NCT02320149

Study SC1401

Title: A Randomized, Multicenter, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of 1.5 mg/kg per Day of Sarecycline Compared to Placebo in the Treatment of Acne Vulgaris.

Protocol Date: December 16, 2015

Statistical Analysis Plan (SAP) Date: March 3, 2017

1 TITLE PAGE

Clinical Trial Protocol: SC1401

Study Title: A Randomized, Multicenter, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of 1.5 mg/kg per Day of Sarecycline Compared to Placebo in the Treatment of Acne Vulgaris

Study Number: SC1401

Study Phase: 3

Study Drug: Sarecycline tablets

IND Number: 107,645

Indication: Treatment of inflammatory lesions of moderate to severe acne vulgaris in subjects 9 years and older

Sponsor: Warner Chilcott (US), LLC, US **Regulatory** Agent of Warner Chilcott Company, LLC, an **Allergan** Affiliate

	Date
Original Protocol:	**15-Aug-2014**
Amendment 1	**15-Sep-2014**
Amendment 2	**13-Mar-2015**
Amendment 3	**16-Dec-2015**

2 SYNOPSIS

Warner Chilcott (US), LLC, US **Regulatory** Agent of Warner Chilcott Company, LLC, an **Allergan** Affiliate
Name of Finished Product: Sarecycline tablets
Study Title: A Randomized, Multicenter, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of 1.5 mg/kg per Day of Sarecycline Compared to Placebo in the Treatment of Acne Vulgaris
Study Number: SC1401
Study Phase: 3
Primary Objective: The primary objective is to evaluate the efficacy of oral sarecycline 1.5 mg/kg/day compared to placebo in treating inflammatory acne lesions in subjects with moderate to severe facial acne vulgaris based on Investigator's Global Assessment (IGA) score and inflammatory lesion counts.
Secondary Objectives: The secondary objectives are to evaluate the safety of oral sarecycline 1.5 mg/kg/day based on adverse events, vital signs, electrocardiograms, physical examinations and clinical laboratory tests.
Study Design: Randomized, double-blind, placebo-controlled, parallel group
Study Population: Males and females, 9 to 45 years of age (inclusive) with moderate to severe facial acne vulgaris
Number of Subjects: Approximately 1000 subjects enrolled at approximately 50 sites
Study drug; Dose; and Mode of Administration: Sarecycline tablets; 60 mg, 100 mg and 150 mg, providing a dose of 1.5 mg/kg/day; oral
Reference Therapy; Dose; and Mode of Administration: Matching placebo tablets; oral
Duration of Treatment: 12 weeks
Efficacy Assessments: IGA scores and lesion counts at baseline and following 3, 6, 9, and 12 weeks of treatment.

The co-primary efficacy endpoints will be the change from baseline (CFB) in inflammatory facial lesion counts at Week 12 and IGA success at Week 12.

Safety Assessments:

Adverse events, vital signs, electrocardiograms, physical examinations and clinical laboratory tests.

Pharmacokinetic Assessments:

Subjects will have the ability to participate in one of two PK sampling options: PK Schedule 1 or PK Schedule 2 (see below). **Additionally, subjects who are 9 to 11 years of age have the ability to participate in PK Schedule 3 (see below).** Subjects that do not participate in PK sampling are still eligible for study participation. For some of the sites, the only choices will be PK Schedule 2 or no PK sampling.

PK Schedule 1

Visit	Sample Time
Visit 1 (Week 3 ± 3 days)	(1) Predose: Within 0.5 hours before dose administration (2) Postdose: Between 0.5 hours and 1 hour after dose administration (3) Postdose: Between 1.5 hours and 3 hours after dose administration
Visit 4 (Week 12 ± 3 days)	(1) Postdose: Between 4 hours and 5 hours after dose administration (2) Postdose: Between 6 hours and 8 hours after dose administration

PK Schedule 2

Visit	Sample Time
Visit 1 (Week 3 ± 3 days)	At any time during the visit
Visit 4 (Week 12 ± 3 days)	At any time during the visit

PK Schedule 3 ***(only for 9-11 year old subjects)***

Subjects who participate in PK Schedule 3 will receive one dose of active study treatment at Visit 4 (Week 12) after all visit assessments are completed regardless of randomized study treatment (active or placebo).

Visit	Sample Time
Visit 1 (Week 3 ± 3 days)	**At any time during the visit**
Visit 4 (Week 12 ± 3 days)	**(1) Postdose: Between 0.5 hours and 1 hour after dose administration** **(2) Postdose: Between 1.5 hours and 2 hours after dose administration** **(3) Postdose: Between 3 hours and 4 hours after dose administration**

Statistical Methods:

Continuous variables will be summarized by visit and treatment, as applicable, using descriptive statistics (mean, median, 25th percentile, 75th percentile, standard deviation, standard error of mean, minimum, maximum, and number of subjects). Categorical variables will be summarized using frequency distributions (counts and percentages).

The co-primary efficacy endpoints, the change from baseline in inflammatory lesion counts and IGA success (defined as at least a 2-point decrease from baseline in the IGA assessment and a score of clear [0] or almost clear [1] on the IGA assessment) at Week 12 will be analyzed at α=0.05 **for** no difference between treatments **using** the Intent-to-Treat

population. The absolute change from baseline in inflammatory lesion counts will be analyzed using an analysis of covariance (ANCOVA) model with factors for treatment and (pooled) site and the baseline value as a covariate. The adjusted means with associated 95% confidence intervals (CIs) from the ANCOVA model will also be presented for each treatment and for the difference between the treatments **at Week 12**. IGA success will be analyzed using a Cochran-Mantel-Haenszel (CMH) test with adjustment for (pooled) site **at Week 12**. The risk difference and the 95% CIs for the risk difference and the relative risk and the 95% CIs for the relative risk will be presented as well. A hierarchical testing approach will be used for the secondary efficacy endpoints, percent change from baseline in inflammatory lesion counts at Week 12**, and absolute and percent CFB in inflammatory lesion counts at Weeks 9, 6, and 3** (**using ANCOVA**), **such** that statistical testing will only be performed if both co-primary efficacy endpoints are statistical**ly** superior to placebo at α=0.05. **Statistical testing of the secondary endpoints will be conducted in the following order, with all tests proceeding at the 0.05 level if and only if the previous tests were all significant at the 0.05 level: (1) Percent CFB for inflammatory lesion counts at Week 12 (must be significant at the 0.05 level to proceed to the next analyses), (2) Absolute and percent CFB for inflammatory lesion counts at Week 9 (both endpoints must be significant at the 0.05 level to proceed to the next analyses), (3) Absolute and percent CFB for inflammatory lesion counts at Week 6 (both endpoints must be significant at the 0.05 level to proceed to the next analyses), (4) Absolute and percent CFB for inflammatory lesion counts at Week 3 (both endpoints must meet the 0.05 level for Week 3 to meet statistical significance). The secondary endpoints listed above** will **all** be analyzed using an analysis of covariance model with factors for treatment and (pooled) site and the baseline value as a covariate for the ITT population. **Missing data for the co-primary and secondary endpoints will be handled using a multiple imputation approach.**

Plasma concentration data of sarecycline will be analyzed by nonlinear mixed effects modeling approach.

Date of Original Protocol: 15-Aug-2014

Date of Protocol Amendment 1: 15-Sep-2014

Date of Protocol Amendment 2: 13-Mar-2015

Date of Protocol Amendment 3: DD-Dec-2015

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4 LIST OF ABBREVIATIONS

ANCOVA	Analysis of covariance
CFB	Change from baseline
CFR	Code of Federal Regulations
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CRO	Contract research organization
CRF	Case report form
ECG	Electrocardiogram
ET	Early termination
FCS	**fully conditional specifications**
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCl	Hydrochloride
ICH	International Conference on Harmonisation
IGA	Investigator's Global Assessment
IP	Investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-treat
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MI	**Multiple Imputation**
MMRM	Mixed-**effects** model repeated measures
NONMEM	Nonlinear mixed-effects modeling
OC	Observed cases
PHI	Protected health information
PK	Pharmacokinetic
PP	Per-protocol
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SEM	Standard error of the mean
SV	Screen Visit
US	United States

WHO	World Health Organization

5 ETHICS

5.1 Ethical Conduct of Study

The study will be conducted in accordance with Good Clinical Practice (GCP) as contained in International Conference of Harmonisation (ICH) Guidelines and United States (US) Code of Federal Regulations (CFR) governing the protection of human subjects (Title 21, Part 50) and the obligations of clinical investigators (Title 21, Parts 312.60 through 312.69). The study will also be conducted in accordance with the World Medical Association Declaration of Helsinki and all amendments.

The Sponsor is responsible for the ongoing safety evaluation of the study drug and will expedite the notification of all participating investigators and regulatory authorities of findings that are both serious and unexpected and/or that could adversely affect the safety of subjects, the conduct of the study or alter the Institutional Review Board's (IRB's) approval to continue the study.

5.2 Institutional Review Board

The protocol and supporting documents for this study will be reviewed and approved by an appropriately constituted Institutional Review Board (IRB) prior to study initiation. All reviews and approvals will be in accordance with Good Clinical Practice (GCP) as contained in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines (E6) and United States (US) Code of Federal Regulations (CFR) governing IRBs (Title 21, Part 56).

A letter from the IRB documenting approval of the Investigator (who must be identified by name), the protocol (must be identified by title), and the subject consent form must be received by Warner Chilcott (US), LLC, US **Regulatory** Agent of Warner Chilcott Company, LLC, an **Allergan** Affiliate (referred to hereafter as the Sponsor) or its designee prior to study initiation. A progress report will be submitted by the Investigator to the IRB at intervals specified by the IRB, but not less than annually. A copy of this progress report will be sent to the Sponsor. After completion of the study, the Investigator will submit a signed clinical safety summary of the study to the IRB.

5.3 Subject Information and Consent

The Investigator will ensure that written informed consent (and/or assent, if applicable) is obtained from each subject (and parent(s) or legal guardian(s), if applicable) in accordance with applicable regulations. Subjects under the age of majority or per IRB requirements must sign the Assent Form. In such cases, it is recommended that both parent(s) or legal guardian(s) sign the Informed Consent Form unless one parent is deceased, unknown, incompetent, or not reasonably available, or when one parent has legal responsibility for the care and custody of the child.

Subjects and their parent(s) or legal guardian(s), if applicable, will be interviewed at the initial screening visit by qualified staff at the site and will be provided with a full description

of the nature and purpose of the study. The subject and their parent(s) or legal guardian(s), if applicable, will be given adequate time to consider the risks associated with participation in the study. Each subject will provide written informed consent (and/or assent if applicable and according to IRB regulations) prior to participating in any study procedures. Original signed consent and assent forms will be retained on file at the clinical site and copies will be given to the subjects. Case histories (subject charts) will also document that informed consent/assent was obtained prior to the subjects' participation in the study.

Each subject will provide a written informed consent (and/or assent if applicable and according to IRB regulations) prior to participating in pharmacokinetic (PK) sampling procedures. Subjects that select no PK sampling as their option will still need to give consent to be able to participate in the main study.

5.4 Subject Confidentiality

The Sponsor ensures that the following have permission to review all study-related documents: monitor, auditor, IRB/IEC and regulatory authorities. The subject's identity and study-related records (including photographs) will remain confidential throughout the duration of the study data collection and reporting process.

A unique subject identification code will be assigned to each potential study subject. The identification code protects the subject's identity and is used in lieu of the subject's name when reporting subject data. The data will always maintain the confidentiality of the subject.

The Investigator or designee will review the subject data, which will be referenced using the subject identifier. At the conclusion of the study, the data obtained may be presented to regional regulatory authorities but the subject's identity will not be revealed. In addition, if any clinical data obtained from the study are published in scientific journals or presented at scientific meetings, the subject's identity will not be revealed.

5.5 Authorization to Disclose Protected Health Information

As required under Health Insurance Portability and Accountability Act regulations, subjects will be informed of the following information:

- the Sponsor of the study;
- any contractors that may be involved in the study;
- the purpose of the protected health information (PHI) being collected;
- the possibility that the PHI may be re-disclosed;
- the duration of the authorization;
- the subject's rights to revoke the authorization; and,
- the right of the subject to refuse signature and limit access to PHI during the conduct of the trial (US CFR Title 45, Parts 160 and 164);
- Authorization to disclose PHI must be obtained before the subject enters the study.

6 INVESTIGATOR AND STUDY ADMINISTRATIVE STRUCTURE

Contact information for study personnel is provided below for information only; the protocol will not be amended if study personnel change after the protocol has been issued.

Sponsor:	Warner Chilcott, LLC 100 Enterprise Drive Rockaway, NJ 07866
Medical Monitor:	**Director, Medical Safety** **Allergan, plc.** **2525 Dupont Drive** **Irvine, CA 92612**
Project Manager:	
Biostatistician:	**Director, Statistical Sciences and Programming** **Allergan, plc.** **2525 Dupont Drive** **Irvine, CA 92612**
Clinical Laboratory Contact:	
ECG Vendor:	

7 INTRODUCTION

Acne vulgaris is a common disease of both males and females, usually manifesting initially during adolescence. The primary pathologic events are initiated in the pilo-sebaceous units, especially of sebaceous-gland-bearing areas of the face, chest, and back as a result of increased androgen stimulation initiated at adrenarche or puberty. As a result of both abnormal keratinization of the infra-infundibular portion of the sebaceous follicle and increased sebum produced in the gland, a blockage of the duct results in the inapparent clinical lesion of the microcomedone. Continued blockage, colonization of the follicle by *Propionibacterium acnes*, and generation of multiple chemoattractant and proinflammatory moieties may result in non-inflammatory clinical lesions, comedones, and inflammatory lesions: papules, pustules, nodules, and cysts.[1]

Sarecycline is a tetracycline-class antibiotic being developed as a treatment for acne vulgaris. Antibiotics, especially erythromycin, minocycline, and doxycycline, have been prescribed as acne treatments for many years. These antibiotics effectively control the signs of inflammatory acne while patients continue to take them. Nonclinical studies have demonstrated that sarecycline exhibits favorable characteristics, including potent gram-positive activity, minimal gram-negative activity, efficacy in tissue-based models of infection, and effective anti-inflammatory activity, which supports its use as a novel treatment for acne.

The Sponsor conducted a Phase 2 study (Study PR-10411) that evaluated the safety and efficacy of three different oral doses of sarecycline (approximately 0.75 mg/kg/day, 1.5 mg/kg/day, and 3.0 mg/kg/day) compared with placebo in the treatment of moderate to severe facial acne vulgaris. The results of this study indicated that a daily dose of sarecycline 1.5 mg/kg was superior to placebo in decreasing the number of inflammatory lesions and improving the Investigator Global Assessment (IGA) of facial acne following 12 weeks of treatment. The 0.75 mg/kg/day dose was not superior to the placebo. No further improvement in efficacy was observed with the 3.0 mg/kg/day dose. Based on the results of this study, the 1.5 mg/kg/day sarecycline dose was selected for continued development.

8 STUDY OBJECTIVES

The primary objective is to evaluate the efficacy of oral sarecycline 1.5 mg/kg/day compared to placebo in treating inflammatory acne lesions in subjects with moderate to severe facial acne vulgaris based on Investigator's Global Assessment (IGA) score and inflammatory lesion counts.

The secondary objectives are to evaluate the safety of oral sarecycline 1.5 mg/kg/day based on adverse events, vital signs, electrocardiograms (ECG), physical examinations and clinical laboratory tests.

The other objective of the study is to characterize the pharmacokinetics of oral sarecycline 1.5 mg/kg/day in the relevant population with acne vulgaris.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This Phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel group study will evaluate efficacy and safety of an approximate 1.5 mg/kg/day dose of oral sarecycline compared to placebo in the treatment of moderate to severe facial acne vulgaris. The study will include approximately 1000 males and females 9 to 45 years of age with moderate to severe facial acne vulgaris and no disorders that would preclude the use of tetracycline-class antibiotics at approximately 50 sites.

The study includes a screening period of up to 35 days to establish eligibility and baseline conditions followed by a 12-week treatment period. Eligible subjects will be randomized in a 1:1 ratio to receive daily oral doses of either 1.5 mg/kg sarecycline tablets or placebo tablets. Subjects will return to the clinic on an outpatient basis following 3, 6, 9 and 12 weeks of treatment. At each clinic visit, facial acne will be evaluated through lesion counts and IGA scores by visual inspection; non-facial inflammatory acne will also be evaluated by IGA of the neck, chest, and back. The co-primary efficacy endpoints of the study are the absolute change from baseline in the facial inflammatory lesion count at Week 12 and a dichotomized IGA (dichotomized to reflect either 'success' or 'failure' with 'success' defined as at least a 2-point decrease from baseline in the IGA assessment and a score of clear [0] or almost clear [1] on the IGA assessment) at Week 12. Safety evaluations (adverse events, vital signs, clinical laboratory evaluations, ECG and physical examinations) will be conducted at specific treatment period visits and at study termination.

The study will collect PK samples for analysis of plasma sarecycline and R-sarecycline concentrations. The sarecycline concentration data will be used to assess population PK and may be used in PK/pharmacodynamic (PD) analyses.

A study schedule of events is provided in Appendix 1. Details and descriptions of study procedures are contained in the following sections.

9.2 Rationale for Study Design and Control Group

A prospective, randomized, double-blind, placebo-controlled, parallel group trial design is an accepted method of evaluating the efficacy and safety of therapeutic agents. The purpose of a placebo group is to account for the effects of treatment that do not depend on the study drug itself. Placebo-controlled trials also provide the maximum ability to distinguish adverse effects caused by a drug from those resulting from underlying disease or intercurrent illness. The study design is representative of designs used to determine drug treatments for acne vulgaris and is consistent with the Food and Drug Administration (FDA) draft guidance "*Acne Vulgaris: Developing Drugs for Treatment*"[2] dated September 2005.

9.3 Selection of Study Population

The study will include approximately 1000 subjects (approximately 500 subjects per arm) who meet all of the inclusion and none of the exclusion criteria.

9.3.1 Inclusion Criteria

A subject will be considered for inclusion in the study if he/she meets all of the following criteria:

IN01. Has signed the informed consent or assent form (Section 9.5.1)
IN02. Is a male or female, 9 to 45 years of age, inclusive
IN03. Has a body weight between 33 kg and 136 kg, inclusive
IN04. Has facial acne vulgaris with:
- 20 to 50 inflammatory lesions (papules, pustules, and nodules)
- up to 100 noninflammatory lesions (open and closed comedones)
- No more than two nodules
- IGA score of moderate (3) or severe (4)

IN05. Has a negative urine pregnancy test at baseline - females of childbearing potential only
IN06. Agrees to use an effective method of contraception throughout the study, if applicable (see Section 9.4.6.3)
IN07. Refrain from use of any other acne medications and medicated cleansers, and avoid excessive sun exposure and tanning booths for the duration of the study
IN08. Is able to fulfill the requirements of the protocol, has indicated a willingness to participate in the study, and agrees to all study procedures (including mandatory photography) by providing written informed consent/assent and an authorization to disclose PHI
IN09. Is able to swallow the tablets

9.3.2 Exclusion Criteria

A subject will be excluded from participation if he/she meets any of the following criteria:

EX01. Has a dermatological condition of the face (e.g., skin burn, sunburn, beard, mustache) that could interfere with the clinical evaluations
EX02. Has a history of any of the following:
- Allergy to tetracycline-class antibiotics or to any ingredient in the study drug
- Pseudomembranous colitis or antibiotic-associated colitis
- Treated for any type of cancer within the last 6 months
- Has known resistance to other tetracyclines

EX03. Has received any of the following treatments within 12 weeks of randomization:
- Systemic retinoids
- Systemic corticosteroids
- Androgens/anti-androgenic therapy (e.g., anabolic steroids, spironolactone)
- Non-medicated procedures for the treatment of acne (e.g., laser, light or ThermaClear)

EX04. Has used any acne affecting treatment without an appropriate washout period (Table 9-3)

EX05. Has initiated hormonal contraceptive use within 12 weeks prior to randomization or plans to initiate or switch hormonal contraceptive products during the study period

EX06. Is pregnant, lactating, or is planning a pregnancy during the study period

EX07. Has any other disorder causing hyperandrogenism including, but not limited to, polycystic ovary syndrome, adrenal or ovarian tumors, Cushing's disease, or congenital adrenal hyperplasia

EX08. Has drug-induced acne

EX09. Has significant intercurrent illness (including clinically significant abnormality in clinical laboratory tests), psychiatric disposition, or other factors that, in the opinion of the Investigator or Medical Monitor, precludes participation in the study

EX10. Is currently participating, or has participated within 30 days prior to the randomization period, in an investigational drug or device study. (Concurrent participation in the sarecycline pharmacokinetic study may be allowed, if approved by Medical Monitor)

EX11. Has previously participated in any clinical trial involving the use of sarecycline

EX12. Is judged by the Investigator to be unsuitable for any reason

9.3.3 Subject Identification

A study identification number will be assigned at the initial screening visit using the system. Subject numbers

Subject study identification numbers will be used throughout the trial. Once a number is assigned, it may not be used by another subject or re-used by a different subject if the first subject withdraws from the study early. Only will be used to assign study subject numbers.

9.3.4 Removal of Subjects from Treatment or Assessment

Withdrawn subjects are those who do not complete all evaluations and procedures outlined in the protocol. Subjects who discontinue taking study drug for any reason must also be withdrawn from the study. All adverse events that are present when the subject withdraws from the study will be followed as described in Section 9.6.2.1.

Subjects must be withdrawn from the study for any of the following events:

- Elevated AST or ALT 3 times upper limit of normal (ULN) or greater and elevated bilirubin greater than 2 times ULN and no other explanation of these abnormal tests
- An SAE assessed as related to study treatment by the Investigator or Medical Monitor
- Clinically significant worsening of acne status requiring change of treatment in acne management (eg. increased size or number of nodules)

Subjects may be withdrawn from the study for one of the following events:

- Adverse Event: An AE that, in the opinion of the Investigator or Sponsor, suggests that continued participation in the study is not in the subject's best interest for safety reasons. Only a primary AE leading to withdrawal should be noted to be the reason for withdrawal.
- Abnormal Laboratory Result: Any clinically significant laboratory abnormality that requires withdrawal of the subject from the study should be considered an AE leading to withdrawal. If possible, laboratory tests will be repeated for any results that were clinically significantly abnormal until the abnormality is resolved or stabilized to the satisfaction of the Investigator in consultation with the Medical Monitor.
- Lost to Follow-up: Confirmed at minimum by 2 phone calls and a traceable letter without answer.
- Subject Request: Subject requests for any reason to be withdrawn or withdraws his/her consent.
- Protocol Deviation: A subject may be withdrawn from the study at the discretion of the Investigator or Sponsor due to poor compliance with protocol requirements that may compromise the study results or subject safety.
- Other: Other reasons include but are not limited to: Investigator decision that it is in the subject's best interest to be withdrawn, administrative reasons, relocation of subject, etc. If a subject becomes pregnant during the study, the subject will be withdrawn from the study and followed through to the conclusion of the pregnancy.

If a subject withdraws, or is withdrawn from the study by the Investigator, the reasons and circumstances for such early termination (ET) must be fully documented. Subjects who are withdrawn from the study will not be reenrolled.

9.4 Study Treatments

9.4.1 Treatments Administered

Subjects meeting the eligibility requirements will be randomized in a 1:1 ratio to receive either active sarecycline tablets or placebo tablets administered orally as 60 mg, 100 mg or 150 mg of sarecycline or matching placebo tablets based on the subject's body weight.

Subjects will ingest one tablet daily at approximately the same time each day, at least 1 hour prior to, or 2 hours after eating.

9.4.1.1 **Subjects Participating in PK Schedule 3**

Subjects who participate in PK Schedule 3 will receive one dose of active study treatment at Visit 4 (Week 12) regardless of randomized study treatment (active or placebo) after all visit assessments are completed. The study treatment will be adjusted to the subject's body weight on the visit date.

9.4.2 Identity of Study drugs

9.4.2.1 Description of Study drugs

[redacted]

9.4.2.2 Packaging, Labeling and Dispensing

The study drug will be packaged in bottles for dispensing at specific visits. The bottles will contain either 30 active or 30 placebo tablets. The bottles will be labeled with the dosing instructions, the investigational drug statement and the Sponsor's name and address. Each bottle will be identified with a unique number (bottle number), which is traceable to the tablet strength and lot number. The study drug will be dispensed to subjects according to the schedule described in Table 9-1.

Table 9-1: Study drug Quantity and Dispensing Schedule

Visit	Quantity Dispensed
Screen Visit (SV) 2	30
1	30
2	30
3	30

Authorized site personnel will use the IRT system to assign a bottle number that corresponds to the randomization schedule.

SUBJECTS PARTICIPATING IN PK SCHEDULE 3

Subjects who participate in PK Schedule 3 will receive one dose of active study treatment at Visit 4 (Week 12) regardless of randomized study treatment (active or placebo). To obtain the active study treatment, the site will contact their clinical research associate (CRA) a full week before the visit. The CRA will notify the clinical supply group to ship 1 bottle of active investigational product. The shipment will be documented on the drug accountability log.

9.4.2.3 Storage and Accountability

The study drugs should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F). Where storage conditions exceed 30°C or drop below 15°C, the Sponsor should be notified immediately.

The investigator or designee will confirm the receipt of the study drug, will verify the condition under which the drug was received and will verify the contents of the shipment using the IRT system, immediately upon receipt of the product.

The Investigator shall maintain accurate study drug inventory records, including the quantities and date of receipt of supplies from the Sponsor, and the quantities and dates of dispensing to study participants. All study drug supplies must be accounted for at study termination and a written explanation provided for any discrepancies. All unused supplies shall be returned to the Sponsor or, if authorized in writing by the Sponsor, destroyed properly at the study site. Shipping and handling of all study drugs will conform to FDA regulations for investigational drug products (CFR 312.57(a), 312.59, 312.61, 312.62(a)).

Reasons for departure from the expected dispensing regimen will also be recorded. At completion of the study, to satisfy regulatory requirements regarding study drug accountability, all study drugs will be stored, inventoried, reconciled, and destroyed or returned to the Sponsor according to applicable state and federal regulations. A written explanation must be provided for any discrepancies. The study monitor must review all records of study drug accountability prior to the return or destruction of any supplies.

SUBJECTS PARTICIPATING IN PK SCHEDULE 3

Subjects who participate in PK Schedule 3 will receive one dose of active study treatment at Visit 4 (Week 12) regardless of randomized study treatment (active or placebo). The shipment of 1 bottle of active investigational product for this study treatment will be documented on the drug accountability log.

9.4.3 Method of Assigning Subjects to Treatment

At Screening Visit 2 (baseline assessment), authorized site personnel will use the IRT system to randomize the subject. The randomization program will assign the subject to a double-blind treatment group and will assign a bottle number that corresponds to the assigned treatment group. Subjects will be randomized to either sarecycline or placebo in a 1:1 ratio using block randomization. At Visit 1, Visit 2 and Visit 3, site personnel will again use the IRT system to dispense subsequent bottles associated with the assigned treatment group. Only bottle numbers provided by the IRT should be dispensed to subjects.

The randomization schedule will be prepared by a statistician not involved with this study (e.g., an independent, randomization statistician) using SAS® PROC PLAN.

9.4.3.1 Subjects Participating in PK Schedule 3

Subjects who participate in PK Schedule 3 will receive one dose of active study treatment at Visit 4 (Week 12) regardless of randomized study treatment (active or placebo).

9.4.4 Selection of Doses and Timing of Administration in the Study

The approximate 1.5 mg/kg/day dose was selected for inclusion in this study based on the results of a Phase 2 study that evaluated three doses of sarecycline (approximately 0.75 mg/kg/day, 1.5 mg/kg/day and 3.0 mg/kg/day) in comparison to placebo in the treatment of moderate to severe facial acne vulgaris.[3] The results indicated that the 1.5 mg/kg dose was superior to placebo in reducing inflammatory lesion counts and the proportion of subjects with a successful outcome based on IGA score from baseline to study conclusion. The 0.75 mg/kg dose was not effective for either co-primary efficacy endpoint and the higher dose did not result in additional efficacy beyond that seen with the 1.5 mg/kg dose group.

The appropriate tablet strength will be determined based on the body weight of the subject as described in Table 9-2.

Table 9-2: Study drug Dose Selection

Body Weight	Tablet Strength	Total Dose per Weight Mass
33 to 54 kg	60 mg tablet	1.8 to 1.1 mg/kg
55 to 84 kg	100 mg tablet	1.8 to 1.2 mg/kg
85 to 136 kg	150 mg tablet	1.8 to 1.1 mg/kg

One tablet should be taken orally at approximately the same time each day, at least 1 hour prior to, or 2 hours after eating.

9.4.4.1 Subjects Participating in PK Schedule 3

Subjects who participate in PK Schedule 3 will receive one dose of active study treatment at Visit 4 (Week 12) regardless of randomized study treatment (active or placebo).

9.4.5 Blinding

This study employs a double-blind design with treatment allocated randomly and blinding maintained throughout the study by the use of identically appearing active and placebo tablets. In the event of an emergency where the subject's well-being requires knowledge of the treatment assignment, the Investigator should make an attempt, if time permits, to contact the Medical Monitor prior to unblinding to discuss the reason(s) for unblinding. If an Investigator, site personnel performing assessments, or a subject is unblinded, the subject must be discontinued from the study. The date of the code break and the reason for the break must be recorded in the subject's source documents.

Before breaking the blind for a subject, the Investigator should determine that the information is necessary (i.e., that it will alter the subject's immediate course of treatment and will contribute to the management of the adverse event). In many cases, particularly when the emergency is clearly not related to study drug, the problem may be effectively managed by assuming that the subject is receiving active study drug without the need for unblinding. Every effort should be made to alert the Medical Monitor before requesting that the blind be broken. If this is not possible, the Medical Monitor should be immediately notified of the breaking of the blind.

If unblinding is necessary, the study drug identity can be obtained by the Investigator through the IRT. The subject will be withdrawn from the study and Week 12/ET assessments will be completed.

The bioanalytical laboratory responsible for analyzing PK samples for sarecycline/ R-sarecycline concentrations will be unblinded so that they can identify which samples were obtained from subjects on active treatment.

9.4.6 Prior and Concomitant Therapy

All medications used in the 30 days prior to SV1, any hormonal contraceptives or any acne medications used in the 3 months prior to SV1 will be documented in the case report form including the name of the drug, the route of administration, date of initiation and discontinuation, and the reason for administration. New medications and changes in medication use during the study will be recorded in a similar manner. If an exclusionary medication is required, the subject should be discontinued from the study.

Non-medicated facial hygiene products are permitted to be used in this study if approved by the Sponsor. Non-medicated facial hygiene products such as cleansers could be provided to randomized subjects for use during the study.

9.4.6.1 Excluded Medications and Therapies

Subjects must abstain from use of all excluded medications and therapies (Section 9.3.2) after the initial screening visit and throughout the treatment period.

Subjects may use non-medicated cleansers approved by the Sponsor as a facial cleanser during the study. All other treatments for acne including topical and medicated cleansers and therapies are prohibited during the study. Subjects should be encouraged to maintain a consistent facial cleansing regimen throughout the study.

The use of systemic antibiotics for indications other than acne will be considered on a case-by-case basis with the Medical Monitor. In addition, initiation or change of hormonal contraception use within 12 weeks of screening is exclusionary, and initiation or change of hormonal contraception during the study is prohibited.

9.4.6.2 Medication Washout Prior to Study Randomization

Subjects receiving excluded medications/therapies at screening may washout from those therapies to continue eligibility in the study as described in Table 9-3. Under no circumstances should a subject be placed at risk by the withdrawal of a current medication.

Table 9-3: Medication Washout Requirements

Medication Type	Minimum Washout (days prior to SV2 baseline)
Medicated facial cleansers Topical acne treatments (other than those listed below)	7 days
Topical antibiotics and azelaic acid containing medication Topical non-prescription anti-inflammatories (other than those listed below)	2 weeks
Topical retinoids Topical corticosteroids Systemic antibiotics	4 weeks

Note: Use of systemic retinoids, systemic corticosteroids, or systemic androgens/anti-androgens within 12 weeks of **randomization** is exclusionary.

9.4.6.3 Use of Contraception

Tetracycline-class antibiotics can cause fetal harm when administered to a pregnant woman. Tetracycline-class antibiotics used during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years) may cause permanent discoloration of teeth (yellow-gray-brown). Also, the effect of sarecycline on sperm is unknown. Due to the teratogenic effects of tetracycline-class antibiotics, male subjects who have female partners of childbearing potential must also use an effective method of birth control throughout the study.

Prior to study enrollment, subjects must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. Females of childbearing potential include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea >12 consecutive months).

Female subjects of childbearing potential must have a negative urine pregnancy test. Male subjects and females of childbearing potential and/or their partners must use an effective method of birth control throughout the study, such as:

- Abstinence
- Diaphragm with spermicide
- Condom (male or female) with spermicide
- Intrauterine device (hormonal or non-hormonal)

- Implants
- Injections
- Transdermal patch
- Intravaginal ring
- Oral contraceptives – however, oral antibiotics such as sarecycline may lessen the effectiveness of oral contraceptives; therefore, a second form of birth control must be utilized by subjects using oral contraceptives.

After the last dose of study drug, subjects should be advised to continue using an effective method of birth control (30 days for females and 90 days for males). In addition, male subjects must be advised not to donate sperm for a period of 90 days after the last dose of study drug.

9.4.7 Treatment Compliance

Compliance with the assigned treatment regimen will be assessed by comparing the number of tablets expected to be used, based on the total number of treatment days, with the actual number used (expressed as a percentage of used/expected) at each clinic visit and for the study overall.

9.5 Study Activities

This study will consist of a screening period to establish eligibility, washout from excluded therapies, and conduct of baseline evaluations; and a study drug treatment period of 12 weeks in duration. The following sections provide details of the study activities which are summarized in the Schedule of Events (Appendix 1).

Any visit/procedure that has a defined time period for evaluation should be completed within the specified window in the protocol.

9.5.1 Screening Period

Prior to conducting any screening procedures, subjects will be given a full description of the nature and purpose of the study and will be required to provide written consent. The investigator or a designated, medically qualified member of the study staff will interview potential participants to establish their eligibility for inclusion in the study. Potential subjects will be screened according to the inclusion and exclusion criteria (Section 9.3.1 and Section 9.3.2.) within 35 days prior to beginning treatment. The investigator will maintain a log of all subjects screened for participation and record the reason(s) for excluding potential subjects.

Subjects will undergo the following procedures at the study visits indicated.

9.5.1.1 Screen Visit 1 (SV1)

- Consent subject
- Assign subject number using the IRT
- Obtain demographic data
- Obtain medical and surgical history
- Collect prior and concomitant medication use (Section 9.4.6)
- Obtain blood and urine samples for clinical laboratory evaluations, hematology, chemistry, urinalysis, and lipids (Appendix 2)
- Obtain blood sample for thyroid function evaluation (Appendix 2)
- Perform urine pregnancy test – females of childbearing potential only
- Record 12-lead ECG
- Adverse event query
- Perform physical exam
- Measure height and weight
- Obtain vital signs

If no drug/therapy washout is required:

- Review inclusion/exclusion criteria
- Schedule SV2

If drug/therapy washout is required:

- Schedule SV2 based on duration of required treatment washout

9.5.1.2 Screen Visit 2 (SV2)/Baseline

For subjects who required medication/therapy washout:

Perform physical exam

All subjects:

- Measure weight
- Obtain vital signs
- Perform the IGA for face

- Perform facial lesion count of inflammatory and noninflammatory lesions
- Obtain facial photographs
- Perform the IGA for neck, chest, and back
- Update concomitant medication use
- Record adverse events
- Perform urine pregnancy test – females of childbearing potential only
- Administer Skindex questionnaire
- If washout duration exceeded 5 weeks, re-draw blood and urine samples for clinical laboratory evaluations
- Review inclusion/exclusion

If all screening assessments are acceptable and all inclusion criteria and no exclusion criteria have been met, the subject may be randomized to study treatment using the IRT system.

- Dispense one bottle (30 tablets) of study drug using the IRT. Instruct the subject on the frequency and timing of study drug administration
- Provide a diary to subjects who consented to PK sampling and remind them to record the dose administration times for the 2 doses taken prior to Visit 1/Week 3 in the diary
- Schedule next clinic visit

9.5.2 Treatment Period

9.5.2.1 Telephone Contact (Week 1 ± 3 days)

Site personnel will contact each subject to ascertain appropriate study drug compliance. Subjects will be queried about the number of tablets used and adherence to study requirements. Subjects will also be queried about adverse events. The subjects participating in PK sampling will be instructed to record the dose administration times for the 2 doses taken prior to Visit 1/Week 3 in the diary.

9.5.2.2 Visit 1 (Week 3 ± 3 days)

The following procedures will be performed:

- Measure blood pressure and heart rate
- Collect blood and urine samples for clinical laboratory tests, hematology, chemistry, urinalysis, and lipids (Appendix 2)
- Perform urine pregnancy test – females of childbearing potential only
- Perform the IGA for face

- Perform facial lesion count of inflammatory and noninflammatory lesions
- Perform IGA for the neck, chest, and back
- Obtain facial photographs
- Record concomitant medications
- Adverse event query
- Review and collect completed subject diary pages
- For subjects participating in PK sampling, collect blood samples as directed in Section 9.6.3.4 for Visit 1/Week 3 for PK Schedule 1**,** PK Schedule 2**, and PK Schedule 3**
- Collect previously dispensed study drug (including empty bottles) and perform study drug accountability
- Dispense one bottle (30 tablets) of study drug using the IRT
- Schedule the next study visit

9.5.2.3 Visit 2 (Week 6 ± 3 days)

The following procedures will be performed:

- Measure blood pressure and heart rate
- Perform urine pregnancy test – females of childbearing potential only
- Perform the IGA for face
- Perform facial lesion count of inflammatory and noninflammatory lesions
- Obtain facial photographs
- Perform IGA for the neck, chest, and back
- Record concomitant medications
- Adverse event query
- Collect previously dispensed study drug and perform study drug accountability and assess study drug compliance
- Dispense one bottle (30 tablets) of study drug using the IRT
- Schedule the next study visit

9.5.2.4 Visit 3 (Week 9 ± 3 days)

The following procedures will be performed:

- Measure blood pressure and heart rate
- Perform urine pregnancy test – females of childbearing potential only
- Perform the IGA for face
- Perform facial lesion count of inflammatory and noninflammatory lesions
- Obtain facial photographs
- Perform IGA for the neck, chest, and back
- Record concomitant medications
- Adverse event query
- Collect previously dispensed study drug and perform study drug accountability and assess study drug compliance
- Dispense one bottle (30 tablets) of study drug using the IRT
- For subjects participating in PK sampling, remind them to record the dose administration times for the 2 doses taken prior to Visit 4/Week 12 in the diary. **Also remind subjects participating in PK Schedule 3 that study drug should not be administered at home or recorded in the diary the day of Visit 4/Week 12 (subjects receive study drug in clinic at Visit 4/Week 12).**
- Schedule the next study visit

9.5.2.5 Visit 4 (Week 12 ± 3 days)

- Perform physical examination, including weight
- Measure blood pressure and heart rate
- Perform 12-lead ECG
- Collect blood and urine samples for clinical laboratory tests hematology, serum chemistry, urinalysis, and lipids (Appendix 2)
- Obtain blood sample for thyroid function evaluation (Appendix 2)
- Perform urine pregnancy test – females of childbearing potential only
- Perform the IGA for face
- Perform facial lesion count of inflammatory and noninflammatory lesions
- Obtain facial photographs
- Perform IGA for the neck, chest, and back

- Record concomitant medications
- Administer Skindex questionnaire
- Adverse event query
- Review and collect completed subject diary pages
- For subjects participating in PK sampling, collect blood samples as directed in Section 9.6.3.4 for Visit 4/Week 12 for PK Schedule 1**,** PK Schedule 2**, and PK Schedule 3**
- Collect previously dispensed study drug and perform study drug accountability and assess study drug compliance
- Record date of last study drug dose **and the dose taken in clinic at the Visit 4/Week 12**
- **For subjects participating in PK Schedule 3, schedule the next study visit at Visit 5/Week 13 ± 3 days**
- Complete Study Termination Form **(unless subject is participating in PK Schedule 3)**

9.5.2.6 **Visit 5 (Week 13 ± 3 days) (for subjects participating in PK Schedule 3)**

- **Perform physical examination, including weight**
- **Measure blood pressure and heart rate**
- **Perform urine pregnancy test – females of childbearing potential only**
- **Record concomitant medications**
- **Adverse event query**
- **Complete Study Termination Form**

9.5.2.7 Early Termination Visit

Study site personnel will attempt to follow the progress of every subject admitted to the study through to study completion. If a subject fails to return for a scheduled visit, a reasonable effort should be made to contact the subject and ascertain the reason(s) for not returning.

If a subject does not complete the study for any reason (including Investigator discretion), the reason and circumstances for the subject's early termination must be fully documented. If possible, the assessments specified for the Visit 4 should be performed. Withdrawn subjects may not be re-enrolled in the study and will not be replaced.

In the event subjects are unable to swallow the sarecycline tablets after enrollment, they will be discontinued from the study and the reason for study discontinuation will be recorded as the inability to swallow tablets.

9.6 Study Assessments

Treatment efficacy will be evaluated based on the co-primary endpoints of IGA scores and absolute change in inflammatory lesion counts recorded at baseline and at Week 12. Safety will be evaluated in terms of adverse events, clinical laboratory evaluations, vital sign measurements, physical examinations and ECGs made during the treatment period.

9.6.1 Efficacy Assessments

9.6.1.1 Facial Investigator's Global Assessment

The IGA scale for inflammatory lesions of acne vulgaris will be used by the Investigator to assess the severity of a subject's facial acne (Table 9-4). The IGA should be representative of the investigator's overall general assessment of the subject's inflammatory lesions and take into account the quality, as well as the quantity, of lesions. The IGA must be performed prior to the lesion counts (Section 9.6.1.3) and will be performed at baseline and at each treatment period visit.

The same evaluator should perform all evaluations for a subject and when this is not possible, another Sponsor-approved evaluator may perform the evaluations.

Table 9-4: Investigator's Global Assessment of Inflammatory Acne

Score	Grade	Description
0	Clear	No evidence of papules or pustules
1	Almost Clear	Rare: inflammatory papules (papules must be resolving and may be hyperpigmented, though not pink-red)
2	Mild	Few: inflammatory lesions (papules/pustules only; no nodulocytic lesions)
3	Moderate	Multiple: inflammatory lesions present; many papules/pustules; there may or may not be a few nodulocytic lesions
4*	Severe	Inflammatory lesions are more apparent, many papules/pustules; there may or may not be a few nodulocytic lesions

*Acne that worsens beyond Grade 4 must be recorded as an adverse event on the case report form (CRF).

9.6.1.2 Non-facial Investigator's Global Assessment

The following body areas will be evaluated for acne using the IGA (Table 9-4)

- Chest
- Back
- Neck

9.6.1.3 Facial Lesion Counts

The facial area lesion counts will be made at the forehead, left and right cheeks, nose and chin at baseline and at each treatment period visit. Facial inflammatory lesions (pustules, papules, and nodular lesions) and noninflammatory lesions (open and closed comedones) will be counted and recorded separately. At baseline, the total of both inflammatory and non-inflammatory lesions will also be calculated.

Lesion counts will be based on the following definitions:

Inflammatory lesions

- Papule: A solid, elevated lesion less than 0.5 cm in diameter (by inspection) with surrounding erythematous halo
- Pustule: An elevated lesion containing pus less than 0.5 cm in diameter (by inspection) with surrounding erythematous halo
- Nodule: Palpable solid erythematous lesion greater than 0.5 cm in diameter (by inspection); has depth, not necessarily elevated

Noninflammatory lesions

- Open comedones (blackhead): Non-infected plugged hair follicle with dilated/open orifice; black in color
- Closed comedones (whitehead): Non-infected plugged hair follicle: small (microscopic) opening at skin surface

9.6.2 Safety Assessments

Safety evaluations will include adverse events, clinical laboratory tests, physical examinations, vital signs, ECGs, and urine pregnancy tests.

9.6.2.1 Adverse Events

Adverse events will be assessed from the time of signing the consent/assent form until exit from the study. At every study visit, subjects will be asked a standard question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed any current medication regimens (both prescription and over-the-counter medications).

Definition of Terms

Adverse Event: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. In addition to novel events, an adverse event may be an exacerbation of a pre-existing medical condition that was present before the subject was assigned to a treatment group. Each adverse event is described using the following classifications: severity, relatedness, and seriousness.

Severity: An adverse event may present in different severities, as categorized below.

Mild: Noticeable to the subject, does not interfere with the subject's daily activities, and usually does not require additional therapy or dose adjustment.

Moderate: May interfere with the subject's daily activities and may require additional therapy.

Severe: May severely limit the subject's daily activities and typically requires therapy or intervention.

Relatedness: The determination of whether an adverse event is related to treatment is based on information regarding the degree to which the study drug has caused or contributed to the event and will be categorized according to the following criteria:

Not Related: There is no medical evidence to suggest that the AE may be related to study drug usage.

Possibly Related: There is medical evidence to suggest that the AE may be related to study drug usage. However, other medical explanations cannot be excluded as a possible cause.

Related: There is strong medical evidence to suggest that the AE is related to study drug usage.

Serious: An adverse event is considered "serious" if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Death: the adverse event causes or contributes to the death. Death is usually considered to be the outcome of an event; the event that leads to death is defined as the serious adverse event (SAE).
- A life-threatening adverse event: if, in the view of the investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization: the adverse event requires at least a 24-hour inpatient hospitalization or prolongs a hospitalization beyond the expected length of stay. Hospital admissions for surgery planned before study entry, for social reasons or for normal disease management procedures are not to be considered an SAE according to this criterion. Where the protocol or the standard management of the disease under study requires planned hospitalizations for disease or treatment management, this should not be considered a serious criterion leading to expedited reporting.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect: an adverse outcome in a child or fetus of a patient exposed to the study drug before conception or during pregnancy.

- Important medical event: such an event may not result in death, be life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment; it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purpose of this study, all events that meet the regulatory definition of an SAE that occur during the treatment period will be reported to the Sponsor as SAEs. Any SAE requires expedited reporting to Sponsor regardless of its relationship to the study drug. Non-serious adverse events are all other adverse events not deemed serious.

Investigator Obligations

Assessing and Following: The Investigator is responsible for assessing all adverse events that occur at any time during the study. The Investigator must make a determination of relatedness, seriousness, and severity on the Adverse Events page of the case report form for each adverse event. All adverse events must be followed to adequate resolution or stabilization. If the adverse event has not resolved or stabilized by the time the subject completes the final study visit, the Investigator will follow the status of the subject's adverse event for at least 30 days beyond the subject's final study visit, unless directed otherwise by the Sponsor. If Investigator becomes aware of any SAEs that occurred within 30 days after the subject completed the study, the SAE must be reported to the Sponsor.

Documenting: All adverse events during the study will be documented in the subject's medical record. This information will then be transcribed on the adverse events page of the case report form by designated study personnel. Required information includes a description of the event, date of onset, date of resolution, if death occurred, the action taken to manage the adverse event, as well as relatedness, seriousness, and severity.

Adverse event information must be recorded regardless of its relatedness to the use of the study drug. Adverse events resulting from concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported.

Reporting: 1) The investigator is responsible for reporting adverse events to the IRB according to agreements and instructions from that board or committee that oversees this research, as well as according to applicable regulations. 2) Additionally, all adverse events will be reported to the Sponsor on the case report form, and all serious adverse events, whether expected or unexpected, related or unrelated, must be reported to the Sponsor, by telephone or facsimile using the "Serious Adverse Event Report" form provided by the Sponsor, within 24 hours after the Investigator first learns of the event.

Warner Chilcott Clinical Pharmacovigilance:
Phone: [redacted] or [redacted]
Fax: [redacted]

Email:

The Investigator is responsible for reporting any new or relevant follow-up information on the adverse event as the information becomes known to the Investigator. The Investigator should cooperate and furnish additional information, including copies of pertinent records if necessary, to assist Sponsor personnel in their evaluation of the event.

Medical Emergencies and Emergency Protocol Deviations

An investigator shall notify the Medical Monitor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible after the emergency occurred. Except in such an emergency, prior approval by the Medical Monitor is required for any changes in or deviations from the protocol.

Sponsor Reporting Obligations

The sponsor will forward all reportable adverse events to the appropriate regulatory authorities and participating investigators according to 21 CFR 312, and any other applicable regulations.

9.6.2.2 Clinical Laboratory Evaluations

Clinical laboratory evaluations (chemistries, hematology, lipid profile, thyroid hormones and urinalysis) outlined in Appendix 2 will be performed on all subjects prior to enrollment to verify eligibility. Clinical laboratory evaluations will be repeated at Visit 1 and at Visit 4/ET to identify changes that may have occurred as a result of participation in the study. If a clinically significantly abnormal laboratory result is a reason for a subject being withdrawn from the study or requiring treatment for the abnormality, this abnormal result must also be reported as an adverse event.

Urine pregnancy test will be performed on females of childbearing potential only at each visit.

9.6.2.3 Physical Examinations

Physical examinations will be performed at screening (SV1 and SV2, as necessary) and at Visit 4/ET **and Visit 5 (for subjects participating in PK Schedule 3)**. Physical examinations will include an evaluation of the following: body as a whole, skin, head, ears, eyes, nose and throat, cardiovascular, respiratory, musculoskeletal, neurologic, lymphatic/thyroid, abdomen, body weight, and height (screening only).

Clinically significant findings identified during screening will be captured in Medical History. Clinically significant changes from baseline during the study will be captured as an adverse event.

9.6.2.4 Height and Body Weight

Body weight and height will be measured at SV1. Only body weight will be measured at SV2 and Visit 4/ET **and Visit 5 (for subjects participating in PK Schedule 3)**.

9.6.2.5 Vital Signs

Vital signs will be measured at screening (SV1 and SV2) and at each treatment period visit and at Visit 4/ET **and Visit 5 (for subjects participating in PK Schedule 3)**.

Vital signs at screening will include oral or auricular temperature, heart rate, systolic and diastolic blood pressure (with the subject seated for at least 5 minutes prior to measurement). Only blood pressure and heart rate will be recorded at treatment period visits.

9.6.2.6 Electrocardiograms

Standard 12-lead ECGs will be performed at screening and at Visit 4/ET.

9.6.2.7 Pregnancy

If, during the course of the study, a subject is found to be pregnant, the study drug will be discontinued and study participation terminated. The site will submit a Pregnancy Notification Form to:

Warner Chilcott Clinical Pharmacovigilance:
Fax:
Email:

The pregnancy itself should not be recorded as an adverse event or serious adverse event; however, the event will be categorized as a protocol deviation on the study termination page.

All pregnancies, including the pregnancy of a partner of the subject, will be monitored to outcome, i.e., 9 month follow up or until outcome information is obtained. Information will also be collected on any maternal or fetal complications. Miscarriage and any congenital abnormalities or birth defects will be classified as serious adverse events. Pregnancy outcome information will be recorded on specific forms and the data will be analyzed within the drug safety assessment. Every attempt should be made to obtain outcome data including hospital or medical records.

9.6.3 Other Evaluations

Other assessments include the following:

- Photography
- Skindex-16 Questionnaire
- Concomitant medication use

9.6.3.1 Photography

Photographs of the face documenting acne distribution will be made at baseline and at each treatment period visit.

9.6.3.2 Skindex-16 Questionnaire

The Skindex-16 is a single-page 16-item quality of life questionnaire that asks patients about bother from their skin condition; responses are reported as three scales: Symptoms, Emotions, and Functioning. The following questions (items) correspond to each scale:

Scale	Items
Symptoms	1-2-3-4
Emotion	5-6-7-8-9-10-11
Functioning	12-13-14-15-16

Item scores are transformed to a 0 – 100 scale. A scale score is determined by the average of scores in each scale. A total score is the average of all 16 items.

The questionnaire will be administered at baseline and at Visit 4/ET.

A copy of the questionnaire is contained in Appendix 4.

9.6.3.3 Concomitant Medication Use

Subjects will be queried at each clinic visit concerning the use of medications (see Section 9.4.6).

9.6.3.4 Pharmacokinetic Sampling

PK SCHEDULE 1

Subjects who elected to participate in PK Schedule 1 will have blood samples collected at the timepoints specified in Table 9-5.

Visit 1/Week 3

Make all efforts to schedule the visit to accommodate the subjects' routine schedule of dosing. For example, if the subject regularly takes the drug at night, an afternoon visit is preferable for PK sampling. In case it is not possible to schedule an afternoon appointment, a minimum of 12 hours should elapse between the dose taken at the visit and the previous dose.

Subjects will be instructed to:

- NOT take their Visit 1/Week 3 dose at home and to wait to take their Visit 1/Week 3 dose at the site
- Take their investigational product (IP) with them to the clinic at Visit 1/Week 3 and take the dose while observed by clinic staff

- Resume their dosing at the regularly scheduled time the next day

Visit 4/Week 12

Subjects will be instructed to take their doses at home approximately 3 hours prior to the visit. At least 12 hours should elapse between the dose taken 3 hours prior to the visit and the dose from the day prior to that.

Table 9-5 Sampling Times for PK Schedule 1

Visit	Sample Times
Visit 1 (Week 3 ± 3 days)	(1) Predose: Within 0.5 hours before dose administration (2) Postdose: Between 0.5 hours and 1 hour after dose administration (3) Postdose: Between 1.5 hours and 3 hours after dose administration
Visit 4 (Week 12 ± 3 days)	(1) Postdose: Between 4 hours and 5 hours after dose administration (2) Postdose: Between 6 hours and 8 hours after dose administration

PK SCHEDULE 2

Subjects who are in PK Schedule 2 will be instructed to take their dose at their usual/regular time and proceed with Visit 1/Week 3 and Visit 4/Week 12 (Table 9-6). During the visit, a blood sample for PK analyses can be taken at any time.

Table 9-6 Sampling Times for PK Schedule 2

Visit	Sample Time
Visit 1 (Week 3 ± 3 days)	At any time during the visit
Visit 4 (Week 12 ± 3 days)	At any time during the visit

PK SCHEDULE 3

PK Schedule 3 will only be an option for 9 to 11 year-old subjects who elect PK sampling. Subjects who elected to participate in PK Schedule 3 will have blood samples collected at the timepoints specified in (Table 9-7).

Visit 1/Week 3

Subjects who are in PK Schedule 3 will be instructed to take their dose at their usual/regular time prior to Visit 1/Week 3.

Visit 4/Week 12

Subjects who are in PK Schedule 3 will be instructed not to take their dose on the day of their Visit 4/Week 12. Instead, subjects will be dosed in clinic with active study treatment after all visit assessments are done. Make all efforts to schedule the visit to accommodate the subjects' routine schedule of dosing. For example, if the subject regularly takes the drug at night, an afternoon visit is preferable for PK sampling. In case it is not possible to schedule an afternoon appointment, a minimum of 12 hours should elapse between the dose taken at the visit and the previous dose.

Subjects will have a follow-up visit (Visit 5/Week 13) 1 week after Visit 4 as described in Section 9.5.2.6.

Table 9-7 Sampling Times for PK Schedule 3

Visit	Sample Time
Visit 1 (Week 3 ± 3 days)	At any time during the visit
Visit 4 (Week 12 ± 3 days)	(1) Postdose: Between 0.5 hours and 1 hour after dose administration (2) Postdose: Between 1.5 hours and 2 hours after dose administration (3) Postdose: Between 3 hours and 4 hours after dose administration

Blood samples will be collected, processed, stored, and shipped as described in Appendix 3.

Diary for Recording Dose Administrations for PK Analysis

For subjects participating in PK Schedule 1**,** PK Schedule 2**, and PK Schedule 3,** a diary will be dispensed at Screening Visit 2/Baseline and at Visit 3/Week 9, the visits prior to PK sampling. The subjects participating in PK sampling will be instructed to record the dose administration times for the 2 doses taken prior to Visit 1/Week 3 and Visit 4/Week 12 in the diary and on the day of Visit 4/Week 12.

The subjects participating in PK sampling will be instructed to record the dose administration times for the 2 doses taken prior to Visit 1/Week 3 in the diary.

During Visit 1/Week 3 and Visit 4/Week 12, the responsible personnel at the site will review and collect the pages from the subjects' diary. The dose date and time will be recorded in the eCRFs.

10 QUALITY CONTROL AND ASSURANCE

The Sponsor will implement and maintain quality control procedures to ensure that this study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulatory requirements.

The Sponsor or designee will routinely conduct monitoring and/or auditing visits to the study centers to verify the adherence to the study protocol, the protection of the rights and well-being of the subjects, and the accuracy and completeness of reported study data recorded on the source documentation.

11 PLANNED STATISTICAL METHODS

Detailed plans for the statistical methods will be provided in a Statistical Analysis Plan which will be finalized prior to database lock.

11.1 Determination of Sample Size

The sample size was selected to provide an adequate number of subjects to compare the efficacy of sarecycline treatment to placebo and to provide an adequate number of subjects needed for a safety database.

Sample size estimates were calculated for each of the co-primary efficacy endpoints, absolute change from baseline (CFB) in facial inflammatory lesion counts and facial IGA success (based on at least 2-point decrease from baseline in IGA score), and the **first** secondary efficacy endpoint, percent CFB in facial inflammatory lesion counts at Week 12 **using a** last observation carried forward (LOCF) **method of imputation**. The results from a recent study (Study PR-10411) of sarecycline compared to placebo treatment were used to estimate the sample size needed to show a significant difference between the treatments at α=0.05 and 90% power using two-sided tests and a 1:1 randomization. It should be noted that one outlier in the data for Study PR-10411 was removed from the estimate for absolute CFB in inflammatory lesion counts in order to provide more accurate estimates for the sample size determination. Results of the calculations and the estimates used in the calculations are provided below:

Continuous Endpoints[1]	Sarecycline CFB or %CFB	Placebo CFB or %CFB	Common SD	Sample per Treatment	Total Sample Size
Absolute CFB in inflammatory lesion counts (co-primary)	16	13	12	338	676
Percent CFB in inflammatory lesion counts (secondary)	39%	52%	41%	210	420

[1] Sample size was based on a two sample t-test of no difference between the treatments.

Dichotomous Endpoints[1]	Sarecycline Rate	Placebo Rate	Difference in Rates	Sample per Treatment	Total Sample Size
IGA Success (2-point decrease in IGA score from baseline and a score of clear/almost clear; co-primary)	23%	10%	13%	170	340

[1] Sample size was based on a χ^2 test of no difference between the proportions.

While the IGA scale proposed for the Phase 3 studies is slightly different than the IGA scale in the Phase 2, the number of subjects to be enrolled (500 per treatment; 1000 total) should provide more than sufficient power for the efficacy evaluations. Additionally, a larger sample is needed in order to provide sufficient numbers of subjects on sarecycline treatment for a safety database.

11.2 Analysis Populations and Datasets

Statistical analysis and data tabulation will be performed using the following analysis populations unless specified otherwise:

- Safety population – includes all randomized subjects who receive at least one dose of study drug. All summaries of this population will be based on the study drug each subject received.
- Intent-to-treat (ITT) population (primary efficacy population) – includes all randomized subjects. All summaries of this population will be based on the study drug each subject was randomized to receive.
- Per-protocol (PP) population (supportive secondary efficacy population) – includes all randomized subjects who complete the treatment period, do not have any major protocol deviations, and have overall study drug compliance of at least 80%. All summaries of this population will be based on the study drug each subject received. Major protocol deviations that could potentially impact the efficacy data may include the following:
    - Entering the study without satisfying the entry criteria;
    - Receiving an excluded concomitant treatment.
    - Receiving wrong study treatment

Three "visit types" will be defined for the purposes of analysis and summaries:

- Observed Cases (OC) – includes assessments collected at each scheduled visit. All applicable efficacy and safety variables will be summarized for OC visits.
- **Multiple Imputation Data – for the primary and secondary efficacy endpoints only, missing data will be imputed using multiple imputation procedures further described in Section 11.4.3.**
- LOCF – defined as the last post-baseline data recorded for each efficacy variable. This visit will be denoted as Week 12 (LOCF) and will only be used to summarize efficacy data. The LOCF visit provides missing value imputation for subjects who do not provide data for the Week 12 visit.

11.3 General Statistical Procedures

11.3.1 Overview

For superiority testing, all inference tests will be conducted at α=0.05 (two-sided) on the null hypothesis of no difference between treatments. All analyses will be conducted with SAS using procedures appropriate for the particular analysis.

11.3.2 Summary Statistics

The descriptive statistics for all the continuous variables will include the mean, median, 25th percentile, 75th percentile, standard deviation (SD), standard error of mean (SEM), minimum, maximum, and number of subjects. Descriptive summaries will be provided for raw, CFB, and %CFB values for continuous efficacy endpoints. Frequency distributions for all the categorical variables will be presented as counts and percentages. Summaries will be provided by visit and treatment, as appropriate.

11.3.3 Site Pooling Algorithm

While every effort will be made to randomize a sufficient number of subjects at each study site, in the event that this is not possible, study sites may be pooled for statistical inference testing. Study sites (centers) will be pooled by geographical location **based on region definitions from the US Census Bureau** (Northeast, Midwest, **South,** and **West**) **(US Census Bureau, 2013)** for analysis purposes so that in each pooled site the number of subjects is reasonably large and consistent in size between pooled sites. Sites within a geographic location will be pooled starting with the sites that have the lowest number of randomized subjects pooled together such that the pooled site has a minimum of 12 randomized subjects after pooling.

The sites to be pooled for each geographic location will be documented in a signed memo prior to unblinding of the treatment code. A list of sites and the corresponding pooled sites will be presented.

11.4 Efficacy Parameters

11.4.1 Co-primary Efficacy Endpoints

There will be two co-primary efficacy endpoints for this study. The first co-primary efficacy endpoint will be the absolute CFB in inflammatory lesion counts at Week 12. This variable will be considered a continuous variable.

The second co-primary efficacy endpoint will be IGA success at Week 12. IGA success will be a dichotomous variable defined as at least 2-point decrease from baseline on the IGA assessment as well as a score of clear (0) or almost clear (1) on the IGA assessment.

11.4.2 Secondary Efficacy Endpoints

There will be **four** secondary efficacy endpoints for this study, percent CFB in inflammatory lesion counts at Week 12**, and absolute and percent CFB in inflammatory lesion counts at Weeks 9, 6, and 3**. **These** variables will be considered continuous variables.

11.4.3 **Missing Data Handling for Co-Primary and Secondary Endpoints**

For the co-primary and secondary efficacy analyses, the primary missing data imputation method is multiple imputation (MI), as outlined in the following procedures:

- **The SAS PROC MI procedure with a fully conditional specifications (FCS) method will be used to create 20 imputations. The FCS is proposed as it allows for accommodation of categorical variables and it has the versatility to handle arbitrary missing data patterns. Based on these 20 imputations, the relative efficiency will be 0.995 for 10% of missing data and 0.990 for 20% of missing data (Rubin, 1976, 1987, 1996).**
- **For inflammatory lesion counts, if any of the subtypes (papules, pustules, and nodules/cysts) is missing, the inflammatory lesion count is missing. The variables included in the imputations are age, sex, and the raw measurements of the corresponding endpoint counts at baseline, Week 3, Week 6, Week 9, and Week 12**
- **For IGA, the raw scores will be used for the imputation. The variables included in the imputations are age, sex, and the measurements of the endpoint at baseline, Week 3, Week 6, Week 9, and Week 12**
- **All imputations will be performed by treatment group based on the randomized study medication. The number of imputations is set at 20 with number of 50 burn-in iterations. The seed used for imputation for all endpoints is [redacted]. For IGA raw scores and lesion counts, regression with predictive mean matching method will be used. The imputed values will be rounded to the nearest integer.**
- **An analysis of covariance (ANCOVA) model for continuous endpoints (inflammatory lesion counts) will be performed for each of the imputed datasets.**
- **A Cochran-Mantel-Haenszel (CMH) analysis for the binary endpoint (IGA success) will be performed for each of the imputed datasets.**
- **The SAS PROC MIANALYZE procedure will be used to produce final parameter estimates, including the point estimates and standard errors, adjusted treatment differences, confidence intervals and p-values for the primary and secondary variables.**
- **For the CMH test, the Wilson-Hilferty transformation (Wilson & Hilferty, 1931, O'Kelly & Ratitch, 2014) will be used. Under the null hypothesis, the transformed statistic is approximately normally distributed:**

$$wh\_CMH^{(m)} = \sqrt[3]{\frac{cmh^{(m)}}{k}} \sim normal\left(1 - \frac{2}{9k}, \frac{2}{9k}\right)$$

Where $cmh^{(m)}$ is the chi-square statistics each with *k* degrees of freedom from $m = 1, \ldots, M$ imputed datasets. In this case, *k=1*. This statistic will be passed to PROC MIANALYZE to obtain the combined p-value for CMH test.

The same method will be used to obtain the p-values from the Breslow-Day test.

11.4.4 Other Efficacy Endpoints

[redacted]

11.5 Analysis of Efficacy Variables

11.5.1 CFB in Inflammatory Lesion Counts

The co-primary endpoint, absolute CFB in inflammatory lesion counts at Week 12, will be analyzed using an analysis of covariance (ANCOVA) model with the baseline value as a covariate and additional terms included to represent effects of treatment and (pooled) site. The primary efficacy analysis will be based on the ITT population. **Missing data will be imputed using the MI approach described in Section 11.4.3.** The adjusted means with associated 95% CIs from the ANCOVA model will also be presented for each treatment and for the difference between the treatments **at Week 12**. Statistical significance between the treatments, sarecycline compared to placebo, will be declared if the p-value of the hypothesis test from the ANCOVA model is less than or equal to 0.05. The ANCOVA model will be performed using SAS® PROC MIXED with the methodology of Littell et al. (1996).

Let X_{ijk} and Y_{ijk} be the baseline and endpoint values for the *k*th subject in the *j*th site and the *i*th treatment, where $k=1,\ldots, n_j$, $j=1, \ldots, c$ (the number of sites after pooling, if applicable) and *i*=sarecycline, placebo. Then

$$Y_{ijk} - X_{ijk} = \mu + \tau_i + \gamma_j + \beta X_{ijk} + \varepsilon_{ijk} \qquad (1)$$

where μ is the overall mean, τ is the fixed effect of the *i*th treatment, γ is the fixed effect of the *j*th site, β is a regression coefficient for baseline and ε_{ijk} is the $NID(0,\sigma^2)$ random error component. Hypothesis tests for the active treatment effect of sarecycline compared to placebo will be conducted using differences of adjusted means.

Residuals will be evaluated using SAS® PROC UNIVARIATE. The assumption of a random error component ~ $NID(0, \sigma^2)$ will be tested by examining skewness and kurtosis following D'Agostino et al. (1990) with the residuals pooled over both treatments. Additionally, homogeneity of variances across treatment groups will be examined using Levene's Test (Glaser 1982) with significance level of 0.05, based on absolute values of the residuals from the residual medians for each treatment. The data will be determined non-normal if the p-value for either the D'Agostino Skewness Test or D'Agostino Kurtosis Test is less than 0.05. **Because of the multiple datasets created by using the MI approach, the**

p-value used for each of these tests will be the median p-value after the analysis has been performed on each dataset. If the data do not meet the normality or homogeneity assumptions of the parametric analyses, then a rank transformation will be applied to the **raw** data **and the primary analysis will proceed using an ANCOVA model on the ranks with the baseline value as a covariate and effects of treatment and (pooled) site**. Tied values will receive the mean value (midranks) of the corresponding ranks.

As site is included in the **primary** ANCOVA model, a treatment-by-site interaction will be investigated as an exploratory analysis to assess the homogeneity of treatment effects across site. This effect will be investigated analytically prior to any pooling of sites by adding the interaction term to the ANCOVA model and testing for significance. Because interactions are not powered in this study, testing for significance will be at the 0.10 level. However, any significant interaction findings at the 0.10 level will also take into account the potential for spurious results. Further exploration may be done graphically with interaction plots to determine the nature of the interaction and to identify any "outlier" sites with attention focused on qualitative differences in treatment effects. If large differences in treatment effects are seen in any "extreme" sites, then sensitivity analyses will be performed that exclude sites with the highest extreme treatment effect values from the analysis. Any such sites may be further investigated for explanation involving study conduct, subject demographics, current medications, etc.

11.5.2 IGA Success

The co-primary efficacy endpoint, percentage of subjects of IGA success at Week 12, will be analyzed for the ITT population using the Cochran-Mantel-Haenszel (CMH) test with adjustment for (pooled) site. **Missing data will be imputed using the MI approach described in Section 11.4.3.** The **rate** difference and the 95% CIs for the **rate** difference and the relative **rate** and the 95% CIs for the relative **rate** will be presented as well. **The CIs for the treatment rate difference will be based on two-sided 95% Wald type CIs with CMH weights (Kim & Won, 2013, Yan & Su, 2012).**

The homogeneity of treatment effects across (pooled) site will be investigated as an exploratory analysis using the Breslow-Day test. If the Breslow-Day test indicates large heterogeneity in the odds ratios across (pooled) site, then further exploration may be done graphically or with further investigation for explanation involving study conduct, subject demographics, current medications, etc.

11.5.3 **Secondary Endpoint Analyses**

A hierarchical testing approach will be used for the secondary efficacy endpoints, percent CFB in inflammatory lesion counts at Week 12**, and absolute and percent CFB in inflammatory lesion counts at Weeks 9, 6, and 3** (**using ANCOVA**), **such** that statistical testing will only be performed if both co-primary efficacy endpoints are statistically superior to placebo at α=0.05**. In addition, statistical testing of the secondary endpoints will be conducted in the following order, with all tests proceeding at the 0.05 level if and only if the previous tests were all significant at the 0.05 level:**

1. Percent CFB for inflammatory lesion counts at Week 12 (must be significant at the 0.05 level to proceed to the next analyses)
2. Absolute and percent CFB for inflammatory lesion counts at Week 9 (both endpoints must be significant at the 0.05 level to proceed to the next analyses)
3. Absolute and percent CFB for inflammatory lesion counts at Week 6 (both endpoints must be significant at the 0.05 level to proceed to the next analyses)
4. Absolute and percent CFB for inflammatory lesion counts at Week 3 (both endpoints must meet the 0.05 level for Week 3 to meet statistical significance)

These secondary endpoints will **all** be analyzed using an analysis of covariance (ANCOVA) model with terms included to represent effects of treatment and (pooled) site and the baseline values as a covariate for the ITT population. **Missing data for the co-primary and secondary endpoints will be imputed using an MI approach, as described in Section 11.4.3.** The adjusted means with associated 95% CIs for the ANCOVA model will also be presented for each treatment and for the difference between the treatments. Statistical significance between the treatments, sarecycline compared to placebo, will be declared if the p-value of the hypothesis test from the ANCOVA model is less than or equal to 0.05. **For percent CFB at Week 12, f**ormal procedures for testing assumptions of the ANCOVA model (and alternative procedures when assumptions are unmet, e.g., nonparametric analysis) will be specified in the SAP. **The percent CFB analysis for Weeks 9, 6, and 3 will use the same methods as determined by the Week 12 analysis (i.e., based on the values or on the ranks). In addition, the absolute CFB analysis for Weeks 9, 6, and 3 will use the same methods as determined by the co-primary CFB Week 12 analysis for inflammatory lesion counts (i.e., based on the values or on the ranks).**

For the Week 12 percent CFB analysis, as site is included in the ANCOVA model, a treatment-by-site interaction will be investigated as an exploratory analysis to assess the homogeneity of treatment effects across site. This effect will be investigated analytically by adding the interaction term to the ANCOVA model and testing for significance. Because interactions are not powered in this study, testing for significance will be at the 0.10 level. However, any significant interaction findings at the 0.10 level will also take into account the potential for spurious results with attention focused on qualitative differences in treatment effects. If large differences in treatment effects are seen in any "extreme" sites, then sensitivity analyses will be performed that exclude sites with the highest extreme treatment effect values from the analysis. Further exploration may be done graphically with interaction plots to determine the nature of the interaction and to identify any "outlier" sites. Any such sites may be further investigated for explanation involving study conduct, subject demographics, current medications, etc.

11.5.4 [redacted]

[redacted]

[redacted]

11.5.5 Additional Analyses

Efficacy data will be analyzed for each OC visit.

11.5.6 Sensitivity Analyses

Sensitivity analyses will investigate the impact of missing data on the robustness of the results. Reasons for missing data and time to drop-out will be explored in a descriptive fashion for each treatment. Efficacy responses through time for each treatment will be investigated for each treatment for subjects that completed the study versus for those subjects that discontinued the study. Additionally, logistic regression models may be used to explore efficacy responses for subjects who completed the study compared to those subjects who dropped out. Finally, the following sensitivity analyses of the co-primary efficacy endpoint data will be provided to explore the impact of missing data on the robustness of the results. Additional sensitivity analyses may be described in the Statistical Analysis Plan prior to database lock.

Sensitivity Analyses for Continuous Variables

- Efficacy data will be summarized and analyzed **according to an ANCOVA model with the baseline value as a covariate and effects of treatment and (pooled) site** using the **per--protocol** (PP) population **with OC data**.

- **LOCF will be used as an imputation method for cases where the Week 12 CFB in inflammatory lesion counts value is missing. The endpoint will then be analyzed according to an ANCOVA model with the baseline value as a covariate and effects of treatment and (pooled) site.**

- Baseline observation carried forward will be used as an imputation method for cases where the Week 12 CFB in inflammatory lesion counts value is missing. The endpoint will then be analyzed according to the **ANCOVA model with the baseline value as a covariate and effects of treatment and (pooled) site**.

- Mixed model repeated measures (MMRM) analysis will be used to explore the sensitivity of data handling for CFB in inflammatory lesion counts for subjects who withdraw from the study. The model will include the fixed effects of treatment, pooled site, and visit, the baseline value as the covariate, and the treatment-by-visit interaction term. An unstructured covariance matrix will be used initially in the model for the correlation pattern among the repeated measures. If this does not converge, then the Toeplitz covariance structure (TYPE=TOEP in SAS MIXED procedure) will be used instead. If the results from the MMRM analyses differ qualitatively with the results from the

primary efficacy analysis, further analyses will be performed to investigate the causes of the difference. However, the results from the primary efficacy analysis will be considered the primary efficacy results.

Sensitivity Analyses for Categorical Variables

- Efficacy data will be summarized and analyzed using **the CMH test with adjustment for (pooled) site using** the PP population **with OC data**.

- For IGA success, subjects who discontinue from the study early will be coded as failures **for the Week 12 analysis**. A sensitivity analysis of IGA success using this data handling convention will be performed using the **CMH test with adjustment for (pooled) site on the ITT population.**

- For IGA success, subjects who discontinue from the study early will be coded as failures for subjects on sarecycline and successes for subjects on placebo **for the Week 12 analysis**. A sensitivity analysis of IGA success using this data handling convention will be performed using the **CMH test with adjustment for (pooled) site on the ITT population.**

11.5.7 Subgroup Analyses

Primary and secondary efficacy variable summaries will be repeated for the following subgroups if sample size allows **by study visit using OC data**:

- Gender: male and female
- Age groups: 9 to 17 years and ≥ 18 years
- Race: white, African-American/Black, other
- Body mass index: < 25 kg/m^2 and ≥ 25 kg/m^2
- Baseline acne severity (IGA score): moderate and severe
- Oral contraceptive use in females: female subjects who use oral contraceptives versus female subjects who do not

11.6 Safety Analyses

11.6.1 Adverse Events

Treatment-emergent adverse events will be classified into a standardized terminology using the Medical Dictionary for Regulatory Activities (MedDRA) system organ classifications and preferred terms. Adverse events with onset on or after the first dose date of test or reference article and prior to or on study completion will be considered as "treatment-emergent."

Although a preferred term or system organ class may be reported more than once for a subject, each subject will only be counted once in the incidence count for that preferred term or system organ class for each particular summary. Summaries of safety data will be generated for the following summary types:

- Overall summaries
- Summaries by MedDRA system organ class, MedDRA preferred term, test or reference article relationship, and severity.
- Summaries by MedDRA preferred term and test or reference article relationship in descending order.
- Summaries of serious adverse events by MedDRA preferred term and test or reference article relationship in descending order.
- Summaries of adverse events by MedDRA system organ class, MedDRA preferred term, and test or reference article relationship for the primary events leading to premature discontinuation from the study.

These summaries will present the number and percentage of subjects reporting an adverse event by treatment and overall as well as the number of events reported. The denominators for calculating the percentages by treatment will be based on the number of subjects exposed in the Safety population to each treatment and overall. The treatment will be based on the **double--blind** treatment received. **For subjects who are in PK Schedule 3, the treatment--emergent adverse event summary described above will comprise data prior to the active dose taken at the Week 12 visit. Further adverse events experienced after this Week 12 dose will be listed separately for these subjects.**

11.6.2 Extent of Exposure

The number of doses taken and the duration of exposure to study drug will be summarized by treatment using descriptive statistics for the Safety population. Duration of exposure will be calculated as the difference between the last **double-blind** dose date and the first dose date plus one day.

Additionally, these summaries will present the number and percentage of subjects for each interval (1 week multiples) of total exposure in each treatment. The denominators for calculating the percentages will be based on the number of subjects with exposure for each treatment.

11.6.3 Clinical Laboratory Evaluations

Continuous clinical laboratory analytes will be summarized by **double--blind** treatment, analyte, and visit using descriptive statistics. Categorical laboratory analytes, classified as normal or abnormal, will be summarized by treatment analyte, and visit using the number and percentage of subjects in each category. The denominators for calculating the

percentages will be based on the number of subjects in each treatment with non-missing assessments at a particular visit for the Safety population.

Shifts to values outside of the normal range will be presented by treatment and analyte and will be summarized by the number and percentage of subjects with evaluable shifts. An evaluable shift is one where both the Screening Visit value and the on-treatment value or early termination value are recorded. The denominators for calculating the percentages will be based on the number of subjects in each treatment group who have an evaluable shift for a particular analyte.

11.6.4 Electrocardiograms

Electrocardiographic evaluations and shifts will be presented by visit and **double-blind** treatment. Evaluations will be summarized by the number and percentage of subjects for each interpretation and shift category. The denominators for calculating the percentages will be based on the number of subjects with assessments in each treatment for the Safety population.

11.6.5 Vital Signs

Vital sign measurements will be summarized for the Safety population by **double-blind** treatment and visit using descriptive statistics. Additionally, descriptive statistics will be presented by treatment and day for the CFB for vital signs. The baseline values will be defined as the last value collected prior to the first dose of the study drug.

11.7 Other Assessments or Analyses

Other study assessments listed below will be summarized or provided in data listings as specified in the statistical analysis plan.

11.7.1 Demographics and Baseline Characteristics

Subject demographic and physical characteristic data will be summarized by treatment and overall for each analysis population using descriptive statistics (mean, median, 25th percentile, 75th percentile, SD, SEM, minimum, maximum, and number of subjects) for continuous variables and frequency distributions (counts and percentage of subjects) for categorical variables.

Medical history items will be coded using standardized terminology from the MedDRA system organ classifications and preferred terms. Medical history will be summarized using counts and percentages of subjects in each system organ class and preferred term by treatment and overall for the Safety population.

11.7.2 Medications

Medication usage will be coded using the World Health Organization (WHO) Drug Dictionary. Medications will be presented by WHO Drug Anatomical/Therapeutic/Chemical

category and WHO Drug preferred name. Summaries will be presented for prior (prior to the first treatment period) medication use and concomitant (after first treatment has been given) medication use. Medications with **an end** date occurring before the first study drug dose date in the treatment period will be identified as prior medications. Medications with a start date occurring on or after the first study drug dose date in the treatment period or medications **with a start date prior to the first dose** that are on-going or **with** end dates that are on or after the first treatment start date will be identified as concomitant medications.

All summaries will present the number and percentage of subjects for each medication by treatment and overall. The denominators for calculating the percentages will be based on the number of subjects in the Safety population for each treatment and overall.

11.7.3 Compliance

Compliance will be assessed by comparing the expected number of doses taken, based on the total number of treatment days within each visit and within the entire treatment period of the study, with the number of returned doses to the clinic at the end of each treatment visit. Treatment compliance will be calculated for each subject/visit and over all visits for the Safety population. Compliance values that are less than 0% will be set to 0%. Summaries will be presented using descriptive statistics for the Safety population.

$$\text{Compliance} = \left[\frac{\#\text{Dispensed} - \#\text{Returned}}{\#\text{Expected to be used}} \right]$$

11.7.4 IGA for Non-facial Sites

IGA scores for neck, chest, and back sites will be summarized by visit and treatment using counts and percentages for each site.

11.7.5 Noninflammatory Lesion Counts

There will be no statistical testing for absolute CFB in noninflammatory lesion counts at Week 12; however, descriptive summaries will be provided including 95% CIs for each treatment and for the treatment difference **using an ANCOVA model with the baseline value as a covariate and additional terms included to represent effects of treatment and (pooled) site with OC visit data and the ITT population**.

11.7.6 Skindex Questionnaire

Scoring, scaling, and the handling of missing data will be handled in accordance with the recommendations accompanying the Skindex-16 and will be described in more detail in the Statistical Analysis Plan. Descriptive summaries will be provided for the ITT population for scale scores and total score by treatment and visit. Additionally, CFB for scale and total scores will be provided for each treatment. Change from baseline in scale and total scores will be analyzed using an ANCOVA model with the baseline value as a covariate and additional terms included to represent effects of treatment and (pooled) site. Analyses will be provided for the ITT population. The adjusted means with associated 95% CIs from the

ANCOVA model will also be presented for each treatment and for the difference between the treatments.

11.7.7 Photographs

No statistical summaries based on photographic images are planned for the clinical study report.

11.7.8 Pharmacokinetics

Individual sarecycline and R-sarecycline plasma concentrations will be listed.

Sarecycline plasma concentration data obtained in the study will be utilized to estimate population PK parameters using nonlinear mixed-effects modeling (NONMEM). The effects of covariates on PK parameters will be evaluated as part of the analysis. The analysis will be described in a separate analysis plan.

12 DOCUMENTATION REQUIREMENTS AND RECORDKEEPING

12.1 Source Documentation

The CRFs represent a record of the subject's experience in the study, therefore, the CRF data must be supported by original (or source) medical records, as appropriate. CRF data recorded directly into the CRF is also considered source data when there are no other written or electronic records preceding the CRF entry.

Prior to enrolling a subject in the study, the Investigator must document his/her review of subject eligibility criteria in the source records for the subject, including the Investigator's signature and date on any medical and laboratory reports indicating a review of the source data occurred. The Investigator will continue to follow this practice for any subsequent medical and laboratory reports generated as a result of the clinical study.

The Investigator agrees that the Sponsor or its designated agents, the IRB, the FDA or foreign regulatory agencies will have reasonable access to study source documentation for purposes of audit and monitoring visit review both during and after completion of the study. Monitoring visits provide the Sponsor with the opportunity to evaluate the progress of the study; to verify the accuracy and completeness of CRFs; to ensure that all protocol requirements, applicable regulations and Investigator's obligations are being fulfilled; and to resolve any inconsistencies in the study records. All participating subjects will be required to signify their approval to permit inspection of their medical records by representatives of Sponsor, the IRB, the FDA and/or foreign regulatory agencies, as needed.

12.2 Data Capture and Discrepancy Management

Site personnel will be responsible for the completion and correction of CRFs according to the protocol and other instructions provided by the Sponsor or their designee. The Investigator is responsible for ensuring the completeness and accuracy of the data as evidenced by the Investigator's signature and date once the subject has completed the study and all required study data has been entered into the CRF.

Since site personnel will enter data directly into a validated electronic CRF, programmatic data validation procedures will be employed to identify data discrepancies to site personnel at the time of entry and/or upon saving the data. Designated site personnel will resolve any discrepancies via the electronic CRF. Any additional findings upon clinical review by the Sponsor or their designee will be entered into the system for review and resolution by site personnel. A full audit trail of data changes following entry will be captured during the study in the electronic data management system. The Investigator will be provided with a copy of all CRF data for retention.

13 OTHER INFORMATION

13.1 Financing and Insurance

Financing and insurance is addressed in a separate agreement.

13.2 Publication and Disclosure Policy

Publication and disclosure policy is addressed in a separate agreement.

13.3 Termination of the Study

If the study is terminated prematurely or suspended, the appropriate IRB and regulatory authority(ies) will be promptly informed of the termination or suspension and will be provided the reason(s) for the termination or suspension. All obligations and responsibilities of the Sponsor and the Investigator under GCP, the US CFR and the Declaration of Helsinki will remain in force if the study is terminated prematurely.

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15 APPENDICES

Appendix 1 **Study Schedule of Events**

Appendix 2 **Clinical Laboratory Evaluations**

Appendix 3 **Collection, Processing, Storage and Shipment Instructions for PK Samples**

Appendix 4 **Skindex Questionnaire**

Appendix 5 **Investigator Signature**

Appendix 6 **Sponsor Signatures**

Appendix 1 Study Schedule of Events

	Screening Period		**Treatment Period**					
	SV1	**SV2 (Baseline Assessment)**	**Telephone Contact Week 1 ± 3 d**	**Visit 1 Week 3 ± 3 d**	**Visit 2 Week 6 ± 3 d**	**Visit 3 Week 9 ± 3 d**	**Visit 4 Week 12 /ET ± 3 d**	**Visit 5[d] Week 13 /ET ± 3 d**
Informed Consent	X							
Assign Subject Number using the IRT	X							
Inclusion/ Exclusion	X	X						
Demographic Data	X							
Medical/ Surgical History	X							
Physical Examination	X	X[a]					X	**X**
Height & Weight	X	Weight only					Weight only	**Weight** only
Vital Signs	X	X		X	X	X	X	**X**
Hematology, Serum Chemistry, Urinalysis and Lipids	X	X[b]		X			X	
TSH, Free T4 and T3	X						X	
Urine pregnancy test	X	X		X	X	X	X	**X**
ECG	X						X	
Facial Investigator's Global Assessment		X		X	X	X	X	
Facial Lesion Counts		X		X	X	X	X	
Facial Photographs		X		X	X	X	X	

	Screening Period		**Treatment Period**					
	SV1	**SV2 (Baseline Assessment)**	**Telephone Contact Week 1 ± 3 d**	**Visit 1 Week 3 ± 3 d**	**Visit 2 Week 6 ± 3 d**	**Visit 3 Week 9 ± 3 d**	**Visit 4 Week 12 /ET ± 3 d**	**Visit 5[d] Week 13 /ET ± 3 d**
Non-facial Investigator's Global Assessment		X		X	X	X	X	
Skindex Questionnaire		X					X	
Dispense Diary for Subjects Participating in PK Sampling		X				X		
PK Blood Sample Collection for PK 1, PK 2, **and PK 3** [C]				X			X	
Review and Collect Diaries				X			X	
Randomization		X						
Dispense Study drug		X		X	X	X	**X[d]**	
Study drug Accountability /Compliance			X	X	X	X	X	
Concomitant Medication Use	X	X		X	X	X	X	**X**
Adverse Events	X	X	X	X	X	X	X	**X**

ECG= electrocardiogram; ET= End of treatment; X[a]: Only for subjects requiring medication/therapy washout; X[b]: Re-draw blood and urine samples for clinical laboratory evaluations only if washout duration exceeded 5 weeks. [C] PK Schedule 1, PK Schedule 2**, or PK Schedule 3** should be performed at selected sites based on what the subject chose in the ICF, [d]**For subjects participating in PK Schedule 3 only**.

Appendix 2 Clinical Laboratory Evaluations

Hematology

Hemoglobin	Mean cell volume
Hematocrit	White blood cell & Differential
Red blood cell count	Platelet count

Serum Chemistry

Albumin	Total protein
Alanine aminotransferase	Serum creatinine
Aspartate aminotransferase	Sodium
Blood urea nitrogen	Potassium
Gamma glutamyl transferase	Calcium
Glucose	Chloride
Lactate dehydrogenase	Bicarbonate
Total bilirubin	Phosphorus
Creatine phosphokinase	

Urinalysis

Color	Protein
Specific gravity	Glucose
Potential for hydrogen (pH)	Blood
Leukocytes	Bilirubin
Ketones	

Lipid Profile

Total cholesterol	Triglycerides

Thyroid Function

Thyroid stimulating hormone	Free T4 and T3

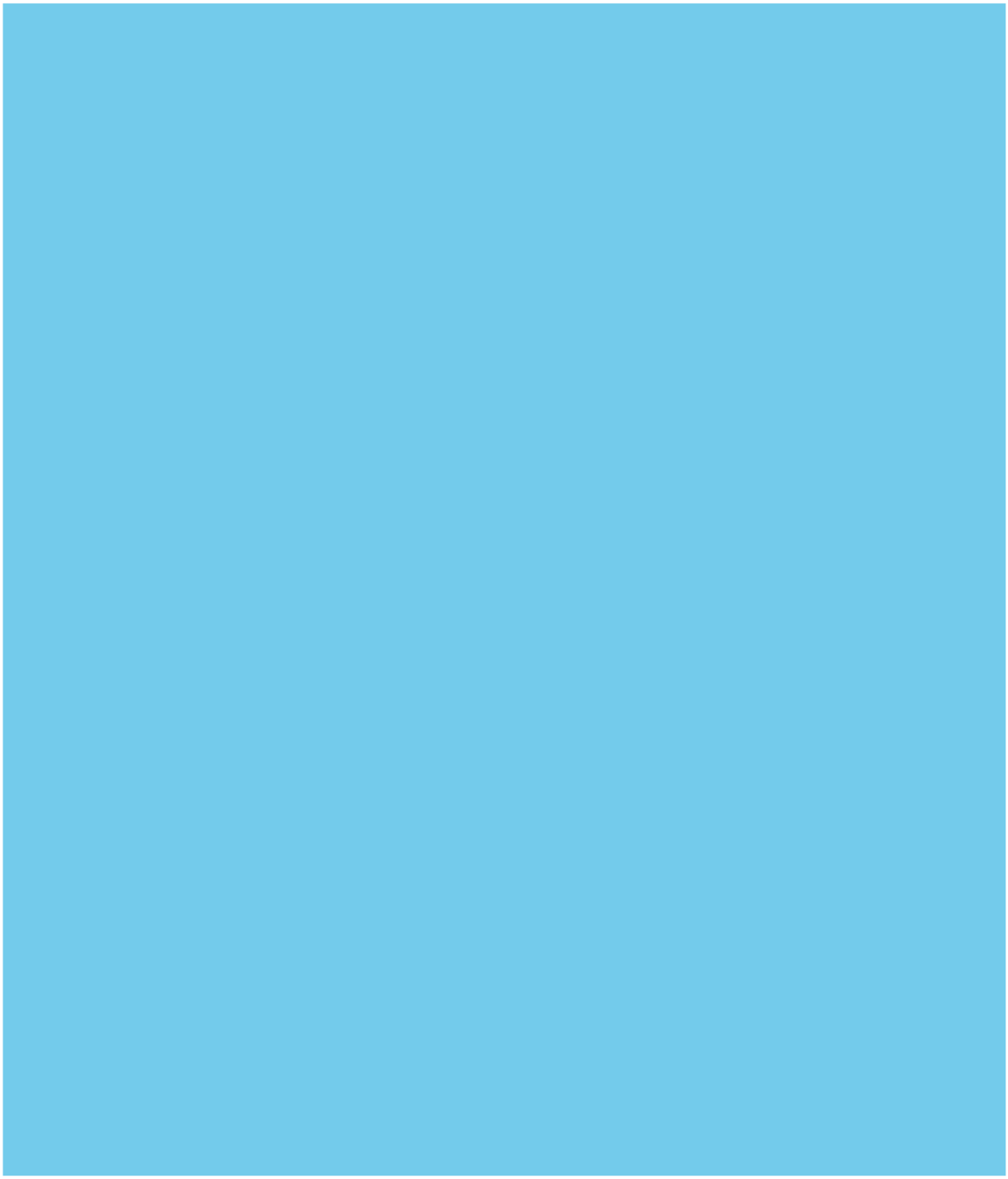
Other

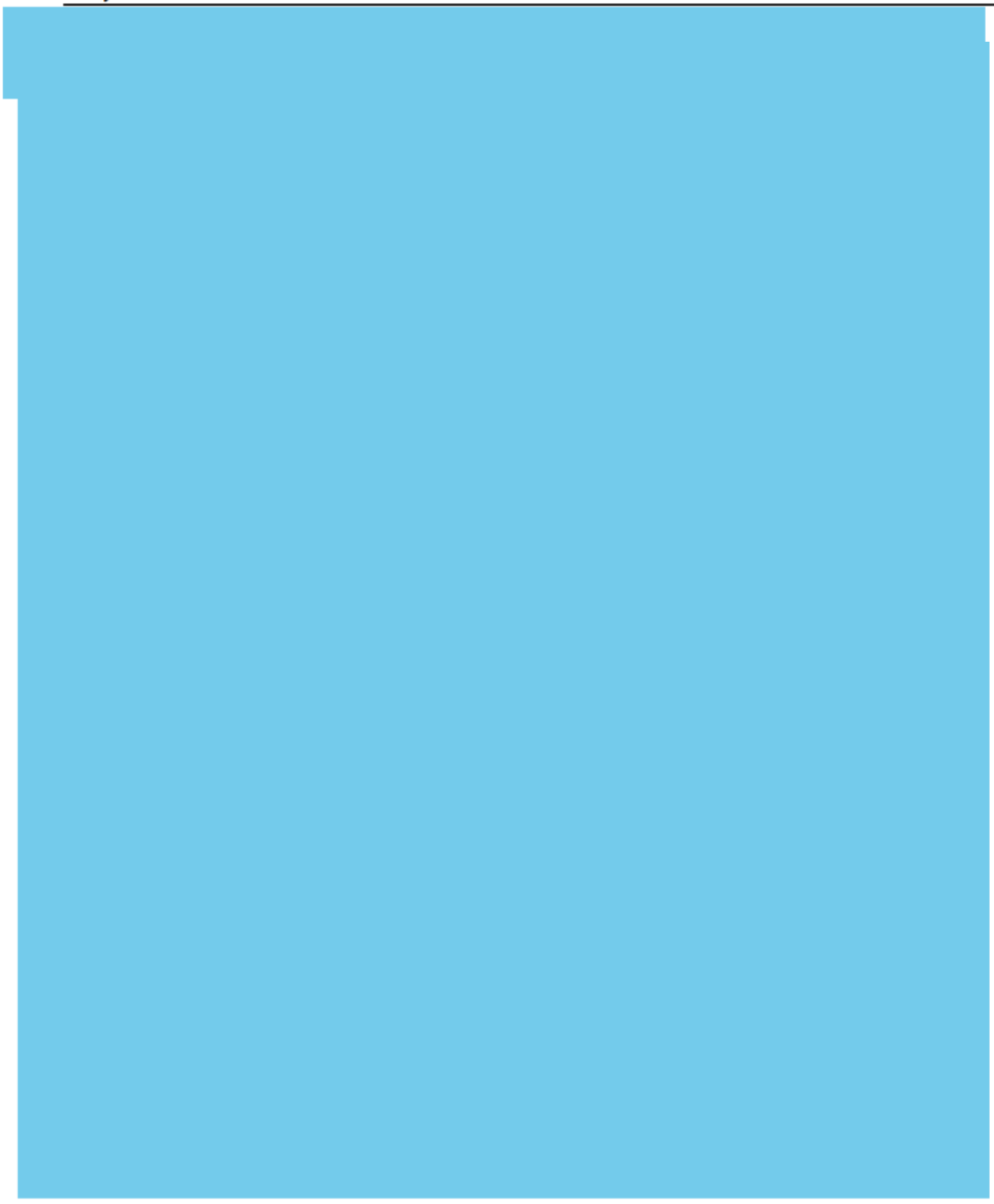
Urine pregnancy test

Appendix 3 Collection, Processing, Storage and Shipment Instructions for PK Samples

Follow detailed instructions as per the PK Laboratory manual.

Appendix 4 Skindex Questionnaire





Appendix 5 Investigator Signature

Study Title:	A Randomized, Multicenter, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of 1.5 mg/kg per Day of Sarecycline Compared to Placebo in the Treatment of Acne Vulgaris
Study Number:	SC1401
Final Date:	**15-Aug-2014**
Amendment 1	**15-Sep-2014**
Amendment 2	**13-Mar-2015**
Amendment 3	**16-Dec-2015**

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed: _____ Date: _____

Appendix 6 Sponsor Signatures

Study Title:	A Randomized, Multicenter, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of 1.5 mg/kg per Day of Sarecycline Compared to Placebo in the Treatment of Acne Vulgaris
Study Number:	SC1401
Final Date:	**15-Aug-2014**
Amendment 1	**15-Sep-2014**
Amendment 2	**13-Mar-2015**
Amendment 3	**16-Dec-2015**

This clinical study protocol was subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving this protocol:

Clinical Development	Signature	Month/Day/Year
Statistical Science	Signature	Month/Day/Year
Medical Writing	Signature	Month/Day/Year