week 12

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

1. Male or female ≥18 years-of-age.
2. Moderate-to-severe rosacea (as per the IGA score; Table 3) on the proposed facial treatment area consisting of:

    a. At least 15 and not more than 50 facial papules and pustules, excluding lesions involving the eyes and scalp;

    b. No more than 2 nodules on the face.

3. Presence of or history of erythema and/or flushing on the face.

4. If a female of child-bearing potential, have a negative urine pregnancy test and agree to use an effective method of contraception. A sterile sexual partner is NOT considered an adequate form of birthcontrol.

5. Willing to minimize external factors that might trigger rosacea flare-ups (eg, spicy foods, thermally hot foods and drinks, hot environments, prolonged sun exposure, strong winds, and alcoholic beverages).

6. Subjects who use make-up must have used the same brands/types of make-up for a minimum period of 14 days prior to study entry and must agree to use the same make-up, brand/type, or frequency of use, throughout the study.

7. Completed and signed an appropriately administered Informed Consent Form (ICF) prior to any study-related procedures.

4.2 Exclusion Criteria

Subjects should be excluded from enrollment in the study for any of the following reasons:

1. Woman who is pregnant, lactating, or planning to become pregnant during the study period.

2. Presence of any skin condition on the face that would interfere with the diagnosis or assessment of rosacea.

3. Moderate or severe rhinophyma, dense telangiectasia (score 3, severe; or plaque-like facial edema.

4. Excessive facial hair (eg, beards, sideburns, moustaches, etc.) that would interfere with diagnosis or assessment of rosacea.

5. History of hypersensitivity or allergy to all tetracyclines, or of any other component of the formulation.

6. Patients with history of C-diff associated colitis, intracranial hypertension will be excluded.

7. Severe erythema, dryness, scaling, pruritus, stinging/burning, or edema.

8. Use within 6 months prior to Day 0/Baseline of oral retinoids (eg, Accutane®) or therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed).

9. Initiation of use of estrogens or oral contraceptives less than 3 months prior to Day 0/Baseline.

10. Use within 1 month prior to Day 0/Baseline of:

    a. Systemic antibiotics known to have an impact on the severity of facial rosacea (eg, containing tetracycline and its derivatives, erythromycin and its derivatives, sulfamethoxazole, or trimethoprim). Subjects requiring systemic antibiotics not known to affect rosacea will be considered on a case-by-case basis.

    b. Systemic corticosteroids (Note: intranasal and inhalational corticosteroids do not require a washout and maybe used throughout the trial if the subject is on a stable dose).

11. Use within 2 weeks prior to Day 0/Baseline of:

    a. Topical corticosteroids.

    b. Topical antibiotics.

    c. Topical medications for rosacea (eg, metronidazole).

12. Use of a sauna during the 2 weeks prior to Day 0/Baseline and during the study.

13. Had wax epilation of the face within 2 weeks prior to Day 0/Baseline.

14. Active bacterial folliculitis.

15. Consumption of excessive alcohol, abuse of licit or illicit drugs, or a condition that, in the opinion of the Investigator, could compromise the subject's ability to comply with study requirements.

16. Participation in activities that involve excessive or prolonged exposure to sunlight or weather extremes, such as wind or cold.

17. Presence of any clinically significant condition or situation, other than the condition being studied, that in the opinion of the Investigator would interfere with the study evaluations or optimal participation in the study.
18. Participation in an investigational drug study (ie, subject has been treated with an investigational drug) within 30 days prior to Day 0/Baseline. Subjects who are participating in non-treatment studies such as observational studies or registry studies can be considered for inclusion.
19. Prior laser therapy (for telangiectasia or other conditions), electrodessication, or phototherapy (eg, ClearLight®) to the facial area within 180 days prior to Day 0/Baseline.
20. Prior cosmetic procedures (eg, facials) that may affect the efficacy and safety profile of the investigational product within 14 days prior to Day 0/Baseline.

4.3 Withdrawal of Subjects

It is the right and duty of the Investigator to discontinue the study participation of a subject when the subject's health or well-being is threatened by continuation in the study. Such subjects should be withdrawn from the study and not continued under a modified regimen. In the event of premature discontinuation from the study, the Investigator should determine the primary reason for discontinuation. A subject withdrawn from the study prior to initiation of treatment may be replaced.

5 TREATMENT OF SUBJECTS AND FOLLOW-UP

5.1 Study Procedures

5.1.1 Assessment Schedule

Schedule of Study Assessments and Procedures

Assessment or Procedure	Screening	Day 0 / Baseline[b]	Visits/Early Follow-up		
Visit	1	2	**3**	**4**	**5**
Week			**4**	**8**	**12**
Informed consent	X				
Demographic data	X				
Assign subject identification	X				
Medical/surgical/medication history	X				
Inclusion/exclusion criteria	X	X			
Physical examination, height, weight[c]		X			X
Blood pressure/heart rate[d]		X	X	X	X
Urine pregnancy test (females of childbearing potential only)	X	X	X	X	X
Lesion counts	X	X	X	X	X
Investigator's Global Assessment	X	X	X	X	X
Subject Global Assessment			X	X	X
DLQI		X			X
Local signs and symptoms assessments[e]	X	X	X	X	X
Randomization		X			
Concomitant medications		X	X	X	X
Adverse events		X	X	X	X
Perform drug accountability			X	X	X
Dispense & Collect study drug		X	X	X	X
Schedule/confirm next visit	X	X	X	X	

Screening visit:

- Informed consent will be obtained
- Demographic data
- Assign subject ID
- Medical / surgical and medication history
- Inclusion and exclusion criteria
- Urine pregnancy test
- Lesion count
- Investigator global assessment
- Local signs and symptoms of adverse events
- Concomitant medications
- Adverse events
- Schedule confirm next visit

Baseline visit:

- Inclusion and exclusion criteria
- Physical exam
- Vitals with height and weight
- Urine pregnancy test
- Lesion count
- Investigator global assessment
- DLQI
- Local signs and symptoms of adverse events
- Randomization
- Concomitant medications
- Adverse events
- Dispense study drug
- Schedule and confirm next visit

Visit 3 & 4:

- Vitals
- Urine pregnancy test
- Lesion count
- Investigator global assessment
- Subject global assessment
- Local signs and symptoms of adverse events
- Concomitant medication
- Adverse events
- Perform drug accountability
- Collect and dispense study drug
- Schedule and confirm next visit

Visit 5 Final visit or Early Termination:

- Physical exam
- Vitals
- Urine pregnancy test
- Lesion count
- Investigator global assessment
- Subject global assessment
- DLQI
- Local signs and symptoms of adverse events
- Concomitant medications
- Adverse events
- Perform drug accountability
- Collect study drug

5.2 Study Treatment

5.2.1 Details of Study Treatment

SEYSARA (sarecycline) tablets are a tetracycline class drug for oral administration. Sarecycline hydrochloride
is chemically described as (4*S*,4a*S*,5a*R*,12a*S*)-4-(dimethylamino)-3,10,12,12a-tetrahydroxy-7-[(methoxy- (methyl)-amino)- methyl]-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide monohydrochloride with an empirical formula of $C_{24}H_{29}N_3O_8$.HCl and a molecular weight of 523.96. SEYSARA tablets contain 64.5 mg, 107.5 mg, and 161.2 mg of sarecycline hydrochloride equivalent to
60 mg, 100 mg, and 150 mg sarecycline respectively. Inactive ingredients in the tablet formulations are: microcrystalline cellulose, povidone, sodium starch glycolate, and sodium stearyl fumarate. The yellow film coating contains D&C yellow #10 aluminium lake, iron oxide yellow, methacrylic acid copolymer type C, polyethylene glycol, polyvinyl alcohol, sodium bicarbonate, talc, and titatnium dioxide.

Centrum Adult Multi Vitamin
Ingredients: Calcium Carbonate, Potassium Chloride, Dibasic Calcium Phosphate, Magnesium Oxide, Microcrystalline Cellulose, Ascorbic Acid (Vit. C), Ferrous Fumarate, dl-Alpha Tocopheryl Acetate (Vit. E), Maltodextrin.
Contains < 2% of: Beta-Carotene, BHT (to preserve freshness), Biotin, Calcium Pantothenate, Cholecalciferol (Vit. D3), Chromium Picolinate, Corn Starch, Crospovidone, Copper Sulfate, Cyanocobalamin (Vit. B12), Folic Acid, Gelatin,

Hydrogenated Palm Oil, Magnesium Stearate, Manganese Sulfate, Modified Corn Starch, Niacinamide, Nickelous Sulfate, Phytonadione (Vit. K), Polyethylene Glycol, Polyvinyl Alcohol, Potassium Iodide, Pregelatinized Corn Starch, Pyridoxine Hydrochloride (Vit. B6), Riboflavin (Vit. B2), Silicon Dioxide, Sodium Ascorbate (to preserve freshness), Sodium Metavanadate, Sodium Molybdate, Sodium Selenate, Stannous Chloride, Talc, Thiamine Mononitrate (Vit. B1), Titanium Dioxide, Tocopherols (to preserve freshness), Vitamin A Acetate, Yellow 6 Lake, Zinc Oxide.

Every patient will receive Cerave moisturizer with sunscreen.

5.2.2 Dispensation and Dosage Schedule

A 12-week supply of study medication will be dispensed at Baseline and subjects will be provided instruction on how to use study medication. A 12 week supply of Cerave moisturizer with sunscreen will also be supplied.

5.2.3 Treatment Assignment

Study medication will be administered only to subjects included in this study following the procedures set out in the Study Protocol.

All subjects who have signed an ICF will receive a 2-digit subject number, starting at 01. This subject number will be used to identify the subject throughout the study. When subjects qualify for the study, they will be randomized to study treatment groups utilizing treatment assignment numbers (TANs) in order to avoid treatment group allocation bias. The randomization schedule will be prepared on a balanced 3:1 basis

5.2.4 Supplies and Accountability

The Investigator or pharmacist will inventory and acknowledge receipt of all shipments of study medication. All study medication must be kept in a locked area with access restricted to designated study personnel. The study medication must be stored in accordance with the instructions provided with the shipment. The Investigator or pharmacist will also keep accurate records of the quantities of study medication dispensed and returned by each subject. At study conclusion, all used and unused study medication will be destroyed as per the typical practice of the investigative site.

5.2.5 Treatment Compliance

Subject compliance to the study treatment regimen will be verbally assessed at each visit; study personnel will ask each subject whether they missed any doses of study medication since the previous visit and will quantify the subject's response. We will follow compliance by counting the total amount used at each visit. If total amount used is less than 50% of the dispensed drug then those subjects will not be included in the statistical analysis.

5.3 Concomitant Medication/Treatment

Any necessary therapies that will not interfere with the response to treatment may be provided at the discretion of the Investigator. The use of any concurrent medication/treatment is to be recorded in the CRF.

6.1 Primary Endpoint

The percent of subjects achieving clear or almost clear on IGA scale and percent reduction of inflammatory lesions at week 12

6.1.2 IGA (Investigator Global Assessment)

The Investigator will score rosacea at each visit as per the following IGA:

Grade	Description
0 = Clear	*No inflammatory lesions present, no erythema*
1 = Almost Clear	*Very few small papules/pustules, very mild erythema present*
2 = Mild	*Few small or large papules/pustules, moderate erythema*
3 = Moderate	*Several small or large papules/pustules, moderate erythema*
4 = Severe	*Numerous small and/or large papules/pustules, severe erythema*

6.2 Secondary Endpoints

The percent of subjects achieving clear or almost clear on IGA and percent reduction of inflammatory lesions at week 4 and 8.

The percent reduction of inflammatory lesion count at week 4, 8, and 12.

All adverse events will be followed.

6.2.1 Lesion Counts (Papules/Pustules)

The Investigator will count the number of papules/pustules at each study visit using the following guidelines: 1) Use only the face in the assessment (the whole face down from the hairline edge to the mandibular line); and 2) Count one side of the face and then the other.

6.2.2 Dermatology Life Quality Index (DLQI)

6.2.3 Tolerability / Local signs and symptoms of adverse events

The Investigator will grade the *current* severity of erythema (disease related and/or related to IP use), dryness, peeling, and oiliness as per the following:

Score	Erythema	Dryness	Peeling	Oiliness
0 = Absent	*No redness*	*None*	*Smooth*	*Normal*
1 = Trace	*Faint red or pink coloration, barely perceptible*	*Barely perceptible dryness by palpation with no accentuation of skin markings, skin desquamation (flakes) or fissure formation*	*Fine peeling, barely perceptible*	*Mild and localized*
2 = Mild	*Light red or pink coloration*	*Easily perceptible dryness by palpation with accentuation of skin markings but no skin desquamation (flakes) or fissure formation*	*Slight peeling*	*Mild and diffuse*
3 = Moderate	*Medium red coloration*	*Easily noted dryness with accentuation of skin markings and skin desquamation*	*Definitely noticeable*	*Moderate and diffuse*

		(small flakes) but no fissure formation	*peeling*	
4 = Severe	*Beet red coloration*	*Easily noted dryness with accentuation of skin markings, skin desquamation (large flakes) and/or fissure formation*	*Extensive peeling*	*Prominent and dense*

The **Investigator** will **interview the subject** to determine the *current* severity of pruritus and burning/stinging; these symptoms will be graded as per the following:

Score	Description
0 = Absent	*Normal, no discomfort*
1 = Trace	*An awareness, but no discomfort and no intervention required*
2 = Mild	*Noticeable discomfort causing intermittent awareness*
3 = Moderate	*Noticeable discomfort causing continuous awareness*
4 = Marked	*Definite discomfort causing continuous awareness interfering occasionally with normal daily activities*
5 = Severe	*Definite, continuous discomfort interfering with normal daily activities*

7 ASSESSMENTS OF SAFETY

7.1 Safety Assessments

Throughout the study, subjects will be monitored for signs and symptoms of adverse events. An *adverse event* is any pathological or unintended change in the structure, function or chemistry of the body that occurs during the study, irrespective of causality, including any illness, injury, toxicity, sensitivity, or sudden death. The condition must either not be present pre-study or must worsen in either intensity or frequency during the study.

A *serious adverse event* is any untoward medical occurrence, that, at any dose:

- results in death;
- is life-threatening;
- requires in-patient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- is an important medical event.

An *unexpected adverse event* is any treatment-related adverse event, which is not identified in nature, severity, or frequency in current literature on the test product.

7.2 Reporting Requirements

7.2.1 Serious and/or Unexpected Adverse Events

Any serious or treatment-related unexpected adverse event occurring in this study must be promptly reported to the IRB as per its reporting guidelines.

7.2.2 Adverse Event Reporting

All adverse events must be recorded by the Investigator into the CRF. The Investigator will be required to describe the adverse event, onset and stop date, severity, the course of action taken, if any, as well as any pertinent data necessary to allow a complete evaluation of the adverse event. For serious adverse events, an additional report (SAE report) must be completed.

7.2.3 Follow-up and Final Reports

Subjects who have had a serious adverse event must be followed clinically until all parameters, including laboratory values (if applicable), have either returned to normal or are otherwise explained. If death was the outcome of the event on the initial SAE Report, a Follow-up/Final Report, including autopsy report, when performed, must be completed.

8 STATISTICS

8.1 Sample Size Justification

A total of 100 subjects will be entered into the study. This is a pilot study and a formal justification for the sample size is not provided.

8.2 Analyses

Statistical analyses will be conducted on an intent-to-treat basis (i.e., all enrolled subjects will be included in the analyses). All statistical tests will be two-sided and interpreted at a 5% significance level. Descriptive statistics (i.e., mean, standard deviation, etc.) will be provided for all continuous variables and frequencies for all categorical variables collected in this study. These will be presented by treatment group. Summary tables will be used to present patient population characteristics at baseline. Data from the study questionnaires will be included. Comparisons between treatment groups will be performed using an ANCOVA technique with the Baseline value as the covariate provided the necessary assumptions for parametric tests are satisfied. The Wilcoxon Rank-Sum test will be used if the necessary assumptions for parametric tests are not satisfied. Mean scores will also be compared.

Safety analyses will be performed in terms of incidence and severity of local tolerance signs and symptoms and adverse and/or unexpected events. Mean scores will also be compared. These will be tabulated and a complete listing of all reports of adverse and/or unexpected events will be presented. Concomitant medication/treatment will be listed by subject and study visit. An interim analysis will not be conducted.

9 RESPONSIBILITIES OF THE INVESTIGATOR

9.1 Good Clinical Practice

Investigators must adhere to the procedures outlined in this Study Protocol. The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Investigators and CRO abide by GCP as described in the ICH Guidelines Topic E6: "Guideline for Good Clinical Practice." Compliance with these regulations also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki. The study will also be carried out in keeping with local legal and regulatory requirements.

9.2 Ethics

The appropriate IRB must review the Study Protocol and the Informed Consent Form prior to initiating the study. Any significant modifications to the IRB-approved protocol or informed consent must be made in consultation with the IRB.

9.3 Confidentiality of Subjects

Any information that identifies subjects with respect to this research study will be kept confidential. However, records identifying the subject may be inspected by representatives of the IRB, the Clinical Research Organization (or its designate) if applicable, and/or the FDA. Subjects' identity will remain

strictly confidential during all record reviews, as well as in any publication that may result from this research. Subjects will be identified by study code only; their names will not be used.

9.4 Informed Consent

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Appropriate discussion of risks and possible benefits of this therapy will be provided to the subjects. Consent forms describing in detail the study interventions/products, study procedures and risks will be given to the subject and written documentation of informed consent is required prior to starting intervention/administration study product. Consent forms will be IRB approved and the subject will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject and answer any questions that may arise. The subjects will sign the informed consent document prior to any procedures being done specifically for the study. The subjects should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

9.5 Data Handling and Record Keeping

Investigators must ensure that proper source documentation for all study activities are diligently maintained and securely kept. Investigators will transfer all relevant data from source documents to the Case Report Form as stipulated in this Study Protocol and his/her signature on the Case Report Form guarantees completeness and integrity of these data. Investigators will maintain reliable study device dispensing/dosing records and will store study supplies in a secure, locked location. In addition, Investigators will ensure that all study-related source documentation and Case Report Forms will be maintained for a period of two years after the conclusion of the study.

9.6 Direct Access to Source Data/Documents

Investigators must ensure that institutional regulations and the Informed Consent Form clearly permit study-related monitoring, audits, IRB review, and regulatory inspections providing direct access to source data and documents.

10 SUPPLEMENTS

I Dermatology Life Quality Index (DLQI)

Key References

SUPPLEMENT I
Dermatology Life Quality Index (DLQI)

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ one box for each question.

1.	Over the last week, how **itchy, sore, painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	☐ ☐	Not relevant ☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐

9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒

Please check you have answered EVERY question. Thank you.

Key References:

Del Rosso JQ, Kircik LH. Update on the management of rosacea: a status report on the current role and new horizons with topical azelaic acid. J Drugs Dermatol. 2014 Dec;13(12):s101-7. PubMed PMID: 25607798.

Kircik LH. Challenges and advances in rosacea management. J Drugs Dermatol. 2014 Dec;13(12):s100. PubMed PMID: 25607797.

Stein Gold L, Kircik L, Fowler J, Jackson JM, Tan J, Draelos Z, Fleischer A, Appell M, Steinhoff M, Lynde C, Sugarman J, Liu H, Jacovella J; Ivermectin Phas 3 Study Group. Long-term safety of ivermectin 1% cream vs azelaic acid 15% gel treating inflammatory lesions of rosacea: results of two 40-week controlled, investigator-blinded trials. J Drugs Dermatol. 2014 Nov;13(11):1380-6. PubMed PMID: 25607706.

Jackson JM, Kircik LH, Lorenz DJ. Efficacy of extended-release 45 mg oral minocycline and extended-release 45 mg oral minocycline plus 15% azelaic acid i the treatment of acne rosacea. J Drugs Dermatol. 2013 Mar;12(3):292-8. PubMed PMID: 23545911.