A RANDOMIZED, DOUBLE-BLIND, VEHICLE-CONTROLLED, EFFICACY AND SAFETY STUDY OF OLUMACOSTAT GLASARETIL GEL IN SUBJECTS WITH ACNE VULGARIS

Protocol Number	**DRM01B-ACN04**
Protocol Final Date	**06 October 2016**
IND Number	**121136**
Study Drug	**Olumacostat Glasaretil Gel**
Sponsor	**Dermira, Inc.** **275 Middlefield Road** **Suite 150** **Menlo Park, CA 94025** **USA**

A RANDOMIZED, DOUBLE-BLIND, VEHICLE-CONTROLLED, EFFICACY AND SAFETY STUDY OF OLUMACOSTAT GLASARETIL GEL IN SUBJECTS WITH ACNE VULGARIS

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SPONSOR SIGNATURE PAGE

A RANDOMIZED, DOUBLE-BLIND, VEHICLE-CONTROLLED, EFFICACY AND SAFETY STUDY OF OLUMACOSTAT GLASARETIL GEL IN SUBJECTS WITH ACNE VULGARIS

Protocol Number **DRM01B-ACN04**

Protocol Final Date **06 October 2016**

The signature below constitutes approval of this protocol. I certify that I have the authority to approve this protocol on behalf of the Sponsor, Dermira, Inc. The study will be conducted in accordance with this protocol and all applicable laws, rules, and regulations and with the International Conference on Harmonisation Good Clinical Practice (ICH GCP), regulations of Canada and the United States (US) Food and Drug Administration (FDA) and the ethical principles that have their origin in the Declaration of Helsinki.

Authorized by:

Sponsor Signature

12 Oct 2016

Date (DD MMM YYYY)

Eugene A. Bauer, MD
Chief Medical Officer

INVESTIGATOR SIGNATURE PAGE

A RANDOMIZED, DOUBLE-BLIND, VEHICLE-CONTROLLED, EFFICACY AND SAFETY STUDY OF OLUMACOSTAT GLASARETIL GEL IN SUBJECTS WITH ACNE VULGARIS

I have read this protocol, including the appendices, and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined herein, according to the ethical principles that have their origin in the Declaration of Helsinki, International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP) and applicable laws, rules and regulatory requirement(s) including those of Canada and the United States (US) Food and Drug Administration (FDA).

I agree to obtain the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval of the protocol and informed consent prior to the start of the study.

I agree to obtain formal written informed consent in accordance with applicable federal and local regulations and international guidelines from all subjects prior to their entry into the study.

I have received and reviewed the Investigator's Brochure including the potential risks and side effects of the product and instructions for use.

I agree to report to the Sponsor any adverse events that occur during the course of the study in accordance with the ICH GCP guideline and the protocol.

I agree to ensure that all associates, colleagues, and employees assisting me with the conduct of the study are informed of their responsibilities in meeting the above commitments and the commitments set forth in the Investigator's Agreement.

I agree to maintain adequate and accurate records and to make those records available for inspection in accordance with the ICH GCP guideline, and federal and local requirements.

I understand that the study may be terminated or enrollment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

_____ _____

Investigator's Signature Date (DD MMM YYYY)

_____

Investigator's Name (print)

PROTOCOL SYNOPSIS

Title:	A Randomized, Double-Blind, Vehicle-Controlled, Efficacy and Safety Study of Olumacostat Glasaretil Gel in Subjects with Acne Vulgaris
Protocol Number:	DRM01B-ACN04
Phase:	3
Number of Sites:	Approximately 50
Study Population	Subjects ≥ 9 years of age with acne vulgaris
Sample Size	Approximately 700 subjects
Study Treatment	Olumacostat Glasaretil Gel, 5.0%, applied twice daily Olumacostat Glasaretil Gel, Vehicle, applied twice daily
Randomization	2:1 (active:vehicle)
Study Objective:	To assess the efficacy and safety of Olumacostat Glasaretil Gel, 5.0% compared to Olumacostat Glasaretil Gel, Vehicle when applied twice daily to the face for 12 weeks in subjects with acne vulgaris.
Duration of Subject Participation:	• Screening: maximum duration of 35 days • Treatment period: 12 weeks Maximum total participation: 17 weeks
Study Visit Schedule	Screening, Baseline/Day 1, Weeks 1, 2 (phone call), 4, 8, 12 (Exit)

Study Design/Summary:

This study is a randomized, double-blind, vehicle-controlled, parallel group study, designed to assess the efficacy and safety of Olumacostat Glasaretil Gel, 5.0% compared to Olumacostat Glasaretil Gel, Vehicle in subjects with acne vulgaris on the face. All subjects will sign an informed consent or assent (pediatric subjects) and undergo screening for study eligibility.

Approximately 700 eligible subjects, ≥ 9 years of age, will be randomized, in a 2:1 fashion, to Olumacostat Glasaretil Gel, 5.0% or Olumacostat Glasaretil Gel, Vehicle treatment, respectively. Study drug will be applied twice daily to the face for 12 weeks. Subjects will return to the study clinic at Weeks 1, 4, 8 and 12 (Study Exit). A follow-up phone call at Week 2 will be made to assess safety (adverse events) only.

Primary efficacy will be assessed through acne lesion counts (inflammatory and non-inflammatory lesions) and investigator global assessment of acne (IGA). All efficacy endpoints will be assessed from baseline to Week 12.

Safety will be assessed through adverse events, local skin reactions (LSRs), serum chemistry, hematology and urinalysis laboratory testing, ECG testing, physical examination and vital signs.

Photographs of the face will be taken in all subjects at a subset of sites in order to visually assess the appearance of acne vulgaris during the course of the study. During clinic visits, subjects will be asked to complete Acne Patient Self-Questionnaire.

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1 INTRODUCTION

1.1 Product Development Rationale

Acne arises from a combination of physiological changes in the skin including altered sebaceous gland cell differentiation, heightened sebum production, localized bacterial colonization and inflammation. Although acne is generally viewed as a benign dermatological disease of adolescence, more severe forms may lead to permanent scar formation, with some of these patients suffering from psychological injury and significant loss of self-worth. Recent scientific advances in the understanding of the complex multi-factorial nature of this common disease offer great opportunity for scientific innovation through selective targeting of key elements of the disease process.

Sebum is a waxy/oily substance comprised of cholesterol, fatty acids, fatty alcohols, triglycerides (TGs), wax esters, sterol esters and squalene produced by sebaceous gland cells [1]. Sebaceous glands are associated with hair follicles. The basal layer of sebocytes just inside the basement membrane consists of small, nucleated cells devoid of lipid droplets. This layer contains the dividing cells that replenish the gland as cells are lost in the process of holocrine rupture. As cells move from the basal layer towards the center of the gland, they differentiate and produce lipids that accumulate in droplets. Eventually the cells become distended with lipid droplets and the nuclei and other sub-cellular structures disappear. As the cells approach the sebaceous duct, they disintegrate and release their contents through holocrine secretion. In acne, diglycerides and free fatty acid levels may be increased by bacterial degradation of diglycerides and triglycerides present within sebum. Free fatty acids may promote inflammatory response in acne by activating local immune cells and their subsequent release of pro-inflammatory factors.

A direct correlation between the degree of acne improvement and the extent of sebum reduction produced by different oral anti-acne medications has been established [2]. The oral retinoid 13-cis-retinoic acid (13-cis-RA, Accutane®) is particularly effective at reducing sebum output although its mode-of-action is not likely related to a direct effect on sebum synthesis pathways [3].

Topical agents routinely prescribed for acne, including antibiotics, retinoids and combinations thereof, often produce only modest therapeutic benefits and do not affect sebum production. A locally-delivered medication that selectively inhibited sebum formation would represent a breakthrough advance in reducing the pathogenic influences of sebum overproduction in acne.

Acetyl-coenzyme A carboxylases (ACCs) have crucial roles in fatty acid metabolism in humans and most other living organisms [4]. ACC catalyzes the carboxylation of acetyl-CoA to form malonyl-CoA. This is the first committed step in fatty acid biosynthesis and is the rate limiting reaction for the pathway [5, 6, 7]. These fatty acids then can be stored or converted to triglycerides (TGs) and phospholipids. In addition to its role as a substrate in fatty acid biosynthesis, malonyl-CoA, also plays an important regulatory role in controlling mitochondrial fatty acid uptake through allosteric inhibition of carnitine palmitoyltransferase I (CPT-I), the enzyme catalyzing the first committed step in mitochondrial fatty acid oxidation [8]. Malonyl-CoA, therefore, is a key metabolic signal for the control of fatty acid production and utilization in response to dietary changes and altered nutritional requirements in animals [6]. As a result of

its unique position in intermediary metabolism, inhibition of ACC offers the ability to inhibit *de novo* fatty acid production in lipogenic tissues, such as liver, adipose tissue, and sebaceous glands.

A variety of structurally diverse ACC inhibitors has recently been described in the scientific and patent literature for potential use in metabolic syndrome. One class of ACC inhibitors, including TOFA (5-(tetradecyloxy)-2-furancarboxylic acid), consists of lipophilic fatty acid mimetics that compete with acetyl-CoA in the ACC-mediated formation of malonyl-CoA. Investigators have demonstrated that TOFA reduced fatty acid synthesis and TG secretion both in cultured hepatic cells [8, 10] and in experimental animals [11, 12], reduced plasma cholesterol and TGs in experimental animals including rhesus monkeys [10, 11], and reduced body weight [13].

The ability to deliver TOFA topically could offer a means to inhibit de novo fatty acid production in sebaceous glands, introducing a new treatment paradigm for acne vulgaris.

1.2 Summary of Investigational Program

Dermira, Inc. is pursuing the development of olumacostat glasaretil, previously referred to as DRM01B, a pro-drug of TOFA, sarcosine ester, as a topically applied sebum inhibitor for the treatment of acne vulgaris. Olumacostat glasaretil is hydrolyzed by esterases in vivo to form the pharmacologically active moiety, TOFA. TOFA is converted to Tofyl-CoA intracellularly, which competes with acetyl-CoA in the ACC-mediated formation of malonyl-CoA. As a result, inhibition of malonyl-CoA synthesis offers a means to inhibit de novo fatty acid production in the sebaceous glands in subjects with acne vulgaris. Olumacostat glasaretil is a new chemical entity and has been formulated for clinical development as Olumacostat Glasaretil Gel, 5.0%.

A summary of clinical and nonclinical pharmacology, toxicology and metabolism data is presented below. Detailed information is provided in the current Investigator's Brochure.

Safety pharmacology studies were conducted with olumacostat glasaretil administered intravenously (IV) which included neurobehavioral and pulmonary function studies in rats and a cardiovascular study in telemetered minipigs. These studies revealed no adverse findings attributable to olumacostat glasaretil. In vitro studies assessing the effects of olumacostat glasaretilel and TOFA upon human ether-à-go-go-related gene (hERG) ionic conductance in human embryonic kidney (HEK) cells also revealed no significant inhibition at the maximum concentrations tested. Overall, the results from the safety pharmacology showed no adverse effects at exposures to parent drug and/or TOFA several orders of magnitude beyond that anticipated to be seen following topical application in humans.

Following IV administration in rats and minipigs, olumacostat glasaretil was quickly metabolized to TOFA; no evidence of any gender-specific differences or accumulation upon repeated dosing of either olumacostat glasaretil or TOFA was observed. With oral administration in rats, low ng/mL levels of olumacostat glasaretil were noted while exposure to TOFA reached levels exceeding 1 µg/mL. In vitro metabolism and plasma protein binding experiments indicated that olumacostat glasaretil was metabolized and bound to plasma protein in a similar manner between humans and the species utilized for toxicology and safety pharmacology assessments (rat and minipig).

Toxicokinetic assessments conducted following the topical dermal application of Olumacostat Glasaretil Gel to minipigs indicated that olumacostat glasaretil and TOFA were poorly absorbed; peak plasma levels recorded in these studies were below the detectable limit for olumacostat glasaretil and while TOFA was detectable following application of the highest strength of Olumacostat Glasaretil Gel (7.5% w/w), mean values did not exceed 6 ng/mL for TOFA. The test article used in this study is the same formulation and concentration that was used in the clinical proof of concept study (DRM01B-ACN01) and the same formulation that was one of the strengths included in the clinical dose ranging trial (DRM01B-ACN02).

Toxicology studies conducted with olumacostat glasaretil included dermal studies in minipigs of up to 13 weeks in duration, IV studies in rats and minipigs of up to 4 weeks in duration, and oral studies in rats of up to 90 days in duration. Based upon the nonclinical studies conducted to date olumacostat glasaretil, has exhibited an acceptable safety profile. No test article-related effects were noted in any nonclinical study, aside from histological findings associated with the non-glandular stomach (fore-stomach) in the 13-week rat oral study. This finding was considered a direct local effect (not due to systemic absorption), reversible and non-adverse, and is of doubtful clinical relevance given the absence of this structure in humans. In the other toxicology studies, there were no remarkable olumacostat glasaretil-related findings and olumacostat glasaretil was well tolerated. No adverse systemic effects were associated with mean peak plasma exposures to olumacostat glasaretil and TOFA up to 9955 and 3630 ng/mL, respectively, which are concentrations exceeding 4000-fold that seen following the dermal application of maximum feasible doses (10 mg/kg) to minipigs. In vivo and in vitro studies conducted to assess dermal sensitization, ocular irritation, and phototoxicity did not reveal any remarkable effects following the exposure of cells/tissues to olumacostat glasaretil. Genetic toxicology results indicated that olumacostat glasaretil was neither mutagenic nor clastogenic. Predictive software assessments indicated there were no potential theoretical manufacturing impurities or metabolic products that were of mutagenic concern. Overall, the results of the nonclinical toxicology and safety pharmacology studies suggest the safety risks posed by Olumacostat Glasaretil Gel are low.

Two clinical studies, DRM01B-ACN01 and DRM01B-ACN02, have been completed as part of the Phase 2 development program. DRM01B-ACN01 was a proof of concept study which assessed the safety and efficacy of one strength of Olumacostat Glasaretil Gel compared to vehicle gel in adult subjects with acne vulgaris. DRM01B-ACN02 was a dose ranging study which assessed the safety and efficacy of multiple strengths and regimens of Olumacostat Glasaretil Gel and vehicle gel in adult subjects with acne vulgaris. In both studies, Olumacostat Glasaretil Gel was shown to be well-tolerated and demonstrated statistically significant improvements in acne lesions counts and severity. Additional information on these studies is provided below.

Study DRM01B-ACN01

DRM01B-ACN01 was randomized, vehicle controlled, parallel group study designed to assess the safety and tolerability of Olumacostat Glasaretil Gel, 7.5% in healthy volunteers (Phase 1) before assessing the safety, tolerability and preliminary efficacy of the drug in subjects with acne vulgaris (Phase 2a). In the Phase 1 portion of the study, 6 healthy volunteers applied study Olumacostat Glasaretil Gel twice daily, to the face, for one week. Review of the data from

Phase 1 showed that Olumacostat Glasaretil Gel was well tolerated with no safety concerns. As such, the Phase 2a portion of the study was conducted.

In the Phase 2a portion of the study, Olumacostat Glasaretil Gel was applied, twice daily, to the face in 108 adult subjects with acne vulgaris for a 12–week treatment period. Similar to Phase 1, Olumacostat Glasaretil Gel was well tolerated with most AEs reported as mild to moderate in severity. Subjects treated with Olumacostat Glasaretil Gel had significantly greater reductions in inflammatory and noninflammatory lesion counts from Baseline to Week 12 compared with subjects treated with vehicle gel. In addition, a significantly greater proportion of subjects treated with Olumacostat Glasaretil Gel had a successful improvement in IGA score (corresponding to less severe acne) than subjects treated with vehicle gel.

Study DRM01B-ACN02

Study DRM01B-ACN02 was a Phase 2 dose-ranging study in adult subjects with acne vulgaris on the face. The study was a randomized, vehicle controlled, parallel group study designed to assess the efficacy and safety of Olumacostat Glasaretil Gel at a concentration of 7.5% BID, 7.5% QD, and 4.0% QD, compared to vehicle BID or QD in subjects with moderate to severe facial acne.

A total of 420 adult subjects were randomized to active and vehicle in a 2:2:2:1:1 fashion. Study treatments continued for 12 weeks. Subjects returned to the study clinic at Weeks 1, 2 (phone call only), 4, 8 and 12 (study exit).

The results of the study showed that all three Olumacostat Glasaretil Gel treatment groups demonstrated statistically significantly greater reductions in the absolute change in inflammatory lesion counts from baseline to Week 12 than the combined vehicle group. The LS mean changes in inflammatory lesion counts were −14.6 and −14.5, and −15.0 for the Olumacostat Glasaretil Gel, 4.0% QD, 7.5% QD, and 7.5% BID groups, respectively, compared with −10.7 for the combined vehicle QD group ($P = 0.011$, $P = 0.014$, and $P = 0.011$ respectively). All 3 Olumacostat Glasaretil Gel treatment groups showed statistically significantly greater reductions in the absolute change in noninflammatory lesion counts from baseline to Week 12 than the combined vehicle group. The LS mean changes in noninflammatory lesion counts at Week 12 were −15.3, −13.4, and −17.5 for the DRM01B Olumacostat Glasaretil Gel 4.0% QD, 7.5% QD, and 7.5% BID groups, respectively, compared with −9.3 for the combined vehicle group ($P = 0.004$, $P = 0.050$, and $P < 0.011$ respectively).

The Olumacostat Glasaretil Gel 4.0% QD and 7.5% BID groups each had a statistically significantly greater proportion of subjects achieve a minimum 2-grade improvement (reduction) in IGA score from baseline at Week 12 compared with the combined vehicle group. The percent of subjects achieving this endpoint was 21.6% in the Olumacostat Glasaretil Gel 4.0% QD and 25.9% of subjects in the Olumacostat Glasaretil Gel 7.5% BID group (compared with 9.8% in the combined vehicle QD group ($P = 0.024$ and $P = 0.004$, respectively).

Pharmacokinetic (PK) results, assessed in a subset of subjects, showed that plasma concentrations of Olumacostat Glasaretil Gel on Day 1 were undetectable for all but 1 subject, who had a plasma concentration of 0.304 at 1 time point (2 hours post-dosing). Plasma concentrations of Olumacostat Glasaretil Gel at Week 8 were undetectable for all tested subjects. Plasma concentrations of TOFA on Day 1 were undetectable in most subjects, but detectable in a few subjects in each dose group, with values ranging from 0.101 to 1.02 ng/mL. Plasma concentration of TOFA at Week 8 were undetectable for most subjects in the DRM01B QD dose groups, but detectable in a few subjects, with values ranging from 0.100 to 0.299 ng/mL. In the Olumacostat Glasaretil Gel, 7.5% BID group, approximately half of the tested subjects had detectable TOFA levels at each time point, with mean values ranging from 0.156 to 0.340 ng/mL.

The most common AEs reported during the study were nasopharyngitis, upper respiratory tract infection, and application site pruritus. Most AEs were mild or moderate in severity. Erythema was the most common LSR. Laboratory values, vital signs, and ECGs measured at the end of the study were generally consistent with baseline values, with no clinically significant trends.

There were no deaths during the study however, one subject in the 7.5% QD group had an SAE of uterine leiomyoma considered unrelated to treatment. Seven subjects prematurely discontinued study drug due to an AE, 4 of these discontinuations were considered to be treatment related.

Study Rationale

Data from the completed Phase 2 dose ranging study, DRM01B-ACN02, and data from study DRM01B-ACN01, have shown that Olumacostat Glasaretil Gel was well tolerated at multiple concentrations. Olumacostat Glasaretil Gel at a strength of 5.0% has been selected as the concentration to take forward in Phase 3 development. Two Phase 3 pivotal trials are planned as part of the Phase 3 development program and will include adults and adolescents (ages 9 years and older) in order to confirm the efficacy and safety of Olumacostat Glasaretil Gel, 5.0% for the treatment of acne vulgaris.

This study, DRM01B-ACN04, is one of the two confirmatory Phase 3 trials being conducted to assess the efficacy and safety of Olumacostat Glasaretil Gel, 5.0% in subjects with acne vulgaris.

1.3 Study Conduct Statement

This study will be conducted in compliance with the protocol, according to current United States federal regulations (Title 21, Code of Federal Regulations [CFR] Parts 11, 50, 54, 56,312, and 314 as appropriate) and the principles of the International Conference on Harmonisation (ICH) (ICH E6 1997) Good Clinical Practice (GCP), Food and Drug Administration (FDA) guidelines, Canadian guidelines and the Declaration of Helsinki, 1964 (as amended in Edinburgh [2000]).

2 STUDY SUMMARY

This study is a randomized, double-blind, vehicle-controlled, parallel group study, designed to assess the efficacy and safety of Olumacostat Glasaretil Gel,5.0% compared to Olumacostat Glasaretil Gel, Vehicle in subjects with acne vulgaris on the face. All subjects will provide informed consent or assent (pediatric subjects) and undergo screening for study eligibility.

Approximately 700 eligible subjects ≥ 9 years of age will be randomized, in a 2:1 fashion, to Olumacostat Glasaretil Gel, 5.0% or Olumacostat Glasaretil Gel, Vehicle treatment, respectively. Study drug will be applied twice daily to the face. Subjects will return to the study clinic at Weeks 1, 4, 8 and 12 (Study Exit). A follow-up phone call at Week 2 will be made to assess safety (adverse events) only.

Primary efficacy will be assessed through acne lesion counts (inflammatory and non-inflammatory lesions) and investigator global assessment of acne (IGA). All efficacy endpoints will be assessed as the change from Baseline to Week 12.

Safety will be assessed through adverse events, local skin reactions (LSRs), serum chemistry, hematology and urinalysis laboratory testing, ECG testing, physical examination and vital signs.

Photographs of the face will be taken for all subjects in subset of study sites in order to visually assess the appearance of acne vulgaris during the course of the study.

During clinic visits, subjects will be asked to complete the Acne Patient Self-Questionnaire.

3 STUDY OBJECTIVES

The objective of this study will be to assess the efficacy and safety of Olumacostat Glasaretil Gel at a concentration of 5.0%, compared to Olumacostat Glasaretil Gel, Vehicle when applied twice daily for 12 weeks in subjects with acne vulgaris.

4 STUDY ENDPOINTS

Primary Efficacy Endpoints:

- Mean absolute change in acne lesion counts (inflammatory and non-inflammatory lesions) from baseline to Week 12.
- Proportion of subjects who achieved ≥ 2-grade improvement and a grade of 0 or 1, in the investigator global assessment of acne (IGA) from baseline to Week 12.

Secondary Efficacy Endpoints:

- Percent change in acne lesion counts (inflammatory and non-inflammatory lesions) from baseline to Week 12.
- Proportion of subjects who achieved ≥ 2-grade improvement in the investigator global assessment of acne (IGA) from baseline to Week 12.

5 STUDY DESIGN

5.1 Duration of the Study

The duration of the study for each subject is approximately 17 weeks (up to 35 days screening and 12 weeks treatment).

5.2 Study Population and Number of Subjects

Approximately 700 subjects, ≥ 9 years of age, with acne vulgaris on the face, will be enrolled.

5.3 Selection of Subjects

Subject selection criteria are outlined below. Any questions on the eligibility of a subject for this study must be referred to the Sponsor or their designee, prior to enrollment. No exceptions to inclusion or exclusion criteria will be made.

5.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for study participation:

1. Signed informed consent and, for subjects under legal adult age, signed assent
2. Age ≥ 9 years
3. Willing to comply with the protocol. Subjects under legal adult age will be assessed by the investigator as to their ability to comply with the protocol
4. Male or non-pregnant (negative serum pregnancy test at screening for female subjects of child-bearing potential), non-lactating females
5. In the case of females of childbearing potential), are using an acceptable form of birth control (Section 5.3.4)
6. In the case of females of childbearing potential, have a negative urine pregnancy test at Baseline/Day 1
7. Clinical diagnosis of facial acne vulgaris defined as:
   - At least 20 inflammatory lesions, and
   - At least 20 non-inflammatory lesions, and
   - Investigator Global Assessment of 3 or greater
8. Willing to refrain from using any treatments for acne vulgaris, other than the investigational product, including topical or systemic antibiotics.

5.3.2 Exclusion Criteria

Subjects meeting any of the following criteria are not eligible for study participation:

1. Previous active treatment in Olumacostat Glasaretil (DRM01B) Gel trials

2. Females who are currently pregnant, lactating or planning to become pregnant during the course of the study
3. Known hypersensitivity to Olumacostat Glasaretil or its excipients
4. Any skin condition which may interfere with the evaluation of safety or, of acne vulgaris (e.g., rosacea; seborrheic dermatitis; perioral dermatitis; corticosteroid-induced acne or folliculitis)
5. Excessive facial hair that would interfere with diagnosis or assessment of acne vulgaris
6. Excessive sun exposure that could affect the clinical state of acne, in the opinion of the investigator or, anticipated use of tanning booths
7. Active cystic acne or acne congoblata, acne fulminans, and secondary acne
8. Two or more active nodulocystic lesions on the face
9. Screening clinical chemistry, hematology, or urinalysis laboratory value, deemed clinically significant, by the Investigator
10. Abnormal findings on screening ECG, deemed clinically significant by the Investigator
11. Subjects who are actively participating in an experimental therapy study or who have received experimental therapy within 30 days or 5 half-lives (whichever is longer) of the Baseline visit
12. Subjects who are a poor medical risk because of other systemic diseases or active uncontrolled infections, in the opinion of the investigator
13. Any other condition which, in the judgment of the investigator, would put the subject at unacceptable risk for participation in the study
14. Treatment with over-the-counter topical medications for the treatment of acne vulgaris including benzoyl peroxide, topical anti-inflammatory medications, corticosteroids, α-hydroxy/glycolic acid on the face within 2 weeks prior to Baseline
15. Treatment with systemic corticosteroids (use of intranasal and inhaled corticosteroids allowed for seasonal allergies and asthma) within 4 weeks prior to Baseline
16. Treatment with systemic antibiotics or systemic anti-acne drugs within 4 weeks prior to Baseline
17. Prescription topical retinoid use on the face within 4 weeks prior to Baseline (e.g., tretinoin, tazarotene, adapalene)
18. Treatment with a new hormonal therapy or dose change to existing hormonal therapy within 12 weeks prior to Baseline (hormonal therapies include, but are not limited to, estrogenic and progestational agents such as birth control pills).
19. Use of androgen receptor blockers (such as spironolactone or flutamide) within 2 weeks prior to Baseline.
20. Oral retinoid use (e.g., isotretinoin) within 12 months prior to Baseline or vitamin A supplements greater than 10,000 units/day within 6 months prior to Baseline

21. Facial procedures (chemical or laser peel, microdermabrasion, etc.) within 8 weeks prior to Baseline or if anticipated during the study

5.3.3 Females – Non-childbearing Potential

Female subjects of non-childbearing potential are women 45 years or older and at least 2 years postmenopausal or surgically sterile (e.g., total hysterectomy, bilateral oophorectomy). All other female subjects will be considered to be of childbearing potential.

5.3.4 Females – Childbearing Potential

Pregnancy hormones may cause acne to flare. To avoid confounding the assessment of efficacy pregnancy should be avoided. Acceptable contraceptive methods for sexually active female subjects of childbearing potential include one of the following:

- Abstinence
- Oral/implant/injectable/transdermal contraceptives
- Intrauterine device
- Condom with spermicide
- Diaphragm with spermicide
- Partner vasectomized or
- Tubal ligation

Abstinence or vasectomies are acceptable if the female subject agrees to implement one of the other acceptable methods of birth control if her lifestyle/partner changes. Female subjects of childbearing potential must use acceptable methods of contraception starting from the Screening Visit and throughout the study.

6 STUDY DRUG

6.1 Investigational Medicinal Product

Study medication, will be supplied as Olumacostat Glasaretil Gel, 5.0% and Olumacostat Glasaretil Gel, Vehicle.

Olumacostat Glasaretil Gel is formulated as an alcohol based gel for topical application. Olumacostat Glasaretil Gel, 5.0% contains 50 mg of olumacostat glasaretil per gram of gel, ethanol, isopropanol, polyethylene glycol 400, dimethyl isosorbide and hydroxypropy-cellulose and appears as a translucent, colorless to faintly yellow gel.

Olumacostat Glasaretil Gel, Vehicle has the same appearance and contains the same ingredients as Olumacostat Glasaretil Gel, 5.0%, with the exception of olumacostat glasaretil.

6.2 Packaging, Labeling and Storage

The Olumacostat Glasaretil Gel, 5.0% and Olumacostat Glasaretil Gel, Vehicle gel will be packaged in identical 45g aluminum tubes. Each tube contains approximately 40g of gel.

Study drug for each subject enrolled will be packaged in a study kit. Each kit will contain 6 tubes to allow for 12 weeks of study drug application.

Study drug tubes and kits will be labeled with the study number, a unique kit number, contents, storage conditions, manufacturer and Sponsor information, and precautionary statements and expiry date, if applicable.

Study drug kits are to be stored at room temperature (25°C with allowable excursion to 15-30°C) in a secure, locked facility accessible only to authorized study personnel. Study drug must not be placed in refrigerator or frozen, exposed to heat or stored at high temperatures. This product is flammable. Avoid fire, flame, or smoking during and immediately following application.

6.3 Treatment Assignment

Randomization and IWRS

At the Baseline/Day 1 visit, qualified subjects will be randomized to treatment using an Interactive Web-based Randomization System (IWRS). The IWRS will assign a study drug kit number based on a predetermined randomization schedule. The kit number will be recorded in the electronic case report form (eCRF). Approximately 467 subjects will be randomized to active treatment and approximately 233 subjects will be randomized to vehicle treatment for a total of approximately 700 subjects. Subjects will be randomized to treatment groups in such a manner to balance treatment allocation within study sites in a 2:1 fashion.

Each subject screened will be assigned a unique subject number.

Study Blinding

The Sponsor, the CRO, the Investigator, study site personnel and subjects will be blinded to the treatment assignment.

The integrity of this clinical study must be maintained by observing the treatment blind. If an adverse event occurs which cannot be managed without knowing whether the subject is receiving active study drug or vehicle solution, the IWR system will be used to obtain treatment assignment information. The Medical Monitor must be notified whenever study medication is unblinded, preferably prior to unblinding a subject.

6.4 Study Drug Dispensing and Return

It is the responsibility of the Investigator to ensure that study drug is only used on study subjects enrolled in this study. The study drug must only be dispensed from official study sites by authorized personnel according to the protocol and local regulations.

Study drug will be dispensed by the study site to the subject at each study visit. Two tubes contain enough study drug for 1 month of application. At each visit, the subject will be dispensed enough tubes to allow dosing until the next visit. Partially used tubes may be re-dispensed at the site's discretion.

Subjects are to return all study medication tubes (used and unused) to the study site. Study tubes will be weighed prior to dispensing and upon return. Sites are allowed to re-dispense tubes. If required, tubes will be re-weighed prior to re-dispensing Weights will be recorded in the source documents and eCRF.

Each subject is to be instructed on the importance of returning study drug at the next study visit. If a subject does not return study drug, they will be instructed to return it as soon as possible. The site staff will visually inspect the tube to ensure product usage is consistent with the subject's dosing diary.

6.5 Study Drug Application

Subjects will be instructed on the application of the study medication. The first dose of the study drug will be applied in the clinic for instructional purposes. Subjects are to apply the study drug twice daily (morning and evening) to a clean dry face.

Study drug is to be applied topically, to the entire face (forehead, nose, cheeks, and chin) by squeezing approximately ½ inch or slightly more than 1 centimeter long line of gel, onto a finger and spreading the gel over the face, avoiding the skin around the eyes, eyelids and mouth, until the face is completely covered.

Subjects are to be instructed to wash their hands prior to and immediately following study drug application.

Subjects should avoid washing the face or swimming within 2 hours after applying study medication.

Missed doses should be applied, provided there is at least an 8 hour window until the next scheduled dose.

6.6 Treatment Compliance

Treatment compliance will be assessed at each visit using a subject-completed diary and visual inspection of the tubes. Subjects will be given a paper diary at each visit in conjunction with study drug. The subject-completed diary will collect application information for the face. Subjects will be instructed to bring all study medication and diaries to the clinic at the next study visit.

A subject deviating significantly from the assigned dosing regimen will be counseled. All diaries will be maintained as source documentation.

The first and last dates of study drug usage, location and any missed applications will be recorded in the eCRF.

6.7 Study Drug Accountability

The Investigator or designee will be responsible for study drug accountability and records at the site. Study drug accountability records will document the receipt, dispensing and return of study drug and provide a complete account of all used and unused drug product. Study drug accountability records will be reviewed regularly throughout the study by the Sponsor/designee. Study medication will be returned to the Sponsor, or designee, at the end of the study, following final study drug accountability.

7 CONCOMITANT MEDICATIONS AND PROCEDURES

All medications (including over-the-counter drugs, vitamins, antacids and skin care products) taken during screening and throughout the study will be recorded on the eCRF. In addition, to ensure that the subject meets the acne treatment and medication exclusion criteria, all acne treatment and medications, including, any past isotretinoin, facial procedures, Vitamin A and hormonal therapy use will be recorded on the eCRF.

Medication entries should be specific to the generic name (if a combination drug, then marketed product name) and will include the dose, unit, frequency, route of administration, start date, discontinuation date, and indication. When listing medications indicated for acne, the area treated will be collected.

The Investigator should examine the acceptability of all concomitant procedures, medications, topical preparations and dietary supplements not explicitly prohibited in this study. In order to ensure that appropriate concomitant therapy is administered, subjects will be instructed to consult with the Investigator prior to taking any medication (either self-administered non-prescription drugs or prescription therapy prescribed by another physician).

7.1 Permitted Treatments and Procedures

The use of concomitant medications for medical conditions (e.g., hypertension, diabetes, acute infections) or treatment of an adverse event is permitted during this study as long as medications are not explicitly prohibited by the protocol.

Non-medicated moisturizers and make-up may be used during study participation, provided application occurs after study medication is applied. On study visit days, non-medicated moisturizers and make-up must be removed prior to each study visit as instructed by the Investigator. Subjects' skin care regimen should remain stable/unchanged during study participation.

Non-medicated moisturizers, soaps, and make-up do not need to be recorded as concomitant medications.

7.2 Prohibited Treatments and Procedures

Subjects should not undergo any elective medical procedure without prior consultation with the Investigator. Elective out-patient procedures (e.g., minor outpatient surgery) that might require

hospitalization or anesthesia should be deferred until after the study, whenever clinically appropriate. However, subjects may continue in the study if not contraindicated by the procedure and if continuation is deemed in the subject's best interest.

The following medications and treatments are prohibited during the study:

- Over-the-counter topical medications for acne vulgaris including benzoyl peroxide, topical anti-inflammatory medications, corticosteroids, α-hydroxy/glycolic acid
- Systemically absorbed anti-acne drugs
- Systemic corticosteroids (use of intranasal and inhaled corticosteroids allowed for seasonal allergies and asthma)
- Systemic antibiotics (except in the case of acute medical need to treat infections)
- Prescription topical retinoid use(e.g., tretinoin, tazarotene, adapalene)
- New hormonal therapy or dose change to existing hormonal therapy. Hormonal therapies include, but are not limited to, estrogenic and progestational agents such as birth control pills.
- Use of androgen receptor blockers (such as spironolactone or flutamide)
- Oral retinoid use (e.g., isotretinoin) or vitamin A supplements greater than 10,000 units/day
- Facial procedures (chemical or laser peel, microdermabrasion, etc.)
- Sun exposure which in the opinion of the investigator could affect the course of acne or any tanning booth use

8 STUDY PROCEDURES

The procedures required for subject evaluation at each study visit are outlined below and in the study Schedule of Visits and Procedures (see Appendix 1). The timing of each study day is relative to the day of initial dosing (Baseline/Day 1). Visit windows are provided to allow study sites some flexibility in maintaining the study visit schedule for participating subjects. Out of window visits may be unavoidable in certain circumstances. Out of window visits are not considered deviations to the protocol.

8.1 Screening (Day -35 to -1)

The screening evaluation period may take up to 35 days in order to provide adequate washout time for subjects taking certain medications. The purpose of the screening visit is to ensure that appropriate subjects are entered into the study and remain stable during the pre-treatment period. Questions on eligibility will be referred to the Sponsor or their designee. Screen failures may be re-screened one time and must be assigned a new screening number. Screen failure information will be recorded in the eCRF. Screening procedures, excluding lab evaluations, may be done any time during the screening period (prior to dosing on Day 1) and after the subject has given informed consent.

- Obtain written informed consent/assent. For subjects under legal adult age, both parents or legal representatives may be required to sign informed consent as applicable.
- Collect demographic information
- Complete medical history
- Query subject for concomitant medication use
- Perform a complete physical examination
- Record height and weight
- Measure vital signs
- Assess Inclusion/Exclusion criteria
- Collect a 12 lead ECG
- Draw blood samples for laboratory tests and urine for urinalysis. Include serum pregnancy test for women of childbearing potential
- Determine concomitant medication washout duration
- Schedule next visit

8.2 Baseline Visit/ Day 1

Evaluations are to be done prior to the first dose of study drug

- Collect concomitant medication information
- Conduct a symptom-directed physical exam – update medical history if appropriate
- Measure vital signs
- Conduct urine pregnancy test for women of childbearing potential
- Conduct Investigator Global Assessment (IGA)
- Collect acne lesion counts
- Collect Acne Patient Self- Questionnaire
- Evaluate face for pre-treatment local skin reactions (LSRs)
- Collect photographs (selected sites)
- Confirm subject eligibility (Inclusion/Exclusion criteria) and randomization to treatment
- Instruct subject on study medication application and diary completion
- Weigh tubes and dispense study drug and diary. Observe subject administering first dose
- Schedule all subsequent visits

8.3 Week 1 (+/-2 days)

- Collect concomitant medication information
- Conduct a symptom-directed physical exam
- Measure vital signs
- Review and record AEs
- Assess LSRs
- Review compliance/weigh tubes and dispense drug and diary
- Schedule Week 2 Telephone Contact and next visit

8.4 Week 2 Telephone Contact (+/-2 days)

- Call subject to review AEs and concomitant medications

8.5 Week 4 (+/-4 days)

- Collect concomitant medication information
- Conduct a symptom-directed physical exam
- Collect urine pregnancy for women of childbearing potential
- Measure vital signs
- Review and record AEs
- Conduct IGA
- Collect acne lesion counts
- Collect Acne Patient Self-Questionnaire
- Assess LSRs
- Collect photographs (selected sites)
- Review compliance/weigh tubes and dispense drug and diary

8.6 Week 8 (+/-4 days)

- Collect concomitant medication information
- Conduct a symptom-directed physical exam
- Collect urine pregnancy for women of childbearing potential
- Measure vital signs
- Review and record AEs
- Conduct IGA

- Collect acne lesion counts
- Collect Acne Patient Self-Questionnaire
- Assess LSRs
- Collect photographs (selected sites)
- Review compliance/weigh tubes and dispense drug and diary

8.7 Week 12 (+/-4 days) Study Exit or Early Termination Visit

- Collect concomitant medication information
- Measure vital signs
- Review and record AEs
- Conduct a complete physical exam
- Measure weight
- Collect a 12-lead ECG
- Draw blood samples for laboratory tests. Include serum pregnancy test for women of childbearing potential.
- Conduct Investigator Global Assessment
- Conduct acne lesion counts
- Collect Acne Patient Self-Questionnaire
- Assess LSRs
- Collect photographs (selected sites)
- Review compliance/weigh tubes and collect all study medication and diary

8.8 Unscheduled Visits

Additional visits may be scheduled as necessary to ensure the safety and well-being of subjects who experience AEs. Laboratory evaluations, if necessary, will be collected and analyzed using the central laboratory for this study. Data will be recorded in the eCRF.

9 DETAILS OF ASSESSMENTS

Parental assistance for study drug application and study conduct procedures may be needed for younger subjects qualifying for study participation.

9.1 Screening Assessments

9.1.1 Demographics

At the screening visit, demographic information including age, gender, race, Fitzpatrick Skin Type (Table 1) and ethnicity will be collected and recorded on the eCRF for each subject.

Table 1: Fitzpatrick Skin Type

Fitzpatrick Skin Type	Definition
I	Burns easily, rarely tans
II	Burns easily, tans minimally
III	Burns moderately, tans gradually
IV	Burns minimally, tans well
V	Rarely burns, tans profusely
VI	Never burns, deeply pigmented

9.1.2 Medical History

A complete medical history will be collected as part of the screening assessment and include all clinically relevant past or coexisting medical conditions or surgeries. The medical history will be updated prior to treatment on Baseline/Day 1, should new findings emerge after the screening visit. Findings will be recorded in the eCRF.

9.1.3 Disease Specific Information

Information on the subject's acne vulgaris will be collected as part of the screening assessment and include the date of onset of acne, anatomical areas affected at baseline, and past treatments used for acne vulgaris. Information will be recorded in the eCRF.

9.2 Assessment of Efficacy

9.2.1 Investigator Global Assessment

The IGA is a static assessment of acne severity (Table 2) on the face only and will be conducted for each subject by the Investigator or designee prior to assessing lesion counts or conducting the LSR assessment. Where possible, the same efficacy assessor should assess acne severity on the same subject at all visits. Individuals performing the IGA will be trained and certified prior to conducting any assessments on the study. IGA grades will be entered into the eCRF.

Table 2: Investigator Global Assessment

Investigator Global Assessment	
Grade	**Description**
0	Clear; normal, clear skin with no evidence of acne vulgaris
1	Almost clear; Rare non-inflammatory lesions present, with rare non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red)
2	Mild; some non-inflammatory lesions are present, with few inflammatory lesions (papules/pustules only; no nodulocystic lesions)
3	Moderate; non-inflammatory lesions predominate, with multiple inflammatory lesions evident: several to many comedones and papules/pustules, and there may or may not be one small nodulocystic lesions
4	Severe; Inflammatory lesions are more apparent, many comedones and papules/pustules, there may or may not be a few nodulocystic lesions

9.2.2 Acne Lesion Count

The investigator/designee will perform a count of inflammatory lesions (papules, pustules and nodules) and non-inflammatory lesions (open and closed comedones) and will be conducted after the IGA assessment is completed. Lesion counts are confined to the face (including forehead, nose, cheeks, and chin) and exclude submental lesions. **Where possible, the same efficacy assessor should perform all lesion count assessments on the same subject at all visits.** Individuals performing the acne lesion counts will be trained and certified prior to conducting any assessments on the study. Lesion counts will be entered into the eCRF.

9.3 Other Assessments

9.3.1 Photographs

Photographs of the face will be collected for all subjects, who have provided consent, at a subset of the study sites participating in this study.

Subjects will have full face and side view photographs taken and anonymized prior to Sponsor use.

Study sites selected for photography will be trained and receive standardized photographic equipment by a centralized photographic vendor. Photographs will be electronically transferred from the site to the vendor.

At the end of the study, the site will receive an electronic file of all subject photographs for archiving.

The central photography vendor will tabulate and transfer all subject photos to the Sponsor during the course of the study.

9.3.2 Acne Patient Self-Questionnaire

Subjects will be asked to complete Acne Patient Self-Questionnaire. The questionnaire is paper-based and will be completed by subjects during clinic visits (see Appendix 2). Subject responses will be entered in the eCRF by the study site and the completed questionnaires kept as part of the subject's source document. Study site staff must review all forms to ensure complete responses prior to a subject leaving the study site.

9.4 Assessment of Safety

9.4.1 Physical Examination

A complete physical examination will be conducted at screening and Week 12 or Early Termination visits and cover general appearance, dermatological, head, ears, eyes, nose, throat, respiratory, cardiovascular, abdominal, neurological, musculoskeletal, and lymphatic body systems. Height and weight will be recorded as part of the screening physical exam and only the subject's weight will be recorded with the end of study physical exam. A symptom-directed physical exam may be performed at subsequent visits as needed. Following baseline, any new findings or findings that have worsened in severity should also be recorded as an AE.

Physical exam findings will be recorded in the eCRF.

9.4.2 Vital Signs

Vital signs, including body temperature, respiratory rate (breath per minute), pulse (beats per minute), and blood pressure (mmHg), will be obtained with the subject in the seated position, after sitting for at least 5 minutes. Any abnormal findings which are new or worsened in severity and clinically significant, in the opinion of the Investigator, will be recorded as an AE.

Vital sign measurements will be recorded in the eCRF.

9.4.3 ECGs

12-lead ECG measurements will be obtained in all subjects. The subject should rest quietly for at least 5 minutes in a supine position prior to ECG collection. The ECG should be obtained either prior to the time of blood collection, or at least 15 minutes afterwards.

At screening, the Investigator will use the machine-read ECG to determine subject eligibility. The medical monitor may be consulted if needed for interpretation of ECGs.

All study sites will be supplied with standardized, validated digital 12-lead ECG (12-lead at 25 mm/sec reporting rhythm, ventricular rate, the RR interval, the PR interval, QRS duration, QT and QTcF intervals) equipment capable of recording, storing, and printing producing high resolution 12-lead ECG data by the central laboratory. Study sites will be trained on the use of the equipment prior to study start.

Machine-read ECG recordings will be collected and analyzed centrally. Data will be transferred electronically to the database.

9.4.4 Laboratory Evaluations

Laboratory tests will be collected to evaluate safety in all study subjects and analyzed using a central laboratory. Labs will be collected per the Schedule of Visits and Procedures (see Appendix 1) or more frequently as clinically indicated. Laboratory samples are to be shipped on the same day as collected. No more than 4 mL/kg total will be collected over an 8 week period in subjects under legal adult age. Laboratory tests are described below.

Hematology: hematocrit, hemoglobin, red blood cell (RBC) count, white blood cell count and differential (%), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume, platelet count, absolute neutrophils, absolute lymphocytes, absolute monocytes, absolute eosinophils, and absolute basophils. RBC morphology should be performed if indicated.

Chemistry: sodium, potassium, chloride, calcium, phosphorus, bicarbonate, uric acid, blood urea nitrogen (BUN), creatinine, total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, bilirubin (total and direct), and glucose (fasting or non fasting).

Serum pregnancy testing will be performed at the screening and Week 12 (study exit) or Early Termination visits. Urine pregnancy testing (beta human chorionic gonadotropin [β-hCG]) will be performed at Baseline/Day 1, and the Weeks 4 and 8 visits for all females unless post-menopausal/sterile.

Urinalysis: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen, leukocyte esterase. A microscopic examination of urine will be performed if clinically indicated (e.g. a positive dipstick for protein, blood, leucocyte esterase) in the opinion of the Investigator based on the findings of the urinalysis or clinical signs and symptoms. Any new or worsened clinically significant laboratory result is to be recorded as an AE after study drug dosing.

Screening laboratory values must be reviewed by the Investigator prior to subject enrollment. Subjects will be screen failed for clinically significant laboratory values. Screening laboratory tests may be repeated one time in order to confirm out of range results clinical significance at the discretion of the investigator.

The central laboratory must be used for any laboratory testing required for a subject during study participation, including laboratory testing needed for unscheduled visits. If an immediate result is required to adequately care for a subject, a duplicate sample may be submitted to a local lab. Clinically significant laboratory results must be recorded as an AE, preferably as a diagnosis rather than individual test results. Any subject who has a clinically significant laboratory test result will be evaluated by the Investigator, and will be treated and/or followed up until the value returns to clinically acceptable level, in the opinion of the investigator.

9.4.5 Local Skin Reactions (LSRs)

All subjects will be assessed for LSRs, on the face, at each visit. LSRs include burning/stinging, pruritus, erythema, dryness and peeling. Each LSR will be scored as 0 (None), 1 (Mild), 2 (Moderate) or 3 (Severe). LSRs observed on a visit day will not be recorded as adverse events

unless scored as 3 (Severe). Local skin reactions experienced by the subject in between study visits are to be recorded as an AE.

Burning/stinging and pruritus will be assessed by the subject (Table 3) and erythema, dryness and peeling will be assessed by the Investigator/designee (Table 4). Subjects will be read the definition of each subject-assessed LSR and asked to select the appropriate definition. The corresponding score will be assigned by the site and entered in the eCRF.

Table 3: Subject Assessed Local Skin Reactions

Score	Grade	Burning/Stinging	Pruritus
0	None	No stinging/burning	No pruritus
1	Mild	Slightly warm, tingling sensation; not really bothersome	Occasional, slight itching/scratching
2	Moderate	Definite warm; tingling/stinging sensation that is somewhat bothersome	Intermittent itching/scratching which does not disturb sleep
3	Severe	Hot, tingling/stinging sensation that has caused definite discomfort	Bothersome itching/scratching which disturbs sleep

Table 4: Investigator Assessed Local Skin Reactions

Score	Grade	Erythema	Dryness	Peeling
0	None	None	None	None
1	Mild	Slight erythema: very light-pink	Perceptible dryness with no flakes or fissure formation	Mild diffuse peeling
2	Moderate	Dull red, clearly distinguishable	Easily noted dryness and flakes but no fissure formation	Moderate diffuse peeling
3	Severe	Deep/dark red	Easily noted dryness with flakes and fissure formation	Moderate to prominent, dense peeling

9.4.6 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of a study drug in humans, whether or not considered drug related. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the study drug, whether or not related to the investigational product.

AEs will be monitored throughout the study. Subjects will be instructed to inform the Investigator and/or study staff of any AEs. At each visit, subjects will be asked about AEs in a non-specific manner using open-ended questions so as not to bias the response (e.g., How have you been since the last visit?). Specific inquiry regarding reported AEs will be conducted when applicable. All AEs will be documented and recorded in the subject's eCRF.

Any subject who has an AE (serious or non-serious) or clinically significant abnormal laboratory test value will be evaluated by the Investigator, and will be treated and/or followed up until the symptoms or values return to normal or to clinically acceptable levels, as judged by the

Investigator. A physician, either at clinical site, or at a nearby hospital emergency room, will administer treatment for any serious adverse events (SAEs), if necessary. When appropriate, medical tests and examinations will be performed to document resolution of event(s).

9.4.6.1 Reporting

Only AEs that occur during or following study treatment with the study drug will be reported in the AE section of the eCRF. Events recorded prior to study treatment with the drug will be reported in the Medical History section of the eCRF as appropriate. All AEs occurring during the course of the study will be individually recorded in the eCRF. A condition that is present prior to administration of study drug and that worsens after administration of study drug should be reported as an AE. Information regarding the onset, duration, severity, action taken, outcome, and relationship to study drug will be recorded.

New or worsening abnormal laboratory values and/or vital signs are to be recorded as AEs if they are considered to be of clinical significance by the Investigator or meet the criteria of an SAE as described in Section 9.4.7.

Unless a diagnosis is available, signs and symptoms must be reported as individual AEs in the eCRF; a diagnosis is preferred.

The severity of an AE will be designated as mild, moderate or severe. The term “severe” is used to describe the intensity of an adverse event; the event itself, however, may be of relatively minor clinical significance (e.g. ‘severe’ upper respiratory infection). Severity is not the same as “serious”. Seriousness of AEs is based on the outcome/action of an AE. (See Section 9.4.7.)

The relationship of the AE to the study treatment should be determined by the Investigator and will be based on the following two definitions:

Not related: An AE is defined as “not related” if the AE is not judged to be associated with the study drug and is attributable to another cause

Related: An AE is defined as “related” where a causal relationship between the event and the study drug is a reasonable possibility (possibly or probably related). A reasonable causal relationship is meant to convey that there are facts (e.g., evidence such as dechallenge/ rechallenge) or other clinical arguments to suggest a causal relationship between the AE and study treatment.

9.4.7 Serious Adverse Events

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose,

- Results in death
- Is immediately life-threatening (i.e., in the opinion of the Investigator, the AE places the subject at immediate risk of death; it does not include a reaction that, had it occurred in a more severe form, might have caused death)
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization

- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may not be immediately life-threatening, result in death, or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, it jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

As soon as the Investigator becomes aware of an AE that meets the criteria for an SAE, the SAE should be documented to the extent that information is available. A report must be submitted by the study site to the Sponsor or designee within 24 hours.

Any SAE, regardless of causal relationship, must be reported to the Sponsor immediately (within 24 hours of the Investigator's knowledge of the event).

SAEs will be recorded from the time of informed consent/assent, through to end of the study. If, in the opinion of the Investigator, an SAE occurring outside the specified time window, (i.e., following subject completion or terminations of the study) is deemed to be drug-related, then the event should be reported with 24 hours as outlined above.

The Investigator should institute any clinically necessary supplementary investigation of SAE information. In the case of subject death, any post-mortem findings/reports will be requested.

9.4.7.1 Reporting of Serious Adverse Events

All SAEs, as defined by the criteria above, must be reported to the Sponsor or designee using the SAE form provided, within 24 hours of the Investigator becoming aware of the event.

Serious adverse events must be recorded on an SAE form. The minimum information required for SAE reporting includes the identity of the PI, site number, subject number, event description, SAE term(s), reason why the event is considered to be serious (i.e., the seriousness criteria), and PI's assessment of the relationship of the event to study drug. Additional SAE information including medications or other therapeutic measures used to treat the event, and the outcome/resolution of the event should also be recorded on the SAE form.

In all cases, the Investigator should continue to monitor the clinical situation and report all material facts relating to the progression or outcome of the SAE. The Investigator may be required to provide supplementary information as requested by the Sponsor or its designee.

When reporting SAEs, the following additional points should be considered:

- When the diagnosis of an SAE is known or suspected, the Investigator should report the diagnosis or syndrome as the primary SAE term, rather than as signs or symptoms; signs, symptoms and tests that support the diagnosis should be provided
- Death should not be reported as an SAE, but as an outcome of a specific SAE, unless the event preceding the death is unknown. If an autopsy was performed, the autopsy report should be provided;

While most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows:

- Hospitalization for elective or previously scheduled surgery or procedure for a pre-existing condition that has not worsened after administration of study drug (e.g., a previously scheduled ventral hernia repair). SAEs must, however, be reported for any surgical or procedural complication resulting in prolongation of the hospitalization;
- Events that result in hospital stays for observation only of fewer than 24 hours and that do not require a therapeutic intervention/treatment (e.g., an emergency room visit for hematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics).

The Sponsor will process and evaluate all SAEs as soon as the reports are received. For each SAE received, the Sponsor will make a determination as to whether the criteria for expedited reporting to relevant regulatory authorities have been met.

The Sponsor will assess the expectedness of each SAE to the study treatment. The current Investigator's Brochure will be used as the reference document to assessed expectedness of the event to study drug.

9.4.8 Dosing Changes due to AEs

Dose interruptions are allowed should a subject experience intolerable treatment-related adverse events (e.g., pruritis) on study. In cases where the Investigator feels a dose interruption is warranted, the subject should be instructed to interrupt study drug application to allow symptoms to resolve. Subjects should be instructed to return to the twice daily application regimen within 2 days of dose interruption.

Dosing interruptions are to be recorded in the subject diary as a missed dose.

Study drug must be discontinued if an adverse event is deemed persistent and if continuation of study drug would not be in the best interest of the subject.

Refer to Section 10.3 for further information regarding discontinuation of study drug or early withdrawal.

9.4.9 Pregnancy

Should a subject become pregnant during study participation, study drug dosing will be discontinued and the subject will be withdrawn from study. The Investigator must perform medical assessments as clinically indicated and continue to follow the subject for at least 4 weeks after delivery. Details for both the mother and baby must be obtained. Pregnancy is not itself an AE or SAE; however, maternal/fetal complications or abnormalities will be recorded as AEs or SAEs, as appropriate. The Investigator must complete a study-specific pregnancy form upon confirmation of a pregnancy. Pregnancy reporting forms will be provided to the study site.

10 STUDY DISCONTINUATIONS

10.1 Discontinuation of the Study

The Sponsor has the right to terminate or to stop the study at any time. Should this be necessary, both the Sponsor and the Investigator will ensure that proper study discontinuation procedures are completed. The entire study will be stopped if:

- Evidence has emerged that, in the collective opinion of the Investigators at each site with the concurrence of the Sponsor or the sole opinion of the Sponsor, makes the continuation of the study unnecessary or unethical
- The stated objectives of the study are achieved
- The Sponsor discontinues the development of the study drug

Regardless of the reason for withdrawal, all data available for the subject at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

10.2 Early Study Termination of Study Subjects

The Investigator will make every reasonable effort to keep each subject in the study; however, a subject may voluntarily withdraw from study participation at any time. If the subject withdraws consent and discontinues from the study, the Investigator will attempt to schedule an Early Termination visit as soon as possible, determine the reason for discontinuation, and record the reason in the subject's study records and in the eCRF.

If at any time during the study, the Investigator determines that it is not in the best interest of the subject to continue, the subject will be discontinued from participation. The Investigator can discontinue a subject at any time if medically necessary. The Investigator may discontinue a subject's participation if the subject has failed to follow study procedures or to keep follow-up appointments. Appropriate documentation in the subject's study record and eCRF regarding the reason for discontinuation must be completed.

All subjects who fail to return to the study site for the required follow-up visits will be contacted by phone to determine the cause(s) why the subject failed to return for the necessary visit or elected to discontinue from the study. If a subject is unreachable by telephone after a minimum of two documented attempts (one attempt on two different days), a registered letter will be sent requesting that subject contact the site regarding study follow-up.

Subjects will be discontinued early from the study if any of the following occur:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event, laboratory abnormality, or inter-current illness which, in the opinion of the Investigator, indicates that continued treatment and/or participation in the study is not in the best interest of the subject
- Death

- Serious protocol violation, including persistent noncompliance or subject requiring medication or procedures prohibited by the protocol, to allow subjects to receive the appropriate medical attention.
- Discontinuation of the study by the Sponsor

10.3 Study Drug Discontinuation

For subjects who decide to prematurely discontinue study drug treatment, all reasonable efforts should be made to obtain all protocol-specified safety assessments and end of study procedures.

The Investigator should stop study drug treatment in the following instances:

- Inter-current illness that would, in the judgment of the Investigator, affect assessments of clinical status to a significant degree.
- Any clinical adverse event which is clinically significant and is deemed persistent and probably or definitely related to study drug in the judgment of the Investigator.
- Unacceptable toxicity

11 STATISTICAL CONSIDERATIONS

11.1 General Statistical Methodology

All statistical processing will be performed using SAS® unless otherwise stated. No interim analyses are planned. Except where noted, all statistical tests will be two-sided and will be performed at the 0.05 level of significance.

Descriptive statistics will be used to provide an overview of the efficacy and safety results. For categorical parameters, the number and percentage of subjects in each category will be presented. For continuous parameters, descriptive statistics will include n (number of subjects), mean, standard deviation (SD), median, minimum and maximum. Appropriate inferential statistics will be used for the primary, secondary, and exploratory efficacy variables.

The primary method of handling missing efficacy data will be the method of Markov Chain Monte Carlo (MCMC) multiple imputation.

Demographic data will be summarized by treatment group using descriptive statistics. Subjects' baseline characteristics related to efficacy analyses will be compared between treatment groups to evaluate baseline balance between the treatment arms.

The number of subjects in each analysis set will be summarized. Reasons for study withdrawal during the blinded study will be summarized using frequencies and percentages by treatment group.

The primary method of dichotomizing the IGA score will be to consider a subject a "success" if the IGA at a post-baseline visit is 0 or 1 and 2 or more grades lower than at baseline; otherwise the subject will be considered a treatment "failure".

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

11.2 Populations Analyzed

Listings and summaries will be provided for all randomized subjects.

Approximately 700 subjects with acne vulgaris on the face will be randomized, in a 2: 1 fashion, to Olumacostat Glasaretil Gel, 5.0% BID, or Olumacostat Glasaretil Gel, Vehicle. Efficacy analyses will be performed using the intent-to-treat (ITT) population and the per-protocol (PP) population. Safety analyses will be performed using the safety population.

All subjects who are randomized and dispensed study drug will be included in the ITT population.

All subjects who are randomized, receive at least one confirmed dose of study drug and have at least one post-baseline safety assessment will be included in the safety population.

The PP population will include all subjects in the safety population who complete the Week 12 evaluation without any significant protocol violations (i.e., 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 PP population will include subjects in the safety population who do not meet any of the following criteria:

- Violated the inclusion/exclusion criteria;
- Have taken any interfering concomitant medications;
- Did not attend the Week 12 visit;
- Have missed both the Week 4 and Week 8 study visits;
- Have not been compliant with the dosing regimen (i.e. subjects must apply 80–120% of the expected applications of study medication during participation in the study);
- Out of visit window at the Week 12 visit by ±5 days;

Subjects that discontinue from the study due to an adverse event related to study treatment or documented lack of treatment effect will be included in the PP population. Prior to breaking the blind, other additional criteria may be added to the list to accommodate for unforeseen events that occurred during the conduct of the trial that result in noteworthy study protocol violations.

11.3 Primary Efficacy

Absolute change from baseline to Week 12 in inflammatory and non-inflammatory lesion counts will be analyzed using either parametric or non-parametric methods consistent with the statistical assumptions required to support the analyses. Specifically, the tests of superiority will be based on an ANCOVA with factors of treatment and analysis center and the respective Baseline lesion count as a covariate or on ranked data submitted to an ANCOVA with factors of treatment and analysis center and the respective Baseline lesion count as a covariate. If the treatment-by-

analysis center interaction effect is significant at an alpha less than 0.10, then the effect will be included in the model; otherwise it will be removed.

A skewness test, based on the methods presented by J.H. Zar (1984) [14], will be applied to the residuals resulting from an ANCOVA. A two-sided p-value for the skewness test significant at 0.01 will imply the use of the non-parametric method. If a parametric analysis is indicated, the results of the parametric analysis will be considered the primary analysis. Should a non-parametric analysis be indicated, the absolute or percent changes in inflammatory and non-inflammatory lesions will be rank transformed prior to submitting them to the ANCOVA. Results of the rank-transformed analyses then will be considered the primary analysis; however, results of the non-ranked transformed analyses will also be presented.

The proportion of subjects who are dichotomized to success at Week 12 will be analyzed using the logistic regression test stratified by analysis center.

11.4 Secondary Efficacy

The percent change from baseline to Week 12 in inflammatory and non-inflammatory lesion counts will be analyzed using the same ANCOVA method described for the primary endpoint.

The proportion of subjects who are dichotomized to success (minimum 2-grade improvement from baseline) at Week 12 will be analyzed using the same logistic analysis method described for the primary endpoint.

The following stepwise process will be conducted for testing the secondary efficacy endpoints in order to control for multiplicity. These tests will be performed for only the ITT population. The testing process will terminate whenever a statistical test for a step is not significant. All subsequent tests for the remaining steps will be considered not significant. The order of testing is percent change in inflammatory lesion count from baseline to Week 12, percent change in non-inflammatory lesion count from baseline to Week 12, and the proportion of subjects who are dichotomized to success (minimum 2-grade improvement from baseline).

11.5 Other Supportive Efficacy Analyses

The percent change and absolute change from baseline to Weeks 4 and 8 inflammatory and non-inflammatory lesion counts will be analyzed using the same ANCOVA method described for the primary endpoint of absolute change in lesion counts from baseline to Week 12. The inclusion of p-values in these efficacy analyses is to assist in characterizing the therapeutic efficacy of the active formulation and dosage regimen. No adjustments will be made for multiple comparisons for the sportive efficacy analyses.

Descriptive statistics will be presented for the following parameters by treatment group for both the ITT and PP populations:

- Frequency and percent distributions of the IGA Score at Baseline and Weeks 4, 8, and 12.
- Frequency and percent distributions of the dichotomized IGA Score at Baseline and Weeks 4, 8, and 12.

- Descriptive statistics including mean, median, standard deviation, minimum, and maximum will be used to summarize inflammatory and non-inflammatory lesion counts at Baseline and Weeks 4, 8, and 12.
- Descriptive statistics including mean, median, standard deviation, minimum, and maximum will be used to summarize the absolute and percent change in inflammatory and non-inflammatory lesion counts at Weeks 4, 8, and 12.
- Descriptive statistics including mean, median, standard deviation, minimum, and maximum will be used to summarize the Acne Patient Self-Questionnaire assessments at Weeks 4, 8, and 12.

Means, standard deviations and frequency counts (rounded to the nearest whole number) will be computed from the multiply imputed MCMC data for the variable.

11.6 Pooling Analysis

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

Prior to investigating the treatment effect within the analysis centers, the magnitude of the site mail effect will be investigated to determine if the main site-to-site variability is such that it could mask the analysis center effects. Thus, if computationally possible, a one-way ANCOVA (for lesion count variables) or a logistic regression analysis (for dichotomized IGA) with a factor of site will be conducted prior to pooling. If the data structure interferes with the logistic regression, a descriptive analysis of the site effect will be undertaken. Conclusions appropriate to the findings of this step will be presented.

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

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

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

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

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

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

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

11.7 Missing Efficacy Data Imputations

Lesion Count Variable Missing Data Imputation

Missing 12 week data will be estimated by multiple imputation and subsequently analyzed. Missing lesion count data will be derived for the analysis using the method of Markov Chain Monte Carlo (MCMC) multiple imputation which does not rely on the assumption of data missing at random. Additionally, the pattern of missing observations in each treatment group

cannot influence the missing value estimation in the other because the imputation is being conducted independently for each treatment group.

Multiple imputation and subsequent analysis will involve 4 distinct phases with these principal tasks:

1. Calculated the number of missing values to be estimated by MCMC (nmiss) for 12-week value.
2. Create a data set of subjects, one for each treatment group, with observed values and those needing estimation by MCMC. The missing lesion count values in each data set will be filled in using the MCMC method '5 x nmiss' times to generate '5 x nmiss' data sets. The resulting data sets for each treatment arm will be combined into one complete data set for each imputation.

   Syntax:

   proc mi data=datain out=dataout seed=&seed. Nimpute=5xnmiss <options>;

   where trtpn=(1, or 2);

   mcmc chain=multiple;

   var baseline week4 week8 week12;

   run;
3. For each complete data set, the absolute change in lesion counts for baseline minus the 12-week value will be computed. Each complete data set will be analyzed as specified for the particular analysis.
4. The results from these analyses will be combined into a single inference using SAS PROC MIANALYZE.

A total of 4 random seeds will be needed to impute inflammatory lesion counts and fcnon-inflammatory lesion counts for the two treatment groups. Those 4 random seeds have been pre-specified by using a random number generator:

- Inflammatory Lesion Counts; Olumacostat Glasaretil Gel: Seed= 195361148
- Inflammatory Lesion Counts; Olumacostat Glasaretil Gel Vehicle: Seed= 2099102059
- Non-Inflammatory Lesion Counts; Olumacostat Glasaretil Gel: Seed= 325230329
- Non-Inflammatory Lesion Counts; Olumacostat Glasaretil Gel: Seed= 936128187

IGA Missing Data Imputation

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

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

1. Calculate the number of missing values to be estimated by MCMC (nmiss) for 12 week value.
2. Create a data set, one for each treatment group, of subjects with observed values and those needing estimation by MCMC. The missing IGA values in each data set will be filled in using the MCMC method '5 x nmiss' times to generate '5 x nmiss' data sets. The resulting data sets for each treatment arm will be combined into one complete data set by imputation.

   Syntax:

   proc mi data=datain out=dataout seed=&seed. Nimpute=5xnmiss <options>;

   where trtpn=(TRT); /* Note TRT = [1, 2]; depending on treatment group */

   ;

   mcmc chain=multiple;

   var baseline week4 week8 week12;

   run;
3. For each complete data set, the dichotomous success rate (clear or almost clear with a 2-point change from baseline) will be computed. The 12-week estimated global values will be rounded to the nearest integer value prior to evaluating the success rate. Each complete data set will be analyzed with a logistic regression with factors of treatment group and analysis center.
4. The results from these analyses will be combined into a single inference using SAS PROC MIANALYZE.

A total of 2 random seeds will be needed to impute IGA for the two treatment groups. Those 2 random seeds have been pre-specified by using a random number generator:

- IGA; Olumacostat Glasaretil Gel: Seed= 322979853
- IGA; Olumacostat Glasaretil Gel Vehicle: Seed= 1313477781

11.8 Sensitivity Efficacy Analyses

Sensitivity analyses for absolute change in lesion count

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

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

1. Calculate the number of missing values (nmiss) for absolute change in lesion count.
2. Missing values will be filled in '5 x nmiss' times to generate '5 x nmiss' complete data sets. The imputation model used will be an ANCOVA with factors of treatment group and analysis center, and a covariate of baseline lesion count (ie, the imputation model will be the same as the analysis model). Appropriate modifications will be made should the analysis be based on a non-parametric method.
3. Each complete data set will be analyzed with an ANCOVA with factors of treatment group, and analysis center, and a covariate of baseline lesion count.
4. Results from these analyses will be combined into a single inference.

Sensitivity analyses for IGA

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

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

1. Calculate the number of missing values (nmiss) for absolute change in lesion count.
2. Missing values will be filled in '5 x nmiss' times to generate '5 x nmiss' complete data sets. The imputation model used logistic regression with factors of treatment group and analysis center (ie, the imputation model will be the same as the analysis model).
3. Each complete data set will be analyzed with a logistic regression a factors of treatment group and analysis center.
4. Results from these analyses will be combined into a single inference.

11.9 Subgroup Analyses

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

11.10 Exposure and Compliance

The extent of exposure to study drug in each treatment group will be summarized by total number of days of exposure, total number of applications, number of missed applications and number and percentage of subjects who are compliant. A subject will be considered compliant

with the dosing regimen if the subject applied 80% to 120% of the expected number of applications while enrolled in the study.

11.11 Adverse Events

All AEs that occur during the study will be recorded and classified on the basis of Medical Dictionary for Regulatory Activities (MedDRA) terminology. Treatment-emergent AEs (TEAEs) are defined as AEs with an onset on or after the date of the first study drug application. Adverse events noted prior to the first study drug administration that worsen after baseline will also be reported as AEs and included in the summaries.

All information pertaining to an AE noted during the study will be listed by subject, detailing verbatim term given by the PI or designee, preferred term, system organ class (SOC), onset date, resolution date, severity, seriousness, action taken, outcome and drug relatedness. The event onset will also be shown relative (in number of days) to date of first application.

Treatment-emergent AEs will be summarized by treatment group, the number of subjects reporting a TEAE, SOC, preferred term, severity, relationship to study drug (causality), and seriousness. When summarizing AEs by severity and relationship, each subject will be counted once within a system organ class or a preferred term by using the event with the highest severity and greatest relationship within each classification.

Serious AEs will be summarized by treatment group, severity and relationship to study drug, and individual SAEs will be listed by subject. In addition, a list of subjects who prematurely discontinue from the study due to an AE will be provided.

11.12 Local Skin Reactions

Local Skin Reactions (LSRs) include erythema, peeling, dryness, burning/stinging and pruritus. These will be scored as 0 (None), 1 (Mild), 2 (Moderate) or 3 (Severe). LSRs will be summarized by treatment group and visit using descriptive statistics. A by-subject listing of subjects with any LSR 3 or higher will be presented.

11.13 Other Safety Data

Laboratory test results will be summarized descriptively at Baseline and Week 12. Additionally, shifts from baseline to Week 12 in laboratory test results based on normal ranges will be summarized with descriptive statistics. Individual laboratory test results will be presented in a by-subject listing. Any clinically significant laboratory abnormalities will be captured as adverse events.

Vital signs will be presented by treatment group and visit as observed values and changes from Baseline using descriptive statistics.

Medical histories will be coded using the MedDRA dictionary and presented in a by-subject listing.

Descriptive statistics by treatment group and visit will be provided for the following ECG parameters: heart rate (HR), RR duration, QRS duration, PR duration, QT duration and QTc duration. Change from Baseline in ECG abnormalities will be summarized using shift tables at the Week 12 visit.

Concomitant medications will be coded using the WHO-Drug dictionary. Concomitant medications will be summarized by treatment, drug class, and preferred term.

Physical examination data will be presented in a by-subject listing.

11.14 Sample Size Determination

The sample size for this study was based on estimates from the DRM01B-ACN02 study observed Week 12 results. Estimates were combined for all three active treatment groups as well for the two vehicle groups. All power calculations were performed with nQuery Advisor Version 7.0 for a two-sided test at alpha = 0.05.

For inflammatory lesion change a sample size of 300 Olumacostat Glasaretil Gel and 150 Olumacostat Glasaretil Gel Vehicle subjects has at least 95% power to detect a statistically significant difference with a significance level of 0.05 using the estimated absolute change from baseline in treatment means of -15.21 and -9.7 for Olumacostat Glasaretil Gel versus its vehicle, respectively, with a standard deviation of 11.00.

For non-inflammatory lesion change a sample size of 450 Olumacostat Glasaretil Gel and 225 Olumacostat Glasaretil Gel Vehicle subjects has 95% power to detect a statistically significant difference with a significance level of 0.05 using the estimated absolute change from baseline in treatment means of -14.73 and -9.70 for Olumacostat Glasaretil Gel versus its vehicle, respectively, with a standard deviation of 16.72.

The success rate for dichotomized IGA is estimated to be 20.5% in the 5.0% BID subjects and 9.6% in vehicle subjects. A sample size of 444 Olumacostat Glasaretil Gel and 222 Olumacostat Glasaretil Gel Vehicle will have 95% power to detect a statistically significant difference in proportions of successes. These calculations were performed with nQuery Advisor Version 7.0 for a two-sided continuity corrected chi-square test at alpha = 0.05.

To allow for a slight loss in power due to dropouts and withdrawals as well as to accommodate sufficient power in all three co-primary variables, a sample of 700 subjects randomized to 2 to 1 for Olumacostat Glasaretil Gel (n=467) and vehicle (n=233), respectively, will be enrolled in the trial.

12 STUDY ADMINISTRATION

12.1 Compliance with the Protocol

The study shall be conducted as described in this protocol. All revisions to the protocol must be prepared by the Sponsor. The Investigator will not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/EC of an Amendment, except where necessary to eliminate an immediate hazard(s) to study subjects. Any significant deviation must be documented and submitted to the: IRB/EC; the Sponsor or designee; and, if required, Regulatory Authority (ies).

Documentation of approval signed by the chairperson or designee of the IRB(s)/EC(s) must be sent to the Sponsor and/or designee.

12.2 Informed Consent Procedures

The Informed Consent Form (ICF) and Assent Forms for subjects under legal adult age must include all elements required by ICH/GCP and applicable regulatory requirements, and must adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. For subjects under legal adult age, both parents or legal representative may be required to sign informed consent as applicable. Assent to participate in a clinical trial applies to all subjects who are not legal adult subjects (in the state or location in which they are participating) and is defined as a child's affirmative agreement to participate in research. Permission of the minor subject's parent or legal guardian must also be obtained in compliance with part 50, subpart B of the Code of Federal Regulations and must include the elements of informed consent as described in Section 50.55 [15] and according to the regulations where the study is being conducted. Appropriate ICFs and assent forms will be provided according to local law/regulations. If a subject reaches legal adult age during the course of the trial, an adult ICF will be signed.

The ICF and Assent Forms must also include a statement that the Sponsor and regulatory authorities have direct access to subject records. Prior to the beginning of the study, the Investigator must have the IRB/EC's written approval/favorable opinion of the written ICF, Assent Forms and any other information to be provided to the subjects.

The Investigator must provide the subject or legally acceptable representative with a copy of the consent form and written information about the study in the language in which the subject is most proficient. The language must be nontechnical and easily understood. The Investigator should allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study, then the ICF must be signed and personally dated by the subject or the subject's legally acceptable representative, by the Investigator and by the person who conducted the informed consent discussion as required by local law. The subject or legally acceptable representative should receive a copy of the signed ICF and any other written information provided to study subjects prior to subjects participation in the study. This also applies to Assent Forms. All subjects and/or the legally acceptable representative (i.e., parents or guardian) will be provided with a contact address where they may obtain further information regarding the study.

The ICF, Assent Forms and any other information provided to the subjects or the subject's legally acceptable representative, should be revised whenever important new information becomes available that is relevant to the subjects consent, and should receive IRB/EC approval/ favorable opinion prior to use. The Investigator or designee should fully inform the subject or the subject's legally acceptable representative of all pertinent aspects of the study and of any new information relevant to the subjects willingness to continue participation in the study. This communication to the subject should be documented in the source documents.

During a subject's participation in the study, any updates to the consent or assent forms and any updates to the written information will be provided to the subject.

12.3 Study Documentation and the Electronic Case Report Form

The Investigator is responsible for ensuring that data are properly recorded in the eCRFs and on related documents. All entries must be supported by the subject's medical records or source documents. The Investigator is to ensure that the observations and findings are recorded correctly and completely.

All Investigator observations/assessments must be reported in the eCRF. The original reports and any traces and films must be reviewed, signed and dated and retained by the Investigator for future reference.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record 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 in the eCRFs that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

The Investigator must certify that the data are complete and accurate at the time the subject ends the study or as instructed by the Sponsor or designee by applying an electronic signature to the eCRF study completion page.

12.4 Study Monitoring

The Sponsor or designee will be responsible for the monitoring of the study. Study monitors will contact and visit the Investigators at regular intervals throughout the study. The study monitor will verify adherence to the protocol and completeness, consistency and accuracy of the data by comparing subjects' medical records with entries in the eCRF. The study monitor must be allowed access to laboratory test reports and other subject records that are needed to verify the entries on the eCRF. The Investigators will allow the study monitor to inspect the various records of the study (eCRFs and other pertinent data), provided that subject confidentiality is maintained in accordance with local requirements. These records, and other relevant data, may also be reviewed by appropriate qualified personnel independent from the Sponsor or designee, who is appointed to audit the study. Subject confidentiality will be maintained at all times.

The Investigators agree to co-operate with the study monitor to ensure that any problems detected in the course of the monitoring visits are resolved.

12.5 Retention of Study Documentation

The Investigator must retain study drug disposition records, copies of eCRFs and all study-related source documents for the maximum period required by applicable regulations and guidelines, or Institution procedures, or for the period specified by the Sponsor, whichever is longer. The Investigator must contact the Sponsor prior to destroying any records associated with the study.

If the Investigator withdraws from the study (e.g., relocation, retirement), the records will be transferred to a mutually agreed upon designee (e.g., another Investigator, IRB/Ethics Committee). Notice of such transfer will be given in writing to the Sponsor or designee.

If the Investigator cannot guarantee this archiving requirement for any or all the documents at the investigational site, arrangements must be made between the Investigator and the Sponsor, to store these in a secure archive facility outside the site; they can therefore be returned to the Investigator in case of a regulatory audit. Where source documents are required for the continued care of the subject, appropriate copies should be made for storing outside the site.

Following the study close-out visit data will be provided to the Investigator to store with the Investigator's study file for archiving purposes.

13 ACRONYMS AND DEFINITIONS

13.1 Acronyms

The acronyms listed below are a non-exhaustive list of those commonly used in Dermira study documents. Not all acronyms listed below are used within this document.

Abbreviation	Definition
ACC	acetyl-coenzyme A carboxylases
AE	adverse event(s)
ALT	alanine amino-transferase
ANCOVA	analysis of covariance
AR	adverse reaction(s)
AST	aspartate amino-transferase
BID	twice daily
BUN	blood urea nitrogen
CFR	code of federal regulations
CMH	Cochran-Mantel-Haenszel
CRO	clinical research organization
eCRF	electronic case report form
ET	early termination
F	Fahrenheit

Abbreviation	Definition
FDA	food and drug administration
GCP	good clinical practice
HCT	hematocrit
HGB	hemoglobin
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	independent ethics committee
IGA	Investigator's global assessment
IRB	institutional review board
ITT	intent-to-treat
IV	Intravenous
LDH	lactate dehydrogenase
LOCF	last observation carried forward
LSR	local skin reactions
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	medical dictionary for regulatory activities
NSAID	non-steroidal anti-inflammatory drug
PP	per protocol
QD	once daily
RBC	red blood cells
SAS	statistical analysis software
SSAR	serious suspected adverse reaction(s)
TG	Triglycerides
TK	toxicokinetic
UPT	urine pregnancy test
US	united states
WBC	white blood cells
WOCBP	women of childbearing potential
β-hCG	beta-human chorionic gonadotropin

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15. 21 CFR §50.55.

15 APPENDIX 1 – SCHEDULE OF EVENTS

Visit	Screening Day -35 to -1	Baseline/ Day 1	Week 1 (+/- 2 day)	Phone Contact Week 2 (+/- 2 day)	Week 4 (+/- 4 days)	Week 8 (+/- 4 days)	Exit / Early Termination Week 12 (+/- 4 days) / ET
Informed Consent/Assent	X						
Demography	X						
Medical History	X						
Inclusion/Exclusion Criteria	X	X					
Complete Physical Exam, Height[c], Weight	X						X
Symptom-directed Physical Exam		X	X		X	X	
Vital Signs	X	X	X		X	X	X
Adverse Events		X[a]	X	X	X	X	X
Local skin reactions		X	X		X	X	X
Concomitant Medications	X	X	X	X	X	X	X
12-Lead ECGs	X						X
Safety labs: Serum Chemistry, Hematology, Serum Pregnancy, Urinalysis	X						X
Urine Pregnancy Test		X			X	X	
Investigator Global Assessment		X			X	X	X
Acne Patient Self-Questionnaire		X			X	X	X
Acne Lesion Counts		X			X	X	X
Photographs[b]		X			X	X	X
Dispense Study Medication/Diary		X	X		X	X	
Study Medication Compliance			X		X	X	X

[a] AEs to be collected after the first dose of study drug is applied.
[b] Selected sites only.
[c] Height not required at Week 12.

16 APPENDIX 2 – ACNE PATIENT SELF- QUESTIONNAIRE

1. Over the past 7 days, rate how oily your face looked:
   - *Asked at BL, wk 4, 8, 12, and OLE 12, 24, 36*

☐ Not at all oily

☐ Slightly oily

☐ Moderately oily

☐ Very oily

☐ Extremely oily

2. Over the past 7 days, rate how your face looked overall as the result of your acne:
   - *Asked at BL, wk 4, 8, 12, and OLE 12, 24, 36*

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

0 1 2 3 4 5 6 7 8 9 10

Bad Excellent

3. Overall, how would you rate your acne <u>now</u> as compared to before starting the study treatment?
   - *Only asked at wk 4, 8, 12, and OLE 12, 24, 36*

☐ Very much improved

☐ Moderately improved

☑ No difference

☑ Moderately worse

☑ Very much worse

4. Over the past 7 days, how <u>self-conscious</u> did you feel about the way your face looks because of your facial acne?
   - *Asked at BL, wk 4, 8, 12, and OLE 12, 24, 36*
     1. Not at all self-conscious
     2. Slightly self-conscious
     3. Moderately self-conscious
     4. Very self-conscious
     5. Extremely self-conscious

5. Over the past 7 days, how insecure did you feel about the way your face looks because of your facial acne?
   - *Asked at BL, wk 4, 8, 12, and OLE 12, 24, 36*
     1. Not at all insecure
     2. Slightly insecure
     3. Moderately insecure
     4. Very insecure
     5. Extremely insecure

6. Over the past 7 days, how often did you avoid interactions with other people because of your facial acne?
   - *Asked at BL, wk 4, 8, 12, and OLE 12, 24, 36*
     1. Never
     2. Rarely
     3. Some of the time
     4. Most of the time
     5. All of the time

7. Over the past 7 days, how embarrassed were you by the way your face looked because of your facial acne?
   - *Asked at BL, wk 4, 8, 12, and OLE 12, 24, 36*
     1. Not at all embarrassed
     2. Slightly embarrassed
     3. Moderately embarrassed
     4. Very embarrassed
     5. Extremely embarrassed

8. Over the past 7 days, how sad were you by the way your face looked because of you facial acne?
   - *Asked at BL, wk 4, 8, 12, and OLE 12, 24, 36*
     1. Not at all sad
     2. Slightly sad
     3. Moderately sad
     4. Very sad
     5. Extremely sad

On a scale of 1 to 5 (*1= Very unsatisfied, 5 = Very satisfied*), how satisfied were you with each of the following?

- *To be asked just at wk 12*

	1 – *Very Unsatisfied*	**2 – *Unsatisfied***	**3 – *Neutral***	**4 – *Satisfied***	**5 – *Very Satisfied***
9. Ease of product application	☐	☐	☐	☐	☐
10. How the product looks on my skin at time of application	☐	☐	☐	☐	☐
11. How the product feels on my skin while applying	☐	☐	☐	☐	☐
12. How well the product fits into my daily skin care routine	☐	☐	☐	☐	☐