AN OPEN-LABEL STUDY ASSESSING LONG-TERM SAFETY OF OLUMACOSTAT GLASARETIL GEL IN SUBJECTS WITH ACNE VULGARIS

Protocol Number	**DRM01B-ACN05**
Protocol Final Date **Amendment 1 Date**	**16 November 2016** **24 April 2017**
IND Number	**121136**
Study Drug	**Olumacostat Glasaretil Gel**
Sponsor	**Dermira, Inc.** **275 Middlefield Road** **Suite 150** **Menlo Park, CA 94025** **USA**

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PROTOCOL AMENDMENT 1 SUMMARY OF CHANGES

Change	Location	Rationale
Changed Medical Monitor name and contact information	Page 2	Change in personnel.
Clarified permitted and prohibited treatments for acne vulgaris on the trunk	Section 7.2	Since subjects originating in DRM01B-ACN03 are allowed, if warranted by the Investigator, to use study drug on the trunk, these subjects are not allowed to use any concomitant medication to treat acne vulgaris in the DRM01B-ACN05 study. Subjects originating in DRM01B-ACN04 are not allowed to use study drug on the trunk, and therefore, may use approved topical acne treatments on the trunk in the DRM01B-ACN05 study.

SPONSOR SIGNATURE PAGE

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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

26 APRIL 2017

Date (DD MMM YYYY)

Eugene A. Bauer, MD
Chief Medical Officer

INVESTIGATOR SIGNATURE PAGE

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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:	An Open-Label Study Assessing Long-Term Safety of Olumacostat Glasaretil Gel in Subjects with Acne Vulgaris
Protocol Number:	DRM01B-ACN05
Phase:	3
Number of Sites:	Approximately 100
Study Population	Subjects who participated in either the DRM01B-ACN03 or DRM01B-ACN04 studies
Sample Size	Approximately 700
Study Treatment	Olumacostat Glasaretil Gel, 5.0%, applied twice daily
Study Objective:	To assess the long term safety of Olumacostat Glasaretil Gel, 5.0% in subjects with acne vulgaris
Duration of Subject Participation:	Up to 36 weeks
Study Visit Schedule	Day 1 (Week 12 visit of DRM01B-ACN03 or DRM01B-ACN04), Weeks 2 (phone call only), 4, 8, 12, 16, 20, 24, 28, 32, 36 (Study Exit)

Study Design/Summary:

This is an open label, long-term safety study enrolling approximately 700 subjects who participated in either the DRM01B-ACN03 or DRM01B-ANC04 studies. All subjects will sign an informed consent (adults)/assent (children) prior to continuing in this open label study.

Eligible subjects will receive open label treatment with Olumacostat Glasaretil Gel, 5.0% and continue to dose twice daily for up to 36 weeks. Study drug will be applied twice daily to the face. Subjects, who participated in DRM01-ACN03 study with acne on the chest, back or shoulders and applied study drug to affected areas will be allowed to continue to apply study drug to the affected areas. Subjects who participated in DRM01-ACN04 study will continue to apply study drug to the face only. Subjects will return to the clinic at Weeks 4, 8, 12, 16, 20, 24, 28, 32, and 36 (Study Exit). A follow-up phone call at Week 2 will be made to assess safety (adverse events) only.

At the Week 12 and 24 visits, if the severity of acne has become worse, the subject should be withdrawn, at the investigator's discretion. Severity of acne will be assessed by IGA and limited to the face only.

Efficacy will be assessed through investigator global assessment of acne (IGA).

Safety will be assessed through adverse events, local skin reactions (LSRs), serum chemistry, hematology and urinalysis laboratory testing, physical examination, ECGs, pulse and blood pressure.

Photographs of the face will be taken for all subjects at a 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.

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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, a topical treatment for 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 glasaretil 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 (DR01B-ACN01) and the same formulation that was included in the clinical dose ranging trial DR01B-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 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 to be mild to moderate 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 doses 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 showed 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 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 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).

A comparison of subjects with a 2-grade improvement in IGA score with or without a concurrent IGA score of clear or almost clear at Weeks 4, 8, and 12 showed that in each treatment group at each IGA assessment time point, most subjects who achieved a 2-grade improvement in IGA score also had an IGA score of clear or almost clear.

Pharmacokinetic (PK) results, assessed in a subset of subjects, showed that plasma concentrations of olumacostat glasaretil on Day 1 were undetectable for all but one subject, who had a plasma concentration of 0.304 ng/mL at one time point (2 hours post-dosing). Plasma concentrations of olumacostat glasaretil 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 Olumacostat Glasaretil Gel 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.

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, DRM01B-ACN03 and DRM01B-ACN04, are planned as part of the Phase 3 development program and will include adults and children (ages 9 years and older) in order to assess the safety and efficacy of Olumacostat Glasaretil Gel for the treatment of acne vulgaris.

The DRM01B-ACN05 study described herein is an open-label study to assess the long term safety of continuous treatment with Olumacostat Glasaretil Gel, 5% for up to an additional 36-weeks in subjects who have completed either of the DRM01-ACN03 or DRM01-ACN04 studies.

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 an open-label, long-term safety study enrolling approximately 700 subjects who participated in either DRM01B-ACN03 or DRM01B-ACN04 studies. All subjects will sign an informed consent / assent prior to continuing in this open label study.

Eligible subjects will receive open label treatment with Olumacostat Glasaretil Gel, 5.0% and continue to dose twice daily for 36 weeks. Subjects, who participated in DRM01-ACN03 study with acne on the chest, back or shoulders and applied study drug to affected areas will be allowed to continue to apply study drug to the affected areas. Subjects who participated in DRM01-ACN04 study will continue to apply study drug to the face only. Subjects will receive a phone call at Week 2 to assess safety, and will return to the clinic at Weeks 4, 8, 12, 16, 20, 24, 28, 32, and 36 (End of Study).

Efficacy will be assessed via a static evaluation of qualitative overall acne severity, the investigator's global assessment of acne (IGA).

At the Week 12 and 24 visit, if the severity of acne has become worse, as determined by the IGA, the subject should be withdrawn, at the investigator's discretion. Severity of acne will be assessed on the face only.

Safety will be assessed through adverse events, local skin reactions (LSRs), serum chemistry, hematology and urinalysis laboratory testing, ECGs, physical examination, pulse and blood pressure.

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

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

3 STUDY OBJECTIVES

The objective of this study is to assess the long-term safety of Olumacostat Glasaretil Gel, 5.0%, in subjects with acne vulgaris.

This study may be stopped once at least 100 subjects have been treated for 36 weeks.

4 STUDY ENDPOINTS

No inferential statistics are planned for this study.

5 STUDY DESIGN

5.1 Duration of the Study

Each subject will participate in this study for up to 36 weeks.

5.2 Study Population and Number of Subjects

Approximately 700 subjects who participated in either of the DRM01B-ACN03 or DRM01B-ACN04 studies may enroll in this trial.

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 its 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 or assent (for subjects under legal adult age)
2. Completed Week 12 visit of either DRM01B-ACN03 or DRM01B-ACN04 studies.
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. Willing to refrain from using any treatments on the face 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. Abnormal clinically significant findings on physical exam, vital signs or ECG at Week 12 visit of either the DRM01-ACN03 or DMR01-ACN04 studies that would make further treatment with Olumacostat Glasaretil Gel contraindicated, as determined by the Investigator
2. Any other condition which, in the judgment of the investigator, would put the subject at unacceptable risk for participation in the study

6 STUDY DRUG

6.1 Investigational Medicinal Product

The study medication is Olumacostat Glasaretil Gel, 5.0%.

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.

6.2 Packaging, Labeling and Storage

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

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

Study drug tubes 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

Subjects will maintain the unique subject number assigned at randomization into their study of origin (either DRM01B-ACN03 or DRM01B-ACN04). All subjects will receive Olumacostat Glasaretil Gel, 5.0%, BID.

6.4 Study Blinding

This is an open-label study. Subjects will not be unblinded to their treatment assignment prior to enrollment into this study (DRM01B-ACN05). Once enrolled, each subject will receive Olumacostat Glasaretil Gel, 5.0%.

6.5 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, and if required, 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.

6.6 Study Drug Application

Subjects will apply the study drug twice daily (morning and evening) to a clean, dry face. Subjects will be re-instructed on the application of the study drug, if needed.

Study drug is to be applied topically, to the entire face (forehead, nose, cheeks, and chin) by squeezing approximately ½ inch or 1.3 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.

For subjects originating in the DRM01B-ACN03 study, subjects may continue to apply study drug may all affected areas on the trunk (i.e., chest, shoulders and back) by spreading a thin layer of gel over the entire affected areas.

Subjects originating in DRM01B-ACN04 should continue to apply study drug to the face only.

Subjects will 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 of applying study medication. Missed doses should be applied, provided there is an 8-hour window until the next scheduled dose.

6.7 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 medication. The subject-completed diary will collect application information for the face, chest, back and shoulders. 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 on the face, will be counseled. All diaries will be maintained as source documentation.

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

6.8 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 drug 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 throughout the study 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 or if continuation is not 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
    - With the following exception: Subjects originating in DRM01B-ACN04 may apply non-systemically-absorbing over-the-counter topical medications for acne vulgaris on truncal acne if warrented by the Investigator
- 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 Day 1 (Week 12 Visit of DRM01B-ACN03 or DRM01B-ACN04 Study)

- 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.
- Assess Inclusion/Exclusion criteria
- Dispense study drug and diary
- Schedule next visit

The following Week 12 data collected as part of the DRM01-ACN03 or DRM01-ACN04 study will be used for the Day 1 visit:

- Query subject for concomitant medication use
- Perform a complete physical examination
- Record weight
- Measure pulse and blood pressure
- Collect a 12-lead ECG
- Conduct Investigator Global Assessment
- Collect Acne Patient Self-Questionnaire
- Draw blood samples for laboratory tests and urine for urinalysis. Include serum pregnancy test for women of childbearing potential
- Assess Local Skin Reactions (LSR)
- Review and record AEs
- Collect photographs (selected sites)

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

- Call subject to review AEs and concomitant medications
- Schedule next visit

8.3 Weeks 4, 8, 16, 20, 28 and 32 (+/-4 days)

- Collect concomitant medication information
- Collect urine pregnancy for women of childbearing potential
- Measure pulse and blood pressure
- Review and record AEs
- Assess LSRs
- Perform symptom-directed physical exam
- Review compliance/Weigh tubes and dispense drug and diary
- Schedule next visit

8.4 Week 12 and 24 (+/-4 days)

- Collect concomitant medication information
- Collect urine pregnancy for women of childbearing potential
- Measure pulse and blood pressure
- Review and record AEs
- Assess LSRs
- Conduct Investigator's Global Assessment and assess subject's eligibility to continue treatment.
- Collect Acne Patient Self-Questionnaire
- Collect photographs at Week 12 only (selected sites)
- Perform symptom-directed physical exam
- Review compliance/Weigh tubes and dispense drug and diary
- Schedule next visit

8.5 Week 36 (+/-4 day) Study Exit or Early Termination Visit

- Collect concomitant medication information
- Measure pulse and blood pressure
- Review and record AEs
- Conduct a complete physical exam

- Measure weight and height
- Collect a 12 lead ECG
- Draw blood samples for laboratory tests. Include serum pregnancy test for women of childbearing potential. Include urinalysis if clinically indicated
- Assess LSRs
- Conduct Investigator Global Assessment
- Collect Acne Patient Self-Questionnaire
- Collect photographs (selected sites)
- Review compliance/Weigh tubes and collect all study medication and diary

8.6 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. If an immediate result is required to adequately care for a subject, a duplicate sample may be submitted to a local lab.

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 Baseline/Day 1 Assessments

The Baseline/Day 1 visit for this study occurs on the same day as the Week 12/study exit visit of the DRM01B-ACN03 or DRM01B-ACN04 visit. Therefore, if subjects choose to enroll in this study, study procedures will not be repeated; study sites will carry over the information from the DRM01B-ACN03 or DRM01B-ACN04 study to the Baseline/Day 1 visit for this study.

The study procedures that are to be carried over are:

- Demographic information: age, gender, race, ethnicity and Fitzpatrick Skin Type
- Medical history
- Adverse events
- Local skin reactions
- Concomitant medications
- Laboratory evaluations: hematology, serum chemistries and urinalysis
- Pregnancy testing
- 12-lead ECG
- Investigator Global Assessment of acne

- Photography (at selected sites)
- Vital signs and weight
- Acne Patient Self-Questionnaire

9.2 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.

9.3 Assessment of Efficacy

9.3.1 Investigator Global Assessment

An Investigator Global Assessment (IGA) of acne severity on the face only will be conducted for each subject every 12 weeks (Table 1).

Where possible, **the same efficacy assessor should assess acne severity on the same subject at all visits**. At the Week 12 and 24 visit, if the severity of acne has become worse, as determined by the IGA, the investigator should assess whether or not the subject should be withdrawn from the study. If the decision is made to withdraw the subject, all Early Termination Visit procedures should be completed. For additional details regarding subject withdrawal, please refer to Section 10.2 Early Study Termination of Study Subjects.

Individuals performing the IGA will be trained and certified prior to study start. IGA grades will be entered into the eCRF.

Table 1: 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

9.4 Assessment of Safety

9.4.1 Physical Examination

A complete physical examination will be conducted at Day 1 and Week 36 (End of Treatment) visit and cover general appearance, dermatological, head, ears, eyes, nose, throat, respiratory, cardiovascular, abdominal, neurological, musculoskeletal, and lymphatic body systems. A symptom directed physical exam may be performed at other clinic visits, if needed, to assess the subject. Weight will be recorded with the end of study physical exam. Findings will be recorded in the source document and eCRF.

9.4.2 Pulse and Blood Pressure

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.

Pulse and blood pressure measurements will be recorded in the source document and eCRF.

9.4.3 ECGs

12-lead ECG measurements will be obtained for all subjects at the Day 1 and Week 36 Study Exit or Early Termination visits. 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.

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, RBC morphology, platelet count, absolute

neutrophils, absolute lymphocytes, absolute monocytes, absolute eosinophils, and absolute basophils.

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 Baseline/Day 1and Week 36 Study Exit or Early Termination visits. Urine pregnancy testing (beta human chorionic gonadotropin [β-hCG]) will be performed at Weeks 4 – 36 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.

The central laboratory should 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 levels, in the opinion of the investigator.

9.4.5 Local Skin Reactions

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) (Table 2). 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 and erythema, dryness and scaling will be assessed by the Investigator/designee (Table 3). Subjects will be read the definition of each subject-assessed LSR and asked to select the appropriate definition. The corresponding grade will be assigned by the site and entered in the eCRF.

Table 2: 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 3: 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).

9.4.7 Reporting

Only AEs that occur during or following study treatment with the drug will be reported in the AE section of the eCRF. Events recorded prior to treatment with the study 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 pulse and blood pressure 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 9.4.8.

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.

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.

9.4.8 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.

9.4.9 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 admission or 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.

9.4.10 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.

9.4.11 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. In such cases, the Investigator must contact the Sponsor or designee, as the need to withdraw the subject will assessed by the Sponsor
- Unacceptable toxicity

11 STATISTICAL CONSIDERATIONS

11.1 General Statistical Methodology

All statistical processing will be performed using SAS® unless otherwise stated. Data will be summarized using descriptive statistics. No inferential testing or imputations for missing data will be performed.

Subject demographic and baseline characteristics will be summarized for the Safety Population. Categorial variables will be tabulated with frequencies and percentages. Continuous variables will be tabulated with mean, median, SD, and range (minimum and maximum).

A statistical analysis plan (SAP), describing all statistical analyses will be provided as a separate document.

11.2 Populations Analyzed

All analyses will be performed using the Safety Population. All subjects who receive at least one confirmed dose of Olumacostat Glasaretil Gel and have at least one post-baseline (where baseline is the day that the subject received their first study drug) assessment will be included in the Safety Population.

The number of subjects included in the Safety Population will be summarized.

11.3 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.

11.4 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.

11.5 Local Skin Reactions

Local Skin Responses (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.

11.6 Other Safety Data

Laboratory data will be presented in a by-subject listing. Any clinically significant laboratory abnormalities will be captured as adverse events. Changes from Baseline in safety laboratory values will be summarized at the final follow up evaluation during the treatment period using descriptive statistics or frequency tables as appropriate.

Additionally, changes from Baseline in safety laboratory values will be summarized using shift tables according to normal ranges.

Pulse and blood pressure will be presented as absolute values and changes from baseline using descriptive statistics.

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.

11.7 Sample Size Determination

The sample size for this study was based on the minimum requirement for a long-term safety study.

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 50.21 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 subject's 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 subject's 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 subject's 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 (eCRF)

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 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
FDA	US Food and Drug Administration
GCP	good clinical practice
GGT	gamma-glutamyl transferase
HCT	hematocrit
HEENT	head, ears, eyes, nose, throat
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

Abbreviation	Definition
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

14 REFERENCES

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15 APPENDIX 1 – SCHEDULE OF VISITS AND PROCEDURES

Visit	Day 1	Week 2 (phone call) (+/- 2 days)	Week 4, 8, 16, 20, 28, 32 (+/- 4 days)	Weeks 12, 24 (+/- 4 days	Week 36 Study Exit/ Early Term. (+/- 4 days)
Informed Consent/Assent	X				
Inclusion/Exclusion Criteria	X				
Complete Physical Exam, Weight, Height	X[b]				X
Symptom-directed Physical Exam			X	X	
Pulse and Blood Pressure	X		X	X	X
Adverse Events	X	X	X	X	X
Local Skin Reactions	X[b]		X	X	X
Concomitant Medications	X	X	X	X	X
Safety labs: Serum Chemistry, Hematology, Serum Pregnancy, Urinalysis	X[b]				X
Urine Pregnancy Test			X	X	
Photographs[a]	X[b]			X[c]	X
12-Lead ECGs	X[b]				X
Dispense Study Medication/Diary	X		X	X	
Investigator Global Assessment	X[b]			X	X
Acne Patient Self-Questionnaire	X[b]			X	X
Study Medication Compliance			X	X	X

[a] Selected sites only
[b] Week 12 data collected as part of the DRM01-ACN03 or DRM01-ACN04 study will be used for the Day 1 visit
[c] Week 12 only

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	☐	☐	☐	☐	☐