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A MULTI-CENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF [REDACTED AS ATS55] IN THE TREATMENT OF ACNE VULGARIS

CLINICAL STUDY PROTOCOL

Protocol Number: ADPS 1602

Protocol Version Number: 1.0

Protocol Version Date: August 2, 2016

Study Sponsor: Taro Pharmaceuticals U.S.A., Inc.

Phase: 2

NCT02935036

PROTOCOL APPROVAL:

I am aware of, and agree to comply with, all of the procedures contained within this protocol and requirements of applicable regulatory agencies:

Sponsor Representative [Redacted]	Signature:	Date:
Medical Monitor [Redacted]	Signature:	Date:
Statistical Consultant [Redacted]	Signature:	Date:
CRO Representative [Redacted]	Signature:	Date:

CONFIDENTIALITY STATEMENT

The information provided in this document is strictly confidential. This information may not be used, published or disclosed without prior written approval from Taro Pharmaceuticals U.S.A., Inc.

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PRINCIPAL INVESTIGATOR AGREEMENT

I have carefully read and understand the foregoing protocol ADPS 1602 "A MULTI-CENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF [Redacted as AT55] IN THE TREATMENT OF ACNE VULGARIS" and agree that it contains all the necessary information for conducting this study safely. I will conduct this study in strict accordance with this protocol, ICH guidelines for Good Clinical Practice, the Code of Federal Regulations, the Health Insurance Portability and Accountability Act (HIPAA) and local regulatory guidelines. I will attempt to complete the study within the time designated.

I will ensure that the rights, safety and welfare, of Subjects under my care are protected. I will ensure control of the drugs under investigation in this study.

I will provide copies of the protocol and all other study-related information supplied by the Sponsor to all personnel responsible to me who participate in the study. I will discuss this information with them to assure that they are adequately informed regarding the drug and conduct of the study.

I agree to keep records on all Subject information (case report forms, shipment and drug return forms and all other information collected during the study) and drug disposition in accordance with FDA regulations.

I will not enroll any Subjects into this protocol until IRB approval and Sponsor approval are obtained.

Principal Investigator

Signature:

Date:

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANOVA	Analysis of Variance
CFR	Code of Federal Regulations
eCRF	Electronic Case Report Form
CRO	Contract Research Organization
DCF	Data Clarification Forms
EC	Ethics Committee
ED	Early Discontinuation
EDC	Electronic Data Capture
EOT	End of Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
hCG	Human Chorionic Gonadotropin
HEENT	Head, Eyes, Ears, Nose and Throat
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IGA	Investigator's Global Assessment
ICH	International Conference on Harmonization
ID	Identification
IRB	Institutional Review Board
IUD	Intrauterine Device
mITT	Modified Intent To Treat
NSAID	Non-Steroidal Anti-Inflammatory Drug
OTC	Over the Counter
SAE	Serious Adverse Event
US	United States
UV	Unscheduled Visit

STUDY SYNOPSIS

Protocol Number: ADPS 1602

Title of Study: A MULTI-CENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF [Redacted as ATS55] IN THE TREATMENT OF ACNE VULGARIS

Sponsor: Taro Pharmaceuticals U.S.A., Inc.

Treatment Duration: The study treatment period will last for 84 days (12 weeks).

Investigational Products:

Test Product: [Redacted as ATS55] (Taro Pharmaceuticals U.S.A, Inc.)

Placebo Control: Vehicle of the test product (Taro Pharmaceuticals U.S.A., Inc.)

Dose and Mode

of Administration: A thin layer of study medication will be applied to cover the entire face and other affected body areas once daily.

Objectives: To evaluate the efficacy and safety of [Redacted as ATS55] (Taro Pharmaceuticals U.S.A, Inc.) in the treatment of acne vulgaris.

Design: Subjects in this randomized, double-blind, placebo controlled, parallel-group, multiple-center study will be randomly assigned in a 1:1 ratio to treatment with the test product or placebo control, respectively.

Clinical Evaluations will be performed at:

- Visit 1: Screening/Baseline Visit (Day 0);
 - Visit 2: Interim Visit (Week 2 / Day 14 ± 4 Days);
 - Visit 3: Interim Visit (Week 4 / Day 28 ± 4 Days);
 - Visit 4: Interim Visit (Week 6 / Day 42 ± 4 Days);
 - Visit 5: Interim Visit (Week 8 / Day 56 ± 4 Days);
 - Visit 6: Interim Visit (Week 10 / Day 70 ± 4 Days);
 - Visit 7: End of Treatment Visit (Week 12 / Day 84 ± 4 Days)
 - Visit 8*: Follow up phone call (Week 13 / Day 91 ± 4 Days)
- *if required for on-going AEs based on PI decision

An Unscheduled Visit is allowed at any time, for any reason, if in the Principal Investigator's opinion it is warranted. If a Subject is discontinued from the study during an Unscheduled Visit, the Unscheduled Visit will be referred to as an Early Discontinuation Visit and all procedures scheduled for Visit 7 will be performed. If the Unscheduled Visit is not an Early Discontinuation Visit (i.e., the Subject will continue to take part in the study), then all procedures will be performed and

treated as an interim visit, with the exception of the collection of Investigational Product and Subject diaries from Subjects.

Subjects will be admitted into the study after informed consent/assent has been obtained, a medical history and physical examination (with vital signs) have been performed and inclusion/exclusion criteria have been met. Subjects must have a clinical diagnosis of acne vulgaris to qualify for inclusion in this study.

Each Subject will be randomly assigned in a double-blind fashion in a 1:1 ratio to treatment with the test product or the placebo control.

At the screening/baseline visit, a physical examination (with vital signs) will be conducted. At each subsequent visit, the following procedures will be performed: counts of the facial comedones (open and closed), papules, pustules, nodules and cysts lesions will be performed, the Investigator's Global Evaluation (IGA) will be performed and the signs and symptoms of irritation will be assessed.

Safety will be assessed by the monitoring of all adverse events and the monitoring of any signs and symptoms of local irritation.

Study Population:

Inclusion Criteria

[Redacted]

Exclusion Criteria

[Redacted]

Number of Subjects:

Approximately 300 Subjects, including approximately 24 in the Subgroup, will be enrolled into the study in a 1:1 ratio to the following study arms:

- [Redacted as ATS55] (Taro Pharmaceuticals U.S.A, Inc.)
- Placebo (Vehicle of test product (Taro Pharmaceuticals U.S.A., Inc.)

Approximately equal numbers of male and female subjects will be enrolled to each of the study arms.

Criteria for Evaluation:

Endpoints:

- 1) Percent change from baseline to weeks 2, 4, 6, 8, 10, and 12 in the inflammatory (papules and pustules) lesion counts on the face;
- 2) Percent change from baseline to weeks 2, 4, 6, 8, 10, and 12 in the non-inflammatory (open and closed comedones) lesion counts on the face;
- 3) The proportion of Subjects with a clinical response (IGA) of "success" at weeks 2, 4, 6, 8, 10, and 12 on the face. Success is defined as an IGA score that is at least 2 grades less than the baseline assessment.

Measures¹:

Lesion Counts will be performed using the following definitions:

Table 2: Definition of inflammatory and non-inflammatory lesions

¹ http://www.nlm.nih.gov/medlineplus/ency/encyclopedia_C.htm

Lesion Type	Definition
Closed Comedone	<u>Non-inflammatory lesion</u> ; white, raised bumps caused by collections of oil and skin in pores. Also known as white heads and pimples
Open Comedone	<u>Non-inflammatory lesion</u> ; tiny, dark spots caused by a small plug in the opening of a follicle (pore) on the skin. Also known as blackheads
Papule	<u>Inflammatory lesion</u> ; raised spot on the skin that is less than 1 centimeter wide
Pustule	<u>Inflammatory lesion</u> ; small, inflamed, pus-filled , blister-like lesions on the skin surface
Nodules	Large, hard bumps under the skin's surface
Cysts	A closed pocket or pouch of tissue. It can be filled with air, fluid, pus, or other material

The Investigator's Global Assessment (IGA) will be performed and documented using the definitions in Table 1 (above).

Application site reactions [*Redacted*] will be recorded at each visit to allow a comparison between treatment groups. A detailed scale is presented in [Section 5.5](#).

Statistical Methods:

Efficacy Analyses

The efficacy assessment, superiority will be evaluated for each lesion type **on the face** using Analysis of Variance (ANOVA), with a statistical model containing terms for treatment and center, and with hypothesis testing at $\alpha = 0.05$. The analyses will evaluate if the mean percent change (reduction) from baseline, in each lesion type, for the Test treatment differs from that of the Vehicle. In case of extreme departure from the assumptions of normal error, defined as skewness of residuals from ANOVA model exceeding 2 in absolute value, a ranked-based, nonparametric method will be used. Superiority will be established if the mean percent change (reduction) from baseline for the Test treatment, for each of the inflammatory and non-inflammatory lesion counts is greater than, and statistically different from ($p < 0.05$), that for the Vehicle (Placebo) Control. For the proportions of subjects with treatment success on the IGA **on the face** the analysis will be conducted using two-sided, $\alpha = 0.05$ Fisher's exact test. Superiority will be established if the success proportion for the Test treatment is greater than, and statistically different from ($p < 0.05$), that of the Vehicle.

In order to preserve an overall type-I error (alpha) of 5%, a hierarchical evaluation scheme will be employed. The comparisons of interest are:

1. percent change from baseline in the inflammatory lesion counts
2. percent change from baseline in the non-inflammatory lesion counts
3. proportions of subjects with treatment success on the IGA

These comparisons will be performed in sequence for weeks 12, 10, 8, 6, 4, and 2.

Statistical testing will begin with comparison 1. If statistical significance is attained with comparison 1 ($p < 0.05$), then a claim of superiority for comparison 1 can be made and the next comparison in the hierarchical evaluation scheme can be tested for statistical significance. If statistical significance is not attained for comparison 1 ($p \geq 0.05$), then testing of all subsequent comparisons is stopped. The hierarchical, conditional-stepwise evaluation scheme allows for each comparison to be evaluated at the 5% level, while preserving an overall type I error rate of no more than 5%.

For **Subgroup** descriptive analyses comparing each lesion type and proportion of subjects with the treatment success on the body will be conducted for information purpose.

Efficacy results will be used to calculate the sample size for the Phase 3 studies.

Analysis of application site reactions

A descriptive analysis comparing the application site reactions for each treatment group will be conducted with regard to the expected and unexpected application site reactions. Application site reactions will also be compared between applications on the face and on the body.

Summary of Subjects who terminate prematurely

Reasons for premature termination will be summarized by treatment group.

Concomitant medication

The start and stop date of concomitant medication use during the study will be provided in the data set in addition to the reason for the medication use.

Safety Analyses

Safety analyses will be conducted on the safety population. Safety Incidence of all adverse events reported during the study will be summarized using the MedDRA dictionary by treatment group, body system, severity and relationship to study drug.

The report of AEs will include date of onset, description of the AE, and date of resolution. Formal statistical evaluation(s) of the comparability of the two treatment groups will be conducted with regard to the frequency and severity of any AE that occurs in at least 5% of the subjects in either treatment group.

1. INTRODUCTION AND BACKGROUND

Acne vulgaris is a disorder of the pilosebaceous unit. Found in greatest concentrations on the face, upper back, shoulders and chest, a pilosebaceous unit is made up of a hair follicle lined with keratinocytes, a sebaceous gland, and a hair. The sebaceous gland produces a substance called sebum. Although sebum normally empties onto the skin's surface through the openings of the follicles, the follicles may become plugged with hair, sebum and keratinocytes, resulting in comedones. Bacteria normally found on the skin may grow in the comedones, resulting in inflammation. Therefore, acne vulgaris is a multi-factorial disease, caused by the interplay of excess sebaceous gland secretion, bacterial growth, keratinization abnormalities, and immune reactivity.

Acne is clinically characterized by the formation of open and closed comedones (non-inflammatory lesions), papules, pustules and nodulocystic lesions (inflammatory lesions). The highest concentration of lesions is often found on the face, shoulders, upper back, and chest. Although acne vulgaris is most common in adolescents and young adults, it can continue to occur in adults older than 50 years of age.

Taro has developed a new formulation [*Redacted as ATS55*], for treatment of acne in patients 9 years of age and older. [*Redacted*] The current study is designed to evaluate the safety and efficacy of this new formulation. Efficacy results will be used to calculate the sample size and establish endpoints for the Phase 3 studies.

2. OBJECTIVES

The objective of this study to evaluate the efficacy and safety of [*Redacted as ATS55*] (Taro Pharmaceuticals U.S.A, Inc.) in the treatment of acne vulgaris.

3. STUDY OVERVIEW

Subjects will be admitted into the study after informed consent/assent has been obtained, a medical history and physical examination (with vital signs) have been performed and inclusion/exclusion criteria have been met. Subjects must have a clinical diagnosis of acne vulgaris to qualify for inclusion in this study.

Approximately 300 Subjects will be assigned in a 1:1 ratio to treatment with the test product, [*Redacted as ATS55*] (Taro Pharmaceuticals U.S.A., Inc.) or placebo (vehicle of the test product) in this multiple-center, double-blind, randomized, placebo controlled, parallel-group study. The assigned Investigational Product will be self-applied topically to the face and other affected body areas once daily for 84 consecutive days. The Investigational Product should be applied around the same time every day after the Subject's treatment areas have been washed with a non-medicated cleanser, and warm water. For the purposes of this study, the face is considered to start at the hairline and end at the jaw line and excludes the eyes, the lips and all mucous membranes. The body is considered as at least one affected area: back, chest and/or shoulders. Subjects will be required to use diaries to document the date of study treatments, any missed treatments and the occurrence of all adverse events.

The duration of each Subject's participation in the study will be 84 days. Scheduled study visits will include:

- Visit 1: Screening/Baseline Visit (Day 0);
 - Visit 2: Interim Visit (Week 2 / Day 14 ± 4 Days);
 - Visit 3: Interim Visit (Week 4 / Day 28 ± 4 Days);
 - Visit 4: Interim Visit (Week 6 / Day 42 ± 4 Days);
 - Visit 5: Interim Visit (Week 8 / Day 56 ± 4 Days);
 - Visit 6: Interim Visit (Week 10 / Day 70 ± 4 Days);
 - Visit 7: End of Treatment Visit (Week 12 / Day 84 ± 4 Days)
 - Visit 8*: Follow up phone call (Week 13 / Day 91 ± 4 Days)
- *if required for on-going AEs based on PI decision

A nine (9) day window (i.e., ± 4 days) will be considered acceptable for each scheduled visit following

the baseline visit.

An Unscheduled Visit is allowed at any time, for any reason, if in the Principal Investigator's opinion it is warranted. If a Subject is discontinued from the study during an Unscheduled Visit, the Unscheduled Visit will be referred to as an Early Discontinuation Visit and all procedures scheduled for Visit 7 will be performed. If the Unscheduled Visit is not an Early Discontinuation Visit (i.e., the Subject will continue to take part in the study), then all procedures will be performed and treated as an interim visit, with the exception of the collection of Investigational Product and Subject diaries from Subjects.

If the Principal Investigator determines that the Subject's condition has worsened to the degree that it is unsafe for the Subject to continue in the study, the Subject may be discontinued from the study as a treatment failure and the Subject may be treated using the standard care.

At the screening/baseline visit, a physical examination (with vital signs) will be conducted. At each subsequent visit, the following procedures will be performed: counts of the facial comedones (open and closed), papules, pustules, nodules and cysts lesions will be performed, the Investigator's Global Evaluation (IGA) will be performed and the signs and symptoms of irritation will be assessed.

Safety will be assessed by the monitoring of all adverse events and the monitoring of any signs and symptoms of local irritation.

At Visit 1, an informed consent/assent and HIPAA authorization will be obtained from the potential study Subject before any study procedures take place. After the Subject has been consented/assented, the Subject's medical history will then be documented, including the Subject's concomitant medications. A urine pregnancy test will be performed for female Subjects of childbearing potential. All female Subjects are considered to be of childbearing potential unless they are premenarchal, have been surgically sterilized or have been postmenopausal for at least 1 year. A baseline acne grade will be assigned to the Subject using the Investigator's Global Assessment (IGA) and a baseline lesion count will be performed. The Subject will undergo a brief physical examination, including the recording of vital signs. The Subject will be evaluated for signs and symptoms of local irritation. The Subject will be reviewed against the inclusion/exclusion criteria. Blinded Investigational Product will be dispensed to Subjects who meet all of the inclusion and exclusion criteria using the lowest patient randomization number available at that investigative site. Subjects will be instructed on the application of Investigational Product and completion of Subject diaries. The Investigational Product should not be opened in the clinic. The first application of Investigational Product will be performed by the Subject at home.

Subjects will return to the study site for visits at Weeks 2, 4, 6, 8, 10, and 12. The Subject's concomitant medications will be reviewed and documented. A urine pregnancy test will be performed for female Subjects of childbearing potential. The Subject will be evaluated for signs and symptoms of local irritation and any adverse events will be documented. The Subject's facial acne will be assessed using the IGA, the Subject's lesions will be counted and these results will be documented. The Subjects are instructed to bring their used Investigational Product and their study diaries to each study visit. Compliance with drug applications will be assessed at each visit. Additional units of Investigational Product will be dispensed and each Subject will receive new diaries during visits at Weeks 2, 4, 6, 8, and 10. In addition, all Investigational Product and diaries will be collected from the Subject during each scheduled visit or the Early Discontinuation Visit.

Study Visit Schedule

PROCEDURE	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	Screening / Randomization / Baseline / Treatment start	Interim - 1	Interim - 2	Interim - 3	Interim - 4	Interim - 5	EOT/UV/ED ¹
Day	0	14 ± 4 (week 2)	28 ± 4 (week 4)	42 ± 4 (week 6)	56 ± 4 (week 8)	70 ± 4 (week 10)	84 ± 4 (week 12)
Informed Consent/Assent and HIPAA	X						
Demographics	X						
Medical History	X						
Concomitant Medication	X	X	X	X	X	X	X
Brief Physical Examination including Vital Signs	X						
Urine Pregnancy Test²	X	X	X	X	X	X	X
Inclusion/Exclusion Criteria	X						
Local Irritation Assessment	X	X	X	X	X	X	X
Lesion Counts	X	X	X	X	X	X	X
Investigator's Global Assessment (IGA)	X	X	X	X	X	X	X
Randomization	X						
Adverse Event Reporting	X ³	X	X	X	X	X	X
Investigational Product Dispensing / Diary Dispensing	X	X	X	X	X	X	
Investigational Product Return / Diary Collection		X	X	X	X	X	X ⁴
Diary Review		X	X	X	X	X	X
Investigational Product Accountability		X	X	X	X	X	X
Review of Instructions with Subject (including Diary Completion Instructions)	X	X	X	X	X	X	
Treatment Area Photograph**	X	X	X	X	X	X	X
Schedule next visit	X	X	X	X	X	X	

¹ EOT - End of Treatment, UV - Unscheduled Visit, ED - Early Discontinuation Visit

² The urine pregnancy test is to be conducted for women of child-bearing potential. Tubal ligation is not considered equivalent to female sterilization. Women with a history of tubal ligation are still considered females of childbearing potential and must complete a urine pregnancy test.

³ Any AEs reported after signing Informed Consent should be reported.

⁴ Investigational product and Subject Diaries will be collected from patients during Visit 7 (End of Treatment Visit) or the Early Discontinuation Visit.

** two sites will be designated to take pictures of the treatment areas from designated subjects from Subgroup at each Clinic Visit

4. STUDY POPULATION

4.1 Number of Subjects

This multi-center study will be comprised of Subjects presenting with a clinical diagnosis of acne vulgaris of severity grade 2, 3, or 4 using the IGA. Approximately 300 Subjects will be enrolled into the study. Male and female Subjects, ≥ 9 years of age, of any race, who meet the inclusion and exclusion criteria, will be enrolled in approximately 5 study sites. Approximately equal numbers of male and female subjects will be enrolled to each of the study arms.

4.2 Inclusion Criteria

[Redacted]

4.3 Exclusion Criteria

[Redacted]

4.4 Prohibited Medications, Procedures, and Activities

[Redacted]

4.5 Precautions

The following precautions are to be taken during this study:

1. To minimize exposure to sunlight, a wide-brimmed hat or other protective clothing should be worn. The non-comedogenic sunscreen with a SPF 15 rating or higher provided by the Sponsor may be used.
2. Exposure to weather extremes including strong wind or cold should be avoided.
3. The Investigational Product should not be applied to cuts, abrasions or eczematous skin.
4. The Investigational Product should not be applied to the eyes, the lips, the angles of the nose or any mucous membranes.

If a reaction suggesting sensitivity or chemical irritation occurs, the Principal Investigator should assess the Subject's condition as soon as possible (i.e., during an Unscheduled Visit) and determine whether treatment should be discontinued. If the Subject is discontinued from the study during an Unscheduled Visit, procedures from Visit 4 should be followed and the visit will be referred to as an Early Discontinuation Visit.

4.6 Subject Disposition and Discontinuation

Investigators are urged to enroll only those eligible Subjects who are likely to complete the entire study and who are willing to comply with the protocol-specified procedures. It is the right and duty of the investigator to interrupt the treatment of any Subject whose health or well-being may be threatened by continuation in this study, or who may be experiencing unmanageable factors that may interfere with the study procedures and/or the interpretation of study results. Such Subjects should be withdrawn from the study rather than continued under a modified regimen.

Subjects will be removed from the study for any of the following reasons:

- If the Subject withdraws his or her consent for any reason;
- If the Subject's condition has worsened beyond grade 4 or to the degree that the Principal Investigator feels it is unsafe for the Subject to continue in the study;

- If the Subject's drug code is unblinded;
- If an adverse event occurs for which the Subject desires to discontinue treatment or the Principal Investigator determines that it is in the Subject's best interest to be discontinued;
- If there is a significant protocol violation;
- If the Subject is lost to follow-up;
- If the Subject becomes pregnant;
- If the Subject becomes a prisoner or become involuntarily incarcerated;
- Any other reason that may affect the outcome of the study or the safety of Subjects; or
- Termination of the study by the Sponsor.

A significant protocol violation is defined as any Subject or Investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy.

The reasons for a Subject discontinuation will be documented. If a Subject is discontinued from the study for any reason, the procedures scheduled for Visit 7 will be completed and any outstanding data and study drug should be collected if possible. Data, in addition to the reason for discontinuation and the date of removal, will be documented on the End of Study eCRF.

Before a Subject is considered to be lost to follow-up, the Principal Investigator will document all attempts to reach the Subject twice by telephone and will send a certified follow-up letter.

In the event that a Subject discontinues from the study at any time due to an adverse event, the reason for discontinuation, the nature of the event and its clinical course must be fully documented. For such a Subject, the Principal Investigator must strive to follow the Subject until the adverse event has resolved, become clinically insignificant, is stabilized or the Subject is lost to follow-up. Should a serious adverse event be noted, procedures stated in [Section 10.3](#) must be followed.

5. SAFETY AND TOLERABILITY EVALUATIONS

5.1 General Safety Evaluations

A complete medical history will be obtained for the Subject's current and past medical conditions. Significant medical history should include, but not be limited to, evidence of hypertension, lipid disorders, obesity, heart attack, stroke, congestive heart failure, kidney disease, auto immune disease and gestational diabetes. Significant surgical history should include, but not be limited to, removal of blockage from an artery and gallbladder removal.

Concomitant medications, including the use of sunscreen, in addition to the reason for the medication use, will be assessed at baseline and at each subsequent study visit. The start and stop date of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use.

A brief physical examination will be performed at baseline. The physical examination will include, at a minimum, examination of the Subject's general appearance, skin, HEENT (head, eyes, ears, nose and throat), heart, lungs, musculoskeletal system, neurological system, lymph nodes, abdomen and extremities. The Subject's body weight will also be measured while the Subject is lightly clothed (e.g., no coat or shoes).

5.2 Physical Examination

The investigator, sub-investigator or appropriately delegated designee, (Physician's Assistant, Advanced Registered Nurse Practitioner, and Registered Nurse as per local regulations) will perform a brief physical examination, prior to the Subject starting study drug.

Vital signs, including blood pressure, pulse rate, respiratory rate and oral body temperature will be documented at Visit 1. Vital signs will be measured after the Subject has rested in a seated position for at least 5 minutes.

The Subject's body weight will also be measured while the Subject is lightly clothed (e.g., no coat or shoes). Height will be measured without shoes.

5.3 Pregnancy Test

All female Subjects of childbearing potential will undergo a urine pregnancy test during Visit 1 and at each subsequent study visit. All female Subjects are considered to be of childbearing potential unless they are premenarchal, have been surgically sterilized or have been postmenopausal for at least 1 year. Women of childbearing potential, in addition to having a negative urine pregnancy test, must be willing to use an acceptable form of birth control during the study from the day of the first dose administration to 30 days after the last administration of study drug. For the purpose of this study the following are considered acceptable methods of birth control: oral or injectable contraceptives, contraceptive patches, Depo-Provera® (stabilized for at least 3 months), NuvaRing® (vaginal contraceptive), Implanon™ (contraceptive implant), double barrier methods (e.g. condom and spermicide), IUD, or abstinence with a 2nd acceptable method of birth control should the Subject become sexually active. A sterile sexual partner is NOT considered an adequate form of birth control. Subjects on hormonal contraception must be stabilized on the same type for at least three months prior to enrollment in the study and must not change the method during the study. Subjects who had used hormonal contraception and stopped must have stopped no less than three months prior to the study.

5.4 Concomitant medications

Concomitant medications, including the use of sunscreen, in addition to the reason for the medication use, will be assessed at baseline and at each subsequent study visit. The start and stop date of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use.

A record of concomitant medications taken by the Subject is to be obtained using generic name, if known, with the corresponding indication. The medications to be recorded will include prescription and over-the-counter (OTC) medications and dietary supplements. All medications taken on a regular basis, including aspirin and acetaminophen, should be recorded.

5.5 Signs/Symptoms of Local Irritation

At each study visit, beginning at Visit 1, Subjects will be evaluated for any signs and symptoms of local irritation [Redacted]. Baseline values will be used for comparative purposes against the scores documented at subsequent visits for each treatment group. Each Subject will be assigned a severity score by an Investigator based on the scale in Table 2.

Application site reactions [Redacted] will be recorded at each visit to allow a comparison between treatment groups.

Table 3: Expected Application Site Reactions

[Redacted]

Subjects with a baseline irritation score of 3 (severe, marked/intense) will not be enrolled. After baseline, severe irritation (i.e., grade 3, described as severe or marked/intense) that requires treatment will be reported as an adverse event.

Local irritation reactions in the treatment area are common and the Investigator may instruct Subjects to stop the application of treatment (“rest period”) to reduce Subject discomfort and to allow local skin reactions to subside based upon the Investigator’s clinical assessment. Treatment should resume as soon as the reaction subsides sufficiently to allow reapplication. All dose modifications must be reported on the appropriate Study Medication Log & Dosing Compliance eCRF.

The treatment period should not be extended beyond 12 weeks due to missed doses or rest periods. Subjects whose condition worsens or lesions do not respond to treatment should be re-evaluated by the Investigator and management reconsidered.

5.6 Adverse Events

An adverse event is defined as any untoward medical occurrence (sign, symptom or laboratory finding), regardless of severity and whether or not attributed to the investigational product. All adverse events, whether observed by an Investigator or Study Coordinator or reported by the Subject, whether related to study drug or not related to study drug, shall be documented on the eCRF and Subject records, together with details, i.e. date of onset, the duration and intensity of each episode, the action taken, the relationship to the investigational product and the degree of severity, the seriousness and the outcome.

6 CLINICAL EVALUATIONS

An examination of the Subject’s acne will be performed at baseline and at each subsequent visit. During the dermatologic examination, evaluations to determine efficacy of treatment will be conducted, including lesion counts and grading of the Subject’s acne using the criteria outlined in the IGA.

Preferably a single Investigator (i.e., Principal Investigator or Sub-Investigator) or qualified staff will perform evaluations of efficacy (i.e., lesion counts and IGA) for each Subject at each visit from the beginning to the end of the Subject’s participation to maintain consistency; however, only up to two Investigators or qualified staff may perform evaluations of efficacy for a single Subject if necessary. [Redacted].

6.1 Lesion Counts and Investigator’s Global Assessment

At each visit, an Investigator or qualified staff will assess the Subject’s acne by counting the number of open and closed comedones, pustules, papules and nodulocystic lesions. All lesions will be counted, including those present on the nose. An Investigator will also assess the overall status of the Subject’s acne vulgaris using the IGA. The IGA scores for each visit will be documented on the eCRF. For the purposes of this study, the face is considered to start at the hairline and end at the jaw line and excludes the eyes, the lips and all mucous membranes. The body is considered as at least one affected area: back, chest and/or shoulders.

[Redacted]

Definition of inflammatory and non-inflammatory lesions

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Lesion Type	Definition
Closed Comedone	Non-inflammatory lesion; whitehead, skin-colored or slightly inflamed “bump” in the skin
Open Comedone	Non-inflammatory lesion; blackhead, surface of the plugged sebaceous follicle has a blackish appearance
Papule	Inflammatory lesion; a small (≤ 5 mm in diameter), solid palpable lesion, usually with inflamed elevation of the skin that does not contain pus
Pustule	Inflammatory lesion; a small (≤ 5 mm in diameter), inflamed skin swelling that is filled with pus
Nodules	Large, hard bumps under the skin's surface
Cysts	Similar to a nodule, but is pus-filled, and ≥ 5 mm in diameter

The following scale will be used for the IGA:

IGA Scale for Acne Vulgaris

Grade	Description
0	Clear skin with no inflammatory or non-inflammatory lesions
1	Almost clear; rare non-inflammatory lesions with no more than one small inflammatory lesion
2	Mild severity; greater than Grade 1; some non-inflammatory lesions with no more than a few inflammatory lesions (papules/pustules only, no nodular lesions)
3	Moderate severity; greater than Grade 2; up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion
4*	Severe; greater than Grade 3; up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than a few nodular lesions

* The eCRF will allow for reporting of lesion worsening beyond Grade 4 with treatment. Subjects who worsen beyond Grade 4 will be described in the safety evaluation.

Please note that nodulocystic lesions will not be included in the inflammatory lesion count. Counts of nodules and cysts will be reported separately and not included in the inflammatory or non-inflammatory lesion counts.

7 STUDY VISITS (SEE [STUDY VISIT SCHEDULE](#))

7.1 Visit 1: Baseline (Day 0)

The following procedures will be performed at Visit 1:

1. **Written informed consent will be obtained.** Subjects who are 18 years of age or older must have provided IRB approved written informed consent. For subjects under the age an assent form for minors must be completed for subjects under the legal age of consent depending on age range required by state laws. Written assent must be accompanied by an IRB approved written informed consent from the Subject's legally acceptable representative (i.e., parent or guardian). Prior to initiating screening for the study, Subjects will be given the approved ICF/assent describing the study and any risks associated with participation. The Subject will be

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allowed as much time as needed to read and understand the information presented in the consent/assent form. Appropriate study personnel will be available to answer any questions the Subject might have regarding the study or study-related procedures. If the Subject chooses to participate in the study, he or she will be asked to sign and date the consent/assent form and will be provided with a copy for his or her records. In addition, the Principal Investigator or the Principal Investigator's Designee will provide a HIPAA authorization form (if applicable) for the Subject or the Subject's legally acceptable representative (i.e., parent or guardian) to review and sign. Both the ICF/assent and the HIPAA authorization form (if applicable) must be signed by the Subject or the Subject's legally acceptable representative (i.e., parent or guardian) before any protocol assessments can be undertaken.

2. A complete medical history will be obtained for the Subject's current and past medical conditions. Significant medical history should include, but not be limited to, evidence of hypertension, lipid disorders, obesity*, heart attack, stroke, congestive heart failure, kidney disease, and auto immune disease and gestational diabetes. Significant surgical history should include, but not be limited to, removal of blockage from an artery and gallbladder removal.
* Obesity = BMI \geq 30 (as defined by Metropolitan Life Insurance Company Chart)
3. Demographics and vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated position for 5 minutes before vital signs are obtained.
4. A brief physical examination, including height (measured in inches) and weight (measured in pounds), will be performed. At a minimum, the physical examination will include the following: assessment of general appearance, skin, HEENT, heart, lungs, musculoskeletal system, lymph nodes, neurological systems, abdomen, extremities.
5. A complete list of current and past (within the previous 30 days) concomitant medications will be obtained for each Subject. (See [Section 4.3](#))
6. A urine pregnancy test will be conducted for all females of childbearing potential.
7. Lesion counts will be done by counting the number of open and closed comedones, pustules, papules and nodulocystic lesions on the treatment areas. All lesions will be counted, including those present on the nose. (See [Section 6.1](#))
8. The overall status of the Subject's acne vulgaris on the treatment areas will be assessed using the IGA. (See [Section 6.1](#))
9. Subjects will be evaluated for any signs and symptoms of facial irritation [*Redacted*]. Each Subject will be assigned a severity score based on the Local Irritation Scale. (See [Section 5.5](#))
10. When the Subject has completed all screening procedures, compliance with the inclusion and exclusion criteria will be reviewed. After the inclusion and exclusion criteria have been confirmed, the Subject will be randomized to a treatment group. The Subject will be assigned a randomization number (See [Section 8.5](#)).
11. Pictures of the treatment areas will be collected from designated subjects from Subgroup
12. The following will be dispensed during Visit 1:
 - The investigational product
[*Redacted*]
13. Randomized Subjects will be instructed on the correct method for the application of the Investigational Product. The first application of the Investigational Product will be performed by the Subject at home. The study restrictions will also be reviewed with the Subject and an instruction sheet will be issued to the Subject. (See [Section 8.5](#))

14. Randomized Subjects will be provided with a diary and instructed how and when to complete the diary. They will be told that they are to document all treatments administered, including the date and all treatments missed. In addition, Subjects will be instructed to document all AEs. Subjects will also be instructed to call the study site if they experience any severe intolerability (i.e., local skin reactions) to Investigational Product.
15. Visit 2 (Day 14 ± 4 days from the date of Visit 1) will be scheduled and the Subject will be instructed to bring all Investigational Product (used, unused, and partially used) and the Subject diary with him or her to this visit.

7.2 Visits 2-6: Interim Visits (weeks 2, 4, 6, 8, and 10)

The following procedures will be performed at Visits 2, 3, 4, 5, and 6:

1. Lesion counts will be done by counting the number of open and closed comedones, pustules, papules and nodulocystic lesions on the treatment areas. All lesions will be counted, including those present on the nose. (See [Section 6.1](#))
2. The overall status of the Subject's acne vulgaris on the treatment areas will be assessed using the IGA. (See [Section 6.1](#))
3. The Subject's facial erythema will be assessed. (See [Section 6.3](#)).
4. Subjects will be evaluated for any signs and symptoms of facial irritation [*Redacted*]. Each Subject will be assigned a severity score based on the Local Irritation Scale. (See [Section 5.5](#))
5. Pictures of the treatment areas will be collected from designated subjects from Subgroup
6. A urine pregnancy test will be conducted for all females of childbearing potential.
7. The occurrence of all AEs will be assessed and documented following procedures in [Sections 5.6](#) and [10.1](#).
8. The use of concomitant medications since the previous study visit will be documented and assessed for each Subject. The use of moisturizer, including the type and how often it has been used, will be included. (See [Section 4.4](#))
9. The Subject's compliance with the study protocol, including use and application of Investigational Product, will be assessed. (See [Section 8.6](#)) The Subject's diary will be reviewed for completion.
10. The following will be dispensed/redispensed:
 - Visit 2 (week 2):
 - The investigational product – redispensed
[*Redacted*]
 - Visit 3 (week 4):
 - The investigational product – new
[*Redacted*]
 - Visit 4 (week 6):
 - The investigational product – redispensed
[*Redacted*]
 - Visit 5 (week 8):
 - The investigational product – new

[Redacted]

Visit 6 (week 10):

- The investigational product – redispensed

[Redacted]

11. Study instructions will be reviewed with the Subject, including the procedure for application of the Investigational Product. (See [Section 8.5](#))
12. Next visit will be scheduled and the Subject will be instructed to bring all Investigational Product (used, unused and partially used) and the Subject diary with him or her to this visit.

7.3 Visit 7: End of Treatment Visit (Week 12; Day 84 ± 4 Days)

The following procedures will be performed at Visit 7:

1. Lesion counts will be done by counting the number of open and closed comedones, pustules, papules and nodulocystic lesions on the treatment areas. All lesions will be counted, including those present on the nose. (See [Section 6.1](#))
2. The overall status of the Subject's acne vulgaris on the treatment areas will be assessed using the IGA. (See [Section 6.2](#))
3. Subjects will be evaluated for any signs and symptoms of the treatment areas irritation [Redacted]. Each Subject will be assigned a severity score based on the Local Irritation Scale. (See [Section 5.5](#))
4. Pictures of the treatment areas will be collected from designated subjects from Subgroup
5. A urine pregnancy test will be conducted for all females of childbearing potential.
6. The occurrence of all AEs will be assessed and documented following procedures in [Sections 5.6](#) and [10.1](#).
7. The use of concomitant medications since the previous study visit will be documented and assessed for each Subject. The use of moisturizer, including the type and how often it has been used, will be included. (See [Section 4.4](#))
8. The Subject's compliance with the study protocol, including use and application of Investigational Product, will be assessed. (See [Section 8.6](#))
9. The Subject's used Investigational Product will be returned to the third-party drug dispenser. (see [Section 8.7](#))

7.4 Unscheduled Visits and Early Discontinuation Visit

An Unscheduled Visit is allowed at any time, for any reason, if in the Principal Investigator's opinion it is warranted. If the Unscheduled Visit is due to an AE, the Principal Investigator will determine whether additional visits are needed.

If a Subject is discontinued from the study during an Unscheduled Visit, the Unscheduled Visit will be referred to as an Early Discontinuation Visit and all procedures scheduled for Visit 7 will be performed. If the Unscheduled Visit is not an Early Discontinuation Visit (i.e., the Subject will continue to take part in the study), then all procedures scheduled for that interim visit will be performed, with the exception of the collection of Investigational Product and Subject diaries from Subjects.

If the Subject's condition has worsened to the degree that it is unsafe for the Subject to continue in the study, the Subject may be discontinued from the study as treatment failure and a standard of care treatment may be advised at the Principal Investigator's discretion.

8 INVESTIGATIONAL PRODUCT

8.1 Description

All study medications will be dispensed by qualified Independent dispenser designated by the Principal Investigator. The investigational product will be dispensed only from the institution(s) specified on FDA Form 1572.

The following treatments will be self-administered or administered by the Subject's caregiver during this study.

The Investigational Product supplied by the Sponsor will consist of the following:

Test Product: [Redacted as ATS55] (Taro Pharmaceuticals U.S.A, Inc.)

Placebo Control: Vehicle of test product (Taro Pharmaceuticals U.S.A., Inc.)

8.2 Storage Conditions

Store at controlled room temperature between 20 – 25°C (68 – 77°F) with excursions permitted to 15° – 30°C (59° – 86°F).

Protect from freezing.

8.3 Packaging, Blinding and Labeling

In order to maintain the study blind the randomization schedule will be generated by a third party. Randomization will be performed according to a computer-generated randomization scheme. The four digit unique randomization number will be designated as the Subject number. Only one Subject number will be assigned to each Subject. The Subject will maintain the same number and treatment assignment throughout the study. [Redacted].

8.4 Treatment Assignment

The subject study identification number will correspond to a computer-generated randomization schedule assigning that number to one of the three study treatment groups. The randomization scheme will be generated, in blocks of 6, so that the test product and the vehicle (placebo) control are assigned in a 1:1 ratio. The subject numbers at the site will correspond to the order in which subjects are enrolled into the study.

8.5 Administration of Investigational Product

At baseline, and as needed during the study, Investigational Product will be dispensed to randomized Subjects along with a diary. Each Subject will also receive written study instructions, which detail the proper application method of the Investigational Product and general study instructions.

Subjects will apply a thin layer of study medication to cover the entire face and other affected body areas once daily, avoiding contact with the mouth, eyes and open wounds. For the face applications subjects will be instructed to apply the product to the hand or cotton pad and gently rub it to the entire face. For the body applications (e.g., on the back, chest and shoulders), the product will be applied to the affected areas and gently rubbed into the skin. Subjects will wash their hands before and after administration of the Investigational Product. Investigational Product will be applied in this manner for 84 consecutive days.

Subjects will be required to use diaries to document the date of study treatments, any missed treatments and the occurrence of all adverse events. [Redacted].

Subjects will be instructed not to bathe, shower, wash or swim for at least 4 hours after the application of the Investigational Product.

At each visit during the study, the Investigator or designee should review proper application of the Investigational Product.

8.6 Assessment of Compliance

Compliance with scheduled application of Investigational Product will be determined from the Subject's diary. The Subject will be instructed to use the diary to document all doses taken by checking the yes or no box for the appropriate date. In addition, Subjects will be instructed to document all AEs on the diary. Used Investigational Product will be returned to the study site at each scheduled visit or Early Discontinuation Visit. If the subject does not return the Diary, patient-reported dosing compliance will be recorded in the source notes and will be used to derive compliance between those visits.

8.7 Investigational Product Accountability

It is the responsibility of the Principal Investigator to ensure that the current disposition of the Investigational Product is maintained at each study site where Investigational Product is inventoried and dispensed. When a drug shipment is received at a study site, the Principal Investigator or the Principal Investigator's Designee must inventory the drug and sign the receipt form provided with the shipment. The receipt form should be faxed to the drug depot as per instructions provided on the receipt. A copy of the receipt should remain at the site.

The Investigator will not supply study test articles to any person not enrolled in this study, or to any physician or scientist except those named as sub-investigators.

A Drug Accountability Log will assist study site staff in maintaining inventory records of study drug.

Subjects must return used, partially used or unused Investigational Product to the study site staff so that any remaining drug supplies can be accounted for and noted in the Drug Accountability Log. Weights of all dispensed units of the Investigational Product will be obtained before dispensing and after the units are returned to the study site.

The original Drug Accountability Log must be provided to the study monitor at the conclusion of the study and a copy should remain at the study site.

8.8 Retention of Study Drug Samples

A sufficient amount of the study drug will be randomly selected for retention by the packaging facility and shipped to the storage facility for a long term storage. [Redacted]

8.9 Return of Clinical Supplies

All used and unused containers of Investigational Product may be returned to the Drug Labeling, Packaging and Shipping Facility for destruction or be destroyed at the site after study close-out and final drug accountability is reconciled.

8.10 Additional Supplies Provided by The Sponsor

- [Redacted]

9. STATISTICAL METHODS

9.1 Scientific and Statistical Considerations of the Study Design

The current study is designed to evaluate the safety and efficacy of this new formulation. Efficacy results will be used to calculate the sample size and establish endpoints for the Phase 3 studies.

The study was designed following FDA Guidance for Industry (Draft). Acne Vulgaris: Developing Drugs for Treatment. Division of Dermatologic and Dental Drug Products. FDA September 2005.

9.2 Sample Size Rationale

The primary statistical analyses of interest are the differences between the Test and the Placebo (Vehicle) treatments in the mITT population for mean inflammatory and non-inflammatory lesion count reductions, and for proportions of subjects with clinical success on the IGA for. In this Phase 2 study, approximately 300 Subjects will be enrolled to obtain at least 286 evaluable in the mITT Subjects (143 in each treatment group).

9.3 Randomization and Unblinding Procedures

Subjects will be randomly assigned in a 1:1 ratio to receive the test product or the vehicle (placebo) control. The randomization assignment will be generated using SAS® by an independent statistician, not involved with the study.

The Drug Labeling, Packaging facility will hold the randomization code throughout the conduct of the study in order to minimize bias. A sealed copy of the randomization scheme (as a scratch off portion of the product label attached to the drug accountability page) will be retained at the study site. In the event of an emergency, the Subject-specific treatment may be identified; however, every effort should be made to maintain the blind. Where possible, the CRO medical monitor should be contacted before breaking the blind for any patient. The Sponsor must be notified in the event the blind is broken.

The treatment assignments will remain blinded until the final database is closed.

9.4 Significance Level

All statistical tests will be two-sided at a significance level of $\alpha = 0.05$. No adjustment will be made for multiplicity.

9.5 Datasets to be Analyzed

Two analysis populations will be used in the analysis of the clinical data:

1. A safety population Subject is any individual who was randomized into the study and used at least one dose of investigational product.
2. The Modified ITT (mITT) population includes all Safety population Subjects who have met all inclusion/exclusion criteria and return for at least one post-baseline efficacy evaluation.

Efficacy analyses will be performed on the ITT. All efficacy data will be listed by treatment and Subject in data listings.

9.6 Handling of Missing Data

Missing safety data will not be imputed. In the analysis of efficacy on mITT population for subjects who discontinue from the study due to lack of efficacy, their IGA success endpoint will always be imputed as failure. In all other cases missing endpoints will be imputed with LOCF by carrying forward the last available post-baseline assessment.

9.7 Measures

Lesion Counts will be performed using the following definitions:

Definition of inflammatory and non-inflammatory lesions

Lesion Type	Definition
Closed Comedone	<u>Non-inflammatory lesion</u> ; white, raised bumps caused by collections of oil and skin in pores. Also known as white heads and pimples
Open Comedone	<u>Non-inflammatory lesion</u> ; tiny, dark spots caused by a small plug in the opening of a follicle (pore) on the skin. Also known as blackheads
Papule	<u>Inflammatory lesion</u> ; raised spot on the skin that is less than 1 centimeter wide
Pustule	<u>Inflammatory lesion</u> ; small, inflamed, pus-filled , blister-like lesions on the skin surface
Nodules	Large, hard bumps under the skin's surface
Cysts	A closed pocket or pouch of tissue. It can be filled with air, fluid, pus, or other material

The Investigator's Global Assessment (IGA) will be performed and documented using the definitions in the table, below:

IGA Scale for Acne Vulgaris

Grade	Description
0	Clear skin with no inflammatory or non-inflammatory lesions
1	Almost clear; rare non-inflammatory lesions with no more than one small inflammatory lesion
2	Mild severity; greater than Grade 1; some non-inflammatory lesions with no more than a few inflammatory lesions (papules/pustules only, no nodular lesions)
3	Moderate severity; greater than Grade 2; up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion
4*	Severe; greater than Grade 3; up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than a few nodular lesions

* The eCRF will allow for reporting of lesion worsening beyond Grade 4 with treatment. Subjects who worsen beyond Grade 4 will be described in the safety evaluation.

Please note that nodulocystic lesions will not be included in the inflammatory lesion count.

Counts of nodules and cysts will be reported separately and not included in the inflammatory or non-inflammatory lesion counts

The following scale will be used for the application site reactions

[Redacted]

9.8 Demographics and Baseline/Randomization Characteristics

Demographic and baseline/randomization characteristics will be evaluated for comparability across treatment groups for the ITT and safety populations. [Redacted].

9.9 Safety Assessment

The extent of exposure will be summarized using descriptive statistics. No inferential analyses are planned.

Incidence of all adverse events reported during the study will be summarized using the MedDRA dictionary by treatment group, body system, severity, and relationship to study drug. The comparability of the Test and Placebo treatment groups for the frequency and severity of any adverse event that occurs in at least 5% of the Subjects in either treatment group will be evaluated using categorical methods.

Incidence of concomitant medications will be summarized by treatment group.

Safety analyses will be performed on the safety population. All safety data will be listed by treatment and Subject in data listings.

9.10 Efficacy Assessment

The efficacy assessment, superiority will be evaluated for each lesion type **on the face** using Analysis of Variance (ANOVA), with a statistical model containing terms for treatment and center, and with hypothesis testing at $\alpha = 0.05$. The analyses will evaluate if the mean percent change (reduction) from baseline, in each lesion type, for the Test treatment differs from that of the Vehicle. In case of extreme departure from the assumptions of normal error, defined as skewness of residuals from ANOVA model exceeding 2 in absolute value, a ranked-based, nonparametric method will be used. Superiority will be established if the

mean percent change (reduction) from baseline for the Test treatment, for each of the inflammatory and non-inflammatory lesion counts is greater than, and statistically different from ($p < 0.05$), that for the Vehicle (Placebo) Control. For the proportions of subjects with treatment success on the IGA on the face the analysis will be evaluated by Fisher's exact test. Superiority will be established if the success proportion for the Test treatment is greater than, and statistically different from ($p < 0.05$), that of the Vehicle.

In order to preserve an overall type-I error (alpha) of 5%, a hierarchical evaluation scheme will be employed. The comparisons of interest are:

- 1) percent change from baseline in the inflammatory lesion counts
- 2) percent change from baseline in the non-inflammatory lesion counts
- 3) proportions of subjects with treatment success on the IGA

These comparisons will be performed in sequence for weeks 12, 10, 8, 6, 4, and 2.

Statistical testing will begin with comparison 1. If statistical significance is attained with comparison 1 ($p < 0.05$), then a claim of superiority for comparison 1 can be made and the next comparison in the hierarchical evaluation scheme can be tested for statistical significance. If statistical significance is not attained for comparison 1 ($p \geq 0.05$), then testing of all subsequent comparisons is stopped. The hierarchical, conditional-stepwise evaluation scheme allows for each comparison to be evaluated at the 5% level, while preserving an overall type I error rate of no more than 5%.

For **Subgroup** descriptive analyses comparing each lesion type and proportion of subjects with the treatment success on the body will be conducted for information purpose.

Efficacy results will be used to calculate the sample size for the Phase 3 studies.

9.11 Analysis of Application Site Reactions

A descriptive analysis comparing the application site reactions for each treatment group will be conducted with regard to the expected and unexpected application site reactions. Application site reactions will also be compared between applications on the face and on the body.

9.12 Concomitant Medication

The start and stop date of concomitant medication use during the study will be provided in the data listings in addition to the reason for the medication use.

9.13 Summary of Subjects who terminate prematurely

Reasons for premature termination will be summarized by treatment group.

10. ADVERSE EVENTS

10.1 Reporting of Adverse Events

Any untoward medical occurrence in a Subject or clinical-trial Subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Any adverse event associated with the use of a drug in humans, whether or not considered product-related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action. Reporting an adverse event does not necessarily reflect a conclusion that the product caused or contributed to the adverse event.

All adverse events, whether observed by an Investigator or Study Coordinator or reported by the Subject, whether related to study drug or not related to study drug, shall be documented in the CRF and Subject records, together with details of the duration and intensity of each episode, the action taken, the relationship to the Investigational Product and the degree of severity, the seriousness and the outcome.

[Redacted]The Principal Investigator must strive to follow the Subject until the adverse event has resolved, becomes clinically insignificant, is stabilized or the Subject is lost to follow-up. The Principal Investigator must immediately report to the Contract Research Organization, by telephone and follow-up in writing, all study drug discontinuations due to adverse events.

Assessment of Severity

The intensity or severity of an adverse event (AE) is characterized as:

- Mild: an AE that is easily tolerated
- Moderate: an AE sufficiently discomforting to interfere with daily activity
- Severe: an AE that prevents normal daily activities

Relationship to Study Medication

The relationship is characterized as:

- Not Related: This applies to any AE that is clearly not related to use of the study drug.
- Possible: This means the association of the AE with the study drug is unknown; however, a relationship between drug and event cannot be ruled out.
- Probable: There is a reasonable temporal relationship between the use of the study drug and the AE. Based upon the Principal Investigator's clinical experience, the association of the event with the study drug seems likely.
- Definite: The AE occurs following the application of the study drug and it cannot be reasonably explained by any known characteristics of the Subject's clinical state, environmental or toxic factors or other modes of therapy administered to the Subject. It disappears or decreases upon discontinuation of the study drug and reappears on a re-challenge of the investigational product.

10.2 Pregnancy

Female Subjects of childbearing potential must have been using and must agree to continue to use accepted methods of birth control, throughout the study. All female Subjects are considered to be of childbearing potential unless they are premenarchal, have been surgically sterilized or have been postmenopausal for at least 1 year. Abstinence is an accepted method of birth control. Alternatively, any of the following methods of birth control are acceptable: oral contraceptives, contraceptive patches/implants (e.g., Norplant®), Depo-Provera®, double barrier methods (e.g., condom and spermicide) or IUD. Prior to study enrollment women of child bearing potential must be advised of the importance of avoiding pregnancy during study participation.

A negative result of a pregnancy test having a minimum sensitivity of at least 50mIU/ml for hCG should be obtained, prior to study participation, at Visit 1. Pregnancy testing will also be performed at every study visit and the results of all pregnancy tests (positive or negative) will be documented.

If following initiation of study treatment, it is subsequently discovered that a study Subject is pregnant or may have been pregnant at the time of Investigational Product exposure, the Investigational Product will be permanently discontinued. The Principal Investigator must immediately notify the Medical Monitor of this event.

Protocol-required procedures for study discontinuation and follow-up must be performed on the Subject. Other appropriate pregnancy follow-up procedures should be considered if indicated. In

addition, the Principal Investigator must report to the sponsor follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants should be followed for a minimum of eight weeks after birth.

10.3 Serious Adverse Events

An **Adverse Event or Suspected Adverse Reaction** is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life threatening adverse event; (Note: the term “life-threatening” as used here refers to an event in which the Subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.)
- In-Subject hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any “other” important medical event

Important medical events that may not result in death, be life-threatening or require hospitalization may be considered Serious Adverse Events when, based on appropriate medical judgment, they may jeopardize the Subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Regardless of the above, any additional adverse events, which the Principal Investigator considers significant, should be immediately reported to the Contract Research Organization.

Any Serious Adverse Event, whether deemed drug-related or not, must be reported by the Investigator to the Contract Research Organization (CRO) Medical Monitor by telephone within 24 hours after the Principal Investigator or Study Coordinator becomes aware of its occurrence. The Principal Investigator or the Principal Investigator’s Designee must complete a Serious Adverse Event (SAE) Form and fax it to the Contract Research Organization, along with the patient’s Adverse Events Log and Concomitant Medications Log within 24 hours of notification of the event. The CRO must notify the Taro Pharmaceuticals U.S.A, Inc.’s Study Manager and Taro Pharmaceuticals U.S.A, Inc.’s Drug Safety Department within 24 hours of the initial notification of the event. When appropriate, Taro Pharmaceuticals U.S.A, Inc.’s Drug Safety Department will notify the U.S. Food and Drug Administration (FDA) of drug related Serious Adverse Events.

Documentation should be sent to Taro Pharmaceuticals U.S.A, Inc.’s Study Manager and/or Taro Pharmaceuticals U.S.A, Inc.’s Drug Safety Department listed below:

[Redacted]

The Principal Investigator or the Principal Investigator’s Designee must be prepared to supply the Medical Monitor with the following information:

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- a. Principal Investigator Name and Site Number
- b. Subject I.D. Number
- c. Subject initials and date of birth
- d. Subject Demographics
- e. Clinical Event
 - 1) Description
 - 2) Date of onset
 - 3) Severity
 - 4) Treatment (including hospitalization)
 - 5) Relationship to study drug
 - 6) Action taken regarding study drug
- f. **If the AE was Fatal or Life-threatening**
 - 1) Cause of death (whether or not the death was related to study drug)
 - 2) Autopsy findings (if available)
 - 3) Death Certificate

The Sponsor must notify FDA as soon as possible but no later than **7 calendar days** for fatal or life threatening adverse event. The Sponsor must notify FDA and all participating investigators within 15 calendar days for any serious adverse events, observed during the conduct of the study.

The Principal Investigator must provide a follow-up written report within **5 calendar days** of reporting the event to the Medical Monitor. The written report must contain a full description of the event and any sequelae. Subjects who have had an SAE must be followed clinically until all parameters (including laboratory) have either returned to normal or are stabilized. The Investigator must also report follow-up information if it becomes known to the Investigator. Taro Pharmaceuticals U.S.A, Inc.'s Study Manager and/or Taro Pharmaceuticals U.S.A, Inc.'s Drug Safety Department must receive any follow-up **within 24 hours** of receipt by Medical Monitor.

Reports of all SAEs must be communicated as soon as possible to the appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and/or reported in accordance with local laws and regulations.

11. ETHICS

This study will be conducted in accordance with the ethical principles that have their origin in the current Declaration of Helsinki and will be consistent with International Conference on Harmonization Good Clinical Practice (ICH GCP) and applicable regulatory requirements. The study will be conducted in compliance with the protocol.

The rights, safety and well-being of the study Subjects are the most important considerations and should prevail over interests of society and science.

11.1 Informed Consent

The Principal Investigator must ensure that Subjects and/or their legally acceptable representative (i.e., parent or guardian) are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical studies in which they volunteer to participate. The principles of Informed Consent/Assent, according to FDA Regulations and ICH GCP will be followed. A copy of the proposed consent form and assent form must be submitted to the IRB, together with the protocol, for approval. Prior

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to beginning of the study, the Principal Investigator must have the IRB's written approval of the written informed consent form, assent form, and any other information to be provided to Subjects.

Informed consent/assent will be obtained from all Subjects using the following procedure: subjects who are 18 years of age or older must have provided IRB approved written informed consent. For subjects under the age an assent form for minors must be completed for subjects under the legal age of consent depending on age range required by state laws. Written assent must be accompanied by an IRB approved written informed consent from the Subject's legally acceptable representative (i.e., parent or guardian). Prior to initiating screening for the study, Subjects will be given the approved ICF/assent describing the study and any risks associated with participation. The Subject will be allowed as much time as needed to read and understand the information presented in the consent/assent form. Appropriate study personnel will be available to answer any questions the Subject might have regarding the study or study-related procedures. If the Subject chooses to participate in the study, he or she will be asked to sign and date the consent/assent form and will be provided with a copy for his or her records. In addition, the Principal Investigator or the Principal Investigator's Designee will provide a HIPAA authorization form (if applicable) for the Subject or the Subject's legally acceptable representative (i.e., parent or guardian) to review and sign. Both the ICF/assent and the HIPAA authorization form (if applicable) must be signed by the Subject or the Subject's legally acceptable representative (i.e., parent or guardian) before any protocol assessments can be undertaken.

11.2 Institutional Review Board

Before study initiation, the Principal Investigator must have written and dated approval from the IRB for the protocol, consent form, Subject recruitment materials and any other written information to be provided to Subjects.

Any changes to the protocol as well as a change of the Principal Investigator, which is approved by the Sponsor, must also be approved by the site's IRB and documentation of this approval provided to the Sponsor/designee. Records of the IRB review and approval of all documents pertaining to this study must be kept on file by the Principal Investigator and are subject to inspection during or after completion of the study. All SAEs must also be reported to the IRB.

Periodic status reports must be submitted to the IRB at least annually, as well as notification of completion of the study and a final report within one (1) month of study completion or discontinuation. A copy of all reports submitted to the IRB must be sent to the Sponsor/designee.

The Principal Investigator will ensure that an IRB that complies with the requirements set forth in 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the proposed clinical study.

11.3 Subject Confidentiality

The monitor(s), the auditor(s), IRB/IEC, and the regulatory authority(ies), will be granted direct access to the Subject's original medical records for verification of the clinical trial procedures and/or data, without violating the confidentiality, to the extent permitted by the applicable laws and regulations and that by signing a written informed consent form, the Subject or the Subject's legally acceptable representative is authorizing such access.

The identifying the Subject will be kept confidential and, to the extent permitted by the applicable laws and regulations, will not be made publicly available. If the results of the trial are published, the Subject's identity will remain confidential.

12. DOCUMENTATION

12.1 Site Regulatory Documents Required for Initiation

The following documents will be received by the Sponsor prior to the initiation of the study:

[Redacted]

12.2 Maintenance and Retention of Records

It is the responsibility of the Principal Investigator to maintain a comprehensive and centralized filing system of all relevant documentation.

Copies of all pertinent records will be retained by the Principal Investigator for at least two years following final approval of the drug and/or notification from the Sponsor. These regulatory documents should be retained for a longer period if required by local regulatory authorities. These records include documents pertaining to the receipt and return of drug supplies, IRB, informed consent, source documents, as well as eCRFs (paper or electronic files). No documents shall be transferred from the site or destroyed without first notifying the Sponsor. If the Principal Investigator withdraws from the study, the records shall be transferred to a mutually agreed upon designee. Notice of such transfer will be given in writing to the Sponsor.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories designed to document all observations and other data pertinent to the investigation on each individual treated with the Investigational Product or entered as a control in the investigation. Data reported on the CRF, which are derived from source documents, must be consistent with the source documents.

12.3 Data Collection and Reporting

Data for individual Subjects will be collected on eCRF designed by the Contract Research Organization. The data management system will be Electronic Data Capture (EDC). The Investigator and his/her study site personnel will be responsible for completing the eCRFs. The Investigator is required to verify that all of the requested information is accurately recorded in the eCRFs. All information requested in the eCRFs needs to be supplied, including subject identification, date(s), assessment values, etc., and any omission or discrepancy will require explanation. All information on eCRFs must be traceable to source documents.

[Redacted]

The study monitor will be responsible for reviewing and verifying the data recorded in the eCRFs, utilizing the original source documentation and will query discrepant findings. The Investigator and study site personnel will be responsible for answering all queries. All queries issued by the CRO's data management personnel will be answered by site personnel and verified by the monitor.

12.4 Primary Source Documents

The Principal Investigator must maintain primary source documents supporting significant data for each Subject's medical notes. These documents, which are considered "source data", should include documentation of:

[Redacted]

12.5 Study Monitoring

The study will be monitored by a representative of the Contract Research Organization to assess compliance with ICH-GCP and applicable regulations. The Principal Investigator will be visited by a monitor prior to the study and at regular intervals during the course of the study. These visits are for the purposes of verifying adherence to the protocol.

The study monitor will review the informed consent forms and verify eCRF entries by comparing them with the source documents (hospital/clinic/office records) that will be made available for this purpose.

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The monitor will review the maintenance of regulatory documentation and drug accountability. The monitor will review on a regular basis the progress of the study with the Principal Investigator and other site personnel.

eCRF sections may be monitored during these visits. At the end of the study, a closeout monitoring visit will be performed. Monitoring visits will be arranged in advance at a mutually acceptable time with site personnel. Sufficient time must be allowed by the site personnel for the monitoring of eCRFs and relevant source documents. The Study Coordinator and/or Principal Investigator should be available to answer questions or resolve data clarifications. Adequate time and space for these visits should be made available by the Principal Investigator.

12.6 Audits and Inspections

During the course of the study and/or after it has been completed, one or more site visits may be undertaken by auditors as authorized representatives of the Sponsor. The purpose of the audit is to determine whether or not the study is being conducted and monitored in compliance with the protocol, recognized GCP guidelines and all applicable regulations.

Additionally, the study may be inspected by regulatory agencies. These inspections may take place at any time during the course of the study and/or after it has been completed.

THE INVESTIGATOR MUST NOTIFY THE CONTRACT RESEARCH ORGANIZATION and SPONSOR PROMPTLY OF ANY INSPECTIONS SCHEDULED BY REGULATORY AUTHORITIES, AND PROMPTLY FORWARD COPIES OF INSPECTION REPORTS TO THE SPONSOR.

12.7 Modifications to the Protocol

The procedures defined in the protocol and in the eCRF will be carefully reviewed to ensure that all parties involved with the study fully understand the protocol. In order to ensure the validity of the data, no violations from the protocol, with minimal exceptions, may be made unless the issue is broad enough to warrant revision of the protocol. Such revisions must be submitted to and have documented approval from the Sponsor and the IRB prior to implementation. All amendments to the protocol, which involve substantial changes in study design, procedure or analyses, may be submitted to FDA for prior approval (if required).

The only circumstance in which an amendment may be initiated without prior IRB approval is to eliminate apparent immediate hazards to a Subject or Subjects. However, the Principal Investigator must notify the Sponsor immediately and the IRB within 5 working days after implementation.

All protocol violations will be reported on the protocol violation log and included in the study reports. A protocol violation is defined as any change, deviation, or departure from the study design or procedures of research project that is NOT approved by the IRB prior to its initiation or implementation, OR deviation from standard operating procedures, Good Clinical Practices (GCPs), federal, state or local regulations.

12.8 Completion of Study

The Principal Investigator is required to sign the eCRFs and forward all other relevant data and records to the Contract Research Organization.

The Principal Investigator is expected to submit a final report to the IRB and the Sponsor within one (1) month of study completion or discontinuation. CRO must submit a final report as agreed in the Study Agreement for this study between Sponsor and CRO.

13. REFERENCES

1. FDA Guidance for Industry (Draft). Acne Vulgaris: Developing Drugs for Treatment. Division of Dermatologic and Dental Drug Products. FDA September 2005.
2. http://www.nlm.nih.gov/medlineplus/ency/encyclopedia_C.htm

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APPENDIX I: REVISION HISTORY

Version # (Version Date)	Affected Sections
Final 1.0 (2 August 2016)	N/A (new)

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APPENDIX II: [REDACTED AS AT55] INVESTIGATOR'S BROCHURE