An Open-label Study to Investigate the Efficacy and Tolerability of Aczone Gel, 7.5% in the Treatment of Acne Vulgaris in Men and Women With Skin of Color

Saakshi Khattri

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Principal Investigator: Saakshi Khattri, M.D.
Mount Sinai

Brief Summary of Research

Acne vulgaris is a common skin disease characterized by inflammatory papules, pustules, and comedones that is prevalent in men and women of color. Research has demonstrated that Aczone ® (dapsone) gel, 7.5% used once daily is effective, safe, and well-tolerated for the treatment of acne in both men and women; however, no data is available regarding its efficacy and safety in skin of color (SOC). The current study aims to investigate the therapeutic impact of Aczone gel 7.5% in SOC males and females ages 18 and older with acne vulgaris. The study will also evaluate the impact of Aczone ® gel on hyperpigmentation and PIH of the face.

Objectives

The purpose of this study is to evaluate the safety and efficacy of Aczone ® gel, 7.5% administered once daily for 24 weeks in males or females with skin of color (SOC), defined as Fitzpatrick Skin Types IV, V, or VI, for the treatment of facial acne vulgaris.

Background

Acne vulgaris is a common skin disease characterized by inflammatory papules, pustules, and comedones that is prevalent in men and women of color. In fact, acne is the most common dermatologic diagnosis made in SOC populations (1). Although individuals of all skin types can develop acne vulgaris, there are important differences in darker skin types that are important to consider when choosing an optimal treatment (2).

From a diagnosis standpoint, acne in women of color is more likely to present on the cheek area, as opposed to a chin and cheek predominance in white women (2). Complications from acne are of great concern in this population, as women of color are more likely to develop keloids, hypertrophic scars, and post-inflammatory hyperpigmentation (PIH) as a result of acne lesions (3). PIH may last for weeks to months and, in many cases, is more troublesome to patients than the acne itself (2). Overall, facial acne and its sequelae have a greater impact on perception of appearance, negative emotions, and social functioning in women of color than white women (2).

Dapsone is a sulfone compound with anti-inflammatory properties that has been shown to be effective in the treatment of acne vulgaris in SOC (4). Aczone ® (dapsone) gel, 5% administered twice daily has been associated with significant improvement in overall acne severity, acne signs, and impact on quality of life in women of color (4). Two phase III trials of a newer formulation of Aczone ® (dapsone) gel, 7.5% used once daily demonstrated that this product is effective, safe, and well-tolerated for the treatment of acne in both men and women (5); however, no data is available regarding its efficacy and safety in SOC.

Further, some investigators of the phase IV study on the safety and efficacy of dapsone gel 5% in SOC anecdotally reported improvement in hyperpigmentation over 12 weeks, although this was not a planned efficacy outcome (4). Further research is needed on the potential effects of dapsone gel on hyperpigmentation and PIH in SOC.

The current study will investigate the therapeutic impact of Aczone gel 7.5% in SOC males and females ages 18 and older with acne vulgaris. The study will also evaluate the impact of Aczone gel on post-inflammatory hyperpigmentation using the Postacne Hyperpigmentation Index (PAHPI) and mexameter-measured melanin index (MI).

Setting of the Human Research

All research activity will take place at Mount Sinai Department of Dermatology.

Resources Available to Conduct the Human Research

The research team consists of the Principal Investigator, Sub-Investigator and Research Coordinator. We do not foresee any difficulties in recruiting the suggested number of patients for this research study.

All members of the study team have several years of research experience and have all completed the required trainings and certifications mandated by our IRB.

All research team members have read and understand the protocol and all study related procedures.

Study Design

a) Recruitment Methods

Subjects will be recruited from the dermatology faculty practices and the dermatology resident clinics in the Mount Sinai Health System. Once approved by the Sponsor, we will use IRB approved flyers, online advertisements (including social media postings and clinical trials listing services) as well as questionnaires and phone scripts.

b) Inclusion and Exclusion Criteria

Inclusion:

1. Provide written, signed and dated informed consent prior to initiating any study-related activities.
2. Male or female subjects who are ≥ 18 years of age
3. Subjects with Fitzpatrick Skin Type IV, V, or VI
4. Subjects with moderate to severe acne as defined by investigator-assessed Global Acne Assessment Score (GAAS) of 3 or 4 at screening
5. Facial acne vulgaris with 20 to 50 (inclusive) inflammatory lesions and 30 to 100 (inclusive) noninflammatory lesion
6. Stable non-progressive or regressive acne vulgaris in the investigator's opinion

7. Females of childbearing potential (FCBP) must have a negative pregnancy test at Screening and Baseline. A female is considered not to be of childbearing potential if she is post-menopausal with at least 12 consecutive months of amenorrhea or has undergone surgical sterilization. While on investigational product and for at least 28 days after taking the last dose of investigational product, FCBP who engage in activity in which conception is possible must use one of the approved contraceptive options described below:

   Option 1: Any one of the following highly effective methods: hormonal contraception (oral, injection, implant, transdermal patch, vaginal ring); intrauterine device (IUD); tubal ligation; or partner's vasectomy;

   OR

   Option 2: Male or female condom (latex condom or nonlatex condom NOT made out of natural [animal] membrane [for example, polyurethane]; PLUS one additional barrier method: (a) diaphragm with spermicide; (b) cervical cap with spermicide; or (c) contraceptive sponge with spermicide.

8. Must be in general good as judged by the Investigator
9. Subject is willing to avoid excessive or prolonged exposure of the treated skin to ultraviolet light (i.e. sunlight, tanning beds) throughout the study
10. Subject is willing to follow study instructions and complete study assessments without assistance and is likely to complete all required visits

Exclusion:

1. Diagnosis of other dermatologic diagnosis that, in the opinion of the investigator, would interfere with diagnosis, examination, or treatment of the studied condition (i.e. psoriasis, atopic dermatitis, lupus, dermatomyositis, seborrheic dermatitis, perioral dermatitis, etc.)
2. Subjects with severe cystic acne, acne conglobate, acne fulminans, or secondary acne (chloracne or drug-induced acne)
3. Uncontrolled systemic disease(s) that, in the opinion of the investigator, would put the patient at significant risk if enrolled in the study or would interfere with subject's participation in the study
4. Subjects with a history of clinically significant hemolysis, anemia, or enteritis (regional enteritis, ulcerative colitis, pseudomembranous colitis, antibiotic-associated colitis)
5. Subjects with allergy or sensitivity to the study drug or its components
6. Subjects who have not complied with the proper wash-out periods:
   a. Topical anti-inflammatory medications, salicylic acid, corticosteroids, antibiotics, antibacterials, peroxide-containing products, or retinoids within 2 weeks of baseline
   b. Systemic antibiotics, corticosteroids, antimalarials or oral dapsone within 4 weeks of baseline

c. Other anti-acne medication, including isotretinoin or spironolactone, within 6 months of baseline

d. Chemical peels or other facial acne procedures (laser therapy, light therapy) within 3 months of baseline

e. Treatment with botulinum toxin of any serotype in the face within 6 months of baseline

f. Estrogens/Birth control pills must have been started ≥ 90 days prior to baseline and use must be continued during the study without alteration or discontinuation.

7. Pregnant or breastfeeding.
8. Subjects with evidence of alcohol or substance abuse.
9. Use of any investigational drug within 4 weeks prior to randomization, or 5 pharmacokinetic/pharmacodynamic half-lives, if known (whichever is longer).

c) Number of Subjects

Up to 40 subjects with acne vulgaris will be screened with a goal of 20 total subjects randomized. All 20 randomized subjects are expected to complete all study procedures. Individuals who provide informed consent and fail to meet all of the inclusion and exclusion criteria during the initial evaluation will be considered a "screening failure."

d) Study Timelines

The study will consist of 6 in-person visits and one phone visit (7 total visits) over up to 28 weeks (4 week screening period plus 24 weeks enrolled in study). Study visits will be conducted at Screening (Visit 1), Baseline (Visit 2, Week 0), Week 4 (Visit 3), Week 8 phone visit (Visit 4), Week 12 (Visit 5), Week 18 (Visit 6), Week 24 (Visit 7).

Enrollment will occur over a 24-36 month period from January 2018 to December 2020. The study is anticipated to be completed by December 2021.

e) Endpoints

Primary Endpoint:

1. Mean change from baseline to week 12 in Global Acne Assessment Score (GAAS)

Secondary Endpoints:

1. Change from baseline in Global Acne Assessment Score (GAAS) at week 4, 18, and 24.
2. Change from baseline in Post Acne Hyperpigmenation Index (PAHPI) at weeks 12, 18, and 24.
3. Change from baseline in Melanin Index (MI) of target lesion at weeks 12, 18, and 24
4. Change from baseline in the proportion of subjects with score of 0 or 1 on ASIS "dark spot" score at weeks 4, 12, 18, and 24.
5. Proportion of subjects with GAAS of 0 (none) or 1 (minimal) at weeks 4, 12, 18, and 24

6. Percent change from baseline in all lesion counts (inflammatory, noninflammatory, and total) at weeks 4, 12, 18, and 24.

f) Procedures Involved in the Human Research

This is a single-center, single-group, open-label study using Aczone ® (dapsone) gel 7.5%. All subjects will receive the study medication. Aczone ® gel is an off-white to yellow gel with suspended particles. It is supplied in an airless pump containing a polypropylene bottle with a high density polyethylene piston. It will be dispensed as a 60g pump.

Subject will apply Aczone ® once daily to the entire face. Study drug must not be applied to other areas of the body, including the upper chest, upper back or shoulders.

Prior to the start of the study, potential subjects will be given an IRB-approved Informed Consent Document (ICD) containing a Health Insurance Portability and Accountability Act (HIPAA) disclosure agreement to read, understand, and sign. All questions about the study should be answered to the satisfaction of the candidate subject. They will have all of their study-related questions answered by the PI or designee, and if they agree to participate, the subject will sign two original copies of the ICD. The subjects will retain one original copy and one original copy will be kept in the study file. The subjects who sign an ICD will be assigned a screening number.

After providing informed consent, subjects will be assessed for study eligibility at the Screening visit (day -28 to day -1), which includes review of medical history and concomitant, acne lesion counting and severity ratings, and serum pregnancy test (if applicable). The PI or a medically qualified designee must review this information (i.e. medical history, concomitant medication, and eligibility review) for each subject to confirm their eligibility before enrollment. A total of 20 subjects who meet eligibility criteria will undergo Baseline / Day 0 assessments. Subjects will return for visits at weeks 4, 12, 18, and 24. There will be a phone visit at week 8.

Study Assessments and Efficacy Measures:

Global Acne Assessment Score (GAAS):
The subject's acne severity will be assessed by the investigator using a 5-point GAAS at screening, baseline, and weeks 4, 12, 18, 24.

Grade		Description
0	None	No evidence of facial acne vulgaris
1	Minimal	Few noninflammatory lesions are present; a few inflammatory lesions (papules/pustules) may be present; no nodulo-cystic lesions present
2	Mild	Several to many noninflammatory lesions are present; a few inflammatory lesions are present; no nodulo-cystic lesions present.
3	Moderate	Many noninflammatory and inflammatory lesions are present; no nodulo-cystic lesions are present.
4	Severe	Significant degree of inflammatory disease; papules and pustules are a predominant feature; a few nodulo-cystic lesions are present (no more than 2)

Lesion Counts:
The lesion counts, including inflammatory and non-inflammatory lesions, will be performed at screening, baseline, and weeks 4, 12, 18, and 24. Inflammatory lesions (papules, pustules, nodules/cysts) and

noninflammatory lesions (open comedone, closed comedone) will be counted individually. The sum of the inflammatory lesion counts and non-inflammatory lesion counts will be totaled.

ASIS ®:
Acne Symptom and Impact Scale (ASIS ®) will be given to subjects' for completion at baseline and weeks 4, 12, 18, and 24. The ASIS ® contains 9 items assessing symptom severity and 8 items assessing the psychosocial impact of acne vulgaris (6). High scores on the ASIS® indicate the presence of more severe symptoms, whereas higher scores on the ASIS indicate better outcomes on acne health-related quality of life.

PAPHI:
The postacne hyperpigmentation index (PAHPI) has been shown to be a reliable and valid score measuring post-inflammatory hyperpigmentation from acne (7). PAHPI will be scored using the following formula:

Total PAHPI = S + I + N
PAHPI Score can range from 6-22.

Lesion Size (S)

Weighted Score (S)	Median Lesion size
2	<3mm
4	3-6mm
6	7-10mm
8	>10mm

Lesion Intensity (I)

Weighted Score (I)	Median Lesion Intensity
3	Slightly darker than surrounding skin
6	Moderately darker than surrounding skin
9	Significantly darker than surrounding skin

Lesion Number (N)

Weighted Score (N)	Number of Lesions
1	1-15
2	16-30
3	31-45
4	46-60
5	>60

Melanin Index:
A narrowband reflectance spectrophotometer (mexameter MX-16) will be used to measure the degree of pigmentation of involved and adjacent uninvolved skin of one representation facial PIH lesion (8).
The mexameter contains 16 light emitting diodes arranged circularly that emit light at wavelengths of 568nm (green), 660nm (red), and 880nm (near infrared). The machine then measures the amount of light absorbed and reflected by the skin to measure the melanin content (melanin index or "M" – red and near infrared light) and hemoglobin content (erythema index or "E" – green and right light).
One target lesion will be chosen by the investigator, which will be the darkest spot involved by post-inflammatory hyperpigmentation without evidence of active acne lesion (inflammatory or non-inflammatory lesion). The target lesion must be on the face and easily accessible with the mexameter probe. The probe will be applied to the target lesion on the skin with light, constant pressure. Both the "M" and "E" indices will be recorded. The location of the target site will be recorded using distance from anatomic landmarks.

Skin Phototype Assessment:
At screening, Fitzpatrick skin type (FST) will be rated by the investigator:
I: always burns, never tans (very pale)
II: always burns, tans minimally (pale)
III: burns moderately, tans gradually (light brown)
IV: burns minimally, always tans well (moderate brown)
V: rarely burns, tans profusely (dark brown)
VI: never burns, deeply pigmented (very dark brown)

Photography:
Standardized photographs will be taken by study personnel at baseline and weeks 12, 18, and 24 using standardized cameras and photographic equipment.

Subject Safety Measures:
The following safety measures will be collected:
- Adverse events
    - The investigator will question the subject at all scheduled visits and one phone visit to determine whether adverse events were experienced since the prior visit. The adverse event and all applicable information (date of onset, date of stop, duration, outcome, severity, relationship to study drug, action or treatment required) will be obtained and recorded on the source documents and adverse event CRF.
- Local tolerability assessments
    - Investigator will ask subject to rate subjective burning/stinging using the following scale: 0 = absent (normal, no discomfort), 1 = trace (an awareness, but no discomfort and no intervention required), 2 = mild (noticeable discomfort causing intermittent awareness), 3 = moderate (noticeable discomfort causing continuous awareness), 4= marked (definite discomfort causing continuous awareness, interfering occasionally with normal daily activities), 5 = severe (definite, continuous discomfort interfering with normal daily activities)
    - Investigator will rate erythema, dryness, peeling, and oiliness using the following scale:

Score	Erythema	Dryness	Peeling	Oiliness
0=absent	No redness	None	Smooth	Normal

1=trace	Faint red or pink coloration, barely perceptible	Barely perceptible dryness by palpation with no accentuation of skin markings, skin desquamation (flakes) or fissure formation	Fine peeling, barely perceptible	Mild and localized
2=mild	Light red or pink coloration	Easily perceptible dryness by palpation with accentuation of skin markings but no skin desquamation (flakes) or fissure formation	Slight peeling	Mild and diffuse
3=moderate	Medium red coloration	Easily noted dryness with accentuation of skin markings and skin desquamation (small flakes) but no fissure formation	Definitely noticeable peeling	Moderate and diffuse
4=severe	Beet red coloration	Easily noted dryness with accentuation of skin marking, desquamation (large flakes) and/or fissure formation	Extensive peeling	Prominent and dense

- Urine pregnancy tests at screening, baseline, and weeks 4, 12, 18, and 24.
- Concomitant medications and procedures

Drug Dispensation:

Drug will be dispensed at the baseline visit and the first dose of study drug will occur during this visit in the office under the investigator's supervision. The subject will gently wash the face and pat it dry. Then the subject will apply a pea-sized amount in a thin layer to the entire face and rub in the product gently and completely until there is no visible mass of gel observed on the face. All subjects will be provided a subject application instruction sheet. Adherence to the instructions will be assessed at subsequent visits and subjects will be re-trained at scheduled visits if necessary. Additional study drug will be dispensed every 4-8 weeks as needed.

Visit Schedule:

Screening:

- Informed Consent
- Demographics
- Inclusion/Exclusion
- Medical History
- Concomitant medications and procedures
- Skin phototype assessment (Fitzpatrick Skin Type)
- Lesion Counting
- Global Acne Assessment Score (GAAS)
- Adverse events
- Urine pregnancy

Baseline

- Inclusion/Exclusion
- Adverse events
- Concomitant medications and procedures
- Lesion Counting
- Melanin index

- GAAS
- Post Acne Hyperpigmentation Index (PAHPI)
- ASIS dark spot score
- Local tolerability assessment
- Photography
- Urine pregnancy
- Product dispensation/return

Week 4 –
- Adverse events
- Concomitant medications and procedures
- Lesion Count
- GAAS
- ASIS dark spot score
- Local tolerability assessment
- Pregnancy test
- Product dispensation/return

Week 8 Phone Visit –
- Adverse events
- Concomitant medications and procedures

Week 12 –
- Adverse events
- Concomitant medications and procedures
- Lesion Counting
- GAAS
- PAHPI
- ASIS dark spot score
- MI
- Photography
- Local tolerability assessment
- Product dispensation/return
- Urine pregnancy test

Week 18 –
- Adverse events
- Concomitant medications and procedures
- Lesion Counting
- GAAS
- PAHPI
- ASIS dark spot score
- MI
- Photography
- Local tolerability assessment
- Product dispensation/return
- Urine Pregnancy test

Week 24 –

- Adverse events
- Concomitant medications and procedures
- Lesion Counting
- GAAS
- PAHPI
- ASIS dark spot score
- MI
- Photography
- Local tolerability assessment
- Product return
- Urine Pregnancy test

Table 1: Assessment Schedule

Visit	1	2	3	4	5	6	7
Week	-4 to BL	0 (BL)	4	8 phone	12	18	24
Visit Window (days)			±3	±3	±3	±3	±3
Assessment							
Informed Consent	X						
Demographics	X						
Inclusion/Exclusion	X	X					
Medical History	X						
Fitzpatrick Skin Type	X						
AE/SAE assessment	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X
Concomitant procedures	X	X	X	X	X	X	X
Photography		X			X	X	X
Urine Pregnancy Test	X	X	X		X	X	X
Lesion Count	X	X	X		X	X	X
GAAS	X	X	X		X	X	X
ASIS ®		X	X		X	X	X
PAHPI		X			X	X	X
Mexameter – Melanin Index		X			X	X	X
Local tolerability		X	X		X	X	X
Study Drug Dispensation and Return		X	X		X	X	X

g) Specimen Banking

Not applicable.

h) Data Management and Confidentiality

As used in this protocol, the term case report form (CRF) should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this trial. All subject source documents are the site's subject records and are to be maintained at the study site. These source documents must be attributable, legible, contemporaneous, original, and accurate.

A CRF/source document is required and should be completed for each included subject. It is the PI's responsibility to ensure completion and to review and approve all CRFs/source documents. These must be signed by the PI or by an authorized staff member. These signatures serve to attest that the information contained on the CRFs/source documents is true. At all times, the PI has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs/source documents. SAE forms and pregnancy notification forms will be provided by the Sponsor.

Good documentation practices should be used on all study documentation. The clinical study will be performed in accordance with the protocol, applicable standard operating procedures (SOPs), the International Conference on Harmonization Good Clinical Practice (ICH GCP) guidelines, and applicable local regulatory requirements and laws.

The Sponsor requires that all records (e.g., ICFs, documents, test article dispensing record, etc.) which support CRFs/source documentation of this study must be retained in the files of the responsible investigator for a period of 2 years from the time the final report is issued.

If the investigator relocates, retires, or for any reason withdraws from the trial, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to the Sponsor. The investigator must obtain Sponsor's written permission before disposing of any records, even if retention requirements have been met. The Sponsor must be notified in writing of the name and address of the new custodian prior to re-assignment/transfer.

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Only the subject number will be recorded in the CRF. The code that links the subject to the subject's ID# is stored on paper in a locked cabinet, accessible only by Department of Dermatology research personnel. Photographs will be stored on the camera for approximately one week before being transferred to the computer database. Study findings stored on a password- protected computer will be encrypted and stored in accordance with local data protection laws. As part of the informed consent process, the subjects will be informed in

writing that representatives of the IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. If the results of the study are published, the subject's identity will remain confidential. Only the investigator will maintain a list to enable subjects to be identified. The data will be stored indefinitely.

i) Provisions to Monitor the Data to Ensure the Safety of Subjects

Part I: Elements of a Data and Safety Monitoring Plan

MSSM Principal Monitor:
Indicate whether this person is the PI, a Team Member, or is Independent:
Last Name: Khattri (PI)
First Name: Saakshi
Academic Title: MD
Department: Dermatology
Mailing Address: [redacted], New York, NY 10023
Phone: 212-523-3812
Fax: 212-523-6293
E-mail: Saakshi.khattr@mountsinai.org

MSSM Additional Monitor:
Indicate whether this person is the PI, a Team Member, or is Independent:
Last Name: Sanabria-Gonzalez (Team Member)
First Name: Ingrid
Academic Title: Research Manager
Department: Dermatology
Mailing Address: [redacted], New York, NY 10023
Phone: 212-523-3812
Fax: 212-523-6293
E-mail: Ingrid.sanabria@mountsinai.org

3. The principal monitor is the Principal Investigator. Please refer to curriculum vitae for further information.
4. The specific items that will be monitored for safety are adverse events, subject compliance with the protocol and withdrawals. Subjects will be monitored for adverse events the day of their participation in the study. Should subjects experience any adverse effects after their participation in the study, they will be instructed to contact the investigator(s) and make an appointment immediately.
5. Accumulated safety and data information will be reviewed annually.
6. N/A
7. N/A

8. Adverse events will be graded using the Common Terminology Criteria for Adverse Events (CTCAE).
9. The study will be conducted in compliance with regulatory requirements and Good Clinical Practice. Quality control will be applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.
10. Should a temporary or permanent suspension of our study occur, the occurrence will be reported to the PPHS, sponsor, and IRB.

Part II. Data Monitoring Committee/Data Safety Monitoring Board (DMC/DSMB)

Not applicable

j) Withdrawal of Subjects

When an individual who has signed the ICF is not enrolled in the study or withdraws/is withdrawn prior to completing the study, the reason is to be documented on the Discontinuation/Completion Form (or equivalent) and in the final study report. Reasons for subject withdrawal may include:

- Not enrolled (e.g. fails to meet inclusion/exclusion criteria, chooses not to enroll, etc.)
- Participant is determined to be ineligible after enrollment
- Subject's choice to withdraw
- Investigator terminated (e.g. noncompliance, etc.)
- Adverse Event
- Pregnancy
- Lost to follow-up
- Other

Subjects may withdraw from the trial at any time at their request, or they may be withdrawn at any time at the discretion of the Sponsor, PI, or designee for safety, behavioral, or administrative reasons. Subjects may be withdrawn from this study without their consent if the research study is being stopped; or if the instructions of the study team have not been followed.

If a subject does not return for a scheduled visit, *three documented attempts will be made to contact the subject in order to establish the reason for withdrawal, and* the outcome will be documented. The PI or designee should inquire about the reason for withdrawal, request that the subject return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events.

Should a subject withdraw from the trial and also withdraw consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The PI and staff may retain and continue to use any data collected before such withdrawal of consent. Removed or withdrawn subjects will not be replaced.

If a subject fails to report to the test facility for a scheduled visit and cannot be rescheduled within the permitted window of time (as applicable), the Site should consult with the Sponsor to determine if the subject should be documented as having withdrawn/dropped from the study.

Risks to Subjects

The following list of side effects is the ones that may be associated with the use of dapsone gel:

Common:

- Application site reactions:
    - Dryness
    - Peeling
    - Oiliness
    - Erythema
    - Pruritus
- Temporary yellow or orange discoloration of treated skin and local facial hair (when used in conjunction with benzoyl peroxide)

Rare:

- Methemoglobinemia – Cases of methemoglobinemia have been reported post-marketing in subjects using dapsone 5% gel twice daily. Initial signs and symptoms include slate grey cyanosis, which may be observed on the buccal mucous membranes, lips, and nail beds. Increased susceptibility to methemoglobinemia is seen patients with glucose-6-phosphate (G6PD) deficiency. The risk is also elevated in individuals taking other medications that induce the formation of methemoglobin (i.e. sulfonamides, acetaminophen, acetanilide, aniline dyes, benzocaine, chloroquine, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine, quinine). Dapsone gel should be avoided in patients with known history of congenital or idiopathic methemoglobinemia. Patients should be instructed to discontinue use of dapsone gel immediately and seek medical attention if they develop any signs of cyanosis.
- Hemolysis – The use of oral dapsone has been associated with the development of hemolysis and hemolytic anemia, particularly in patients with G6PD deficiency. G6PD deficiency is most common in individuals of Mediterranean, African, South Asian, and Middle Eastern descent. Studies and post-marketing on dapsone gel has not demonstrated any clinically relevant hemolysis of hemolytic anemia in treated subjects. Lab changes suggestive of hemolysis have been seen in patients with G6PD deficiency using dapsone gel 5%. Dapsone gel should be used with caution in patients taking oral medications known to increase serum levels of dapsone, including trimethoprim/sulfamethoxazole, and should be avoided in patients taking oral dapsone and anti-malarial medications due to risk of hemolytic reactions.

- Peripheral neuropathy – peripheral neuropathy has been observed with use of oral dapsone. No cases have been reported in patients using dapsone gel.
- Significant skin reactions (toxic epidermal necrolysis, erythema multiforme, morbilliform and scarlitiniform reactions, bullous and exfoliative dermatitis, erythema nodosum, urticarial) – With the exception of urticaria, no significant skin reactions have been observed during clinical trials and post-marketing with use of dapsone gel.

Aczone gel is designated as pregnancy category C, meaning that there are no adequate and well controlled studies in pregnant women. Dapsone administered orally in rats and rabbits has demonstrated embryocidal effects during the period of organogenesis when dosed at 425 to 1400 times the maximum recommended human dose (MRHD).
Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject or the female partner of a male subject occurring while the subject is on study drug, or within 30 days of the subject's last dose of study drug, are considered immediately reportable events. Study drug is to be discontinued immediately and the subject instructed to return any unused portion of the study drug to the investigator(s). The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Allergan Safety immediately facsimile using the Pregnancy Report form provided by the company. The female should be referred to an obstetrician-gynecologist experienced in reproductive toxicity for further evaluation and counseling. The Investigator(s) will follow the female subject until completion of the pregnancy, and must notify Allergan Safety of the outcome of the pregnancy as a follow-up on the follow up Pregnancy Reporting form.

Provisions for Research Related Harm/Injury

If a subject experiences a research injury, Mount Sinai West will provide or arrange for medical treatment at no cost. If the subject chooses to see their own personal doctor we will not offer to pay for the expenses. A research injury is any physical injury or illness caused by participation in the study. If a subject is injured by a medical treatment or procedure that would have been received even if the subject weren't in the study; that is not a research injury. Payment for things such as lost wages, expenses other than medical care, or pain and suffering is not offered. To help avoid injury, it is very important to follow all study directions.

Please be aware that some insurance plans may not pay for research-related injuries. Subjects should contact their insurance company for more information.

Unreimbursed medical expenses not covered by insurance or other third party coverage will be reimbursed by the sponsor for medical treatment for any injury that, in the opinion of the study doctor and the sponsor, is directly caused by the study drug/investigational product or by procedures required by the study protocol which would not have been performed as part of regular medical care.

Provisions to Protect the Privacy Interests of Subjects

Only subjects who have given us permission to contact them for studies will be contacted. All conversations with subjects and potential subjects will be conducted in a private examination room with the subject. Subjects' privacy will be protected by performing any study-related procedures in a private examination room. Family members will be allowed to remain in the room only if the subject allows this. No information regarding the subject's disease, treatment or the fact that he/she is involved in a study will be conveyed. Subjects will be made to feel at ease, by allowing them sufficient time to discuss the study and any potential queries.

All parties will ensure protection of subject personal data and will not include subject names on any Sponsor forms, reports, publications, or in any other disclosures. In case of data transfer, Sponsor will maintain high standards of confidentiality and protection of subject personal data.

The ICF (containing the HIPAA disclosure agreement) must be agreed to by Sponsor and the IRB and be in compliance and consistent with ICH GCP, local regulatory requirements, and legal requirements.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the trial, possible risks associated with participation. The investigator, or a trained person designated by the investigator, will obtain written informed consent on two copies from each subject before any trial-specific activity is performed. The subject will retain one copy, and one will be kept in the study file. The ICF used in this trial, and any changes made during the course of the trial, must be prospectively approved by both the IRB and Sponsor before use.

Economic Impact on Subjects

Allergan, the manufacturer of the study drug, will provide the study drug. Allergan also covers the cost of all study-related tests and procedures. While in the study, the subject will still need to get regular medical care. The subject will still have to pay for the costs of regular medical care that is not a part of this study.

Taking part in this research study may lead to added costs to the subject. If the laboratory tests or physical examinations reveal information about his/her health, additional tests, treatments and doctors appointments may be required which could present additional costs to him/her or his/her insurance company.

Payments to Subjects

Subjects will be compensated $25.00 per completed in-person visit for a total of $150.00 upon completion of the study. Subjects will not be compensated for the week 8 phone visit. Subjects who complete only the screening visit will not be eligible for compensation. If the subject withdraws or is withdrawn before completing the study, he/she will receive an amount of money for the visits which have been completed. They will not have to submit receipts to receive this reimbursement. This payment will come in the form of a check at the end of the subject's participation in the study.

Consent Process

We will be obtaining written consent as a part of this study. No subject will be evaluated without a signed Informed Consent Form (ICF).

The consent process will take place in a private exam room where the subject will have ample time to review and read the consent form. Subjects will be given time to ask questions and may take additional time to consider their options. Subjects will be informed that they do not have to participate and may withdraw consent at any time.

After understanding and agreeing, the subject will express their consent to participate in the study by signing an original copy of the ICF. The subject will receive a copy of their signed document for their records.

We will follow the SOP HRP-090 Informed Consent Process for Research.

Process to Document Consent in Writing

We will be using the standard IRB Informed Consent template. The ICF must be agreed to by the Sponsor and the IRB and must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The consent process and date that the consent is signed is documented in our source notes.

Study personnel will adhere to "SOP HRP-091 Written Documentation of Consent".

Vulnerable Populations

This project will not include any vulnerable population subjects.

Multi-Site Human Research (Coordinating Center)

This project is a single site study.

Community-Based Participatory Research

This project will not involve any community-based participation.

Sharing of Results with Subjects

At the completion of the study, subjects will have the right to access their protected health information that is created during this research study that relates to their treatment or to payment,

provided such information is not exempted under certain laws and regulations. To request this information, subjects should contact the study doctor at the address listed above.

Subject to certain exceptions prescribed by law, subjects have a right to request access to the health information that we hold about and to request changes if the health information is incorrect or incomplete. Any request for access or corrections should be made to the principal doctor conducting this study.

Once all data and results are finalized, a summary will be made available to subjects.

External IRB Review History

This project is not using an external IRB.

Control of Drugs, Biologics, or Devices

Study drug is stored in a combination-locked room accessible only by clinical trials personnel. All study materials should be stored at room temperature (59°-77°F), and the Site is responsible for maintaining temperature logs. All study products received and dispensed will be inventoried and accounted for throughout the study. The investigator must maintain adequate records documenting the receipt, use, loss, or other disposition of the products on the Product Accountability Log. The log must identify the investigational product and account for its disposition by subject, including specific dates and quantities dispensed and returned. The log must be signed by the individual who dispensed/retrieved the study product and copies must be provided to the sponsor for inclusion in the Trial Master File.

At the completion of the study, all units of product dispensed (whether empty or containing unused product) must be collected by the Site and returned, along with un-dispensed product, to the Sponsor. Any container not returned by the Site must be accounted for in writing.

k) Statistical Analysis Plan

The adverse events will be tabulated according to their date of onset, duration, severity and relationship to the treatment. We will build Clopper-Pearson 90% confidence intervals for the proportion of adverse events considering their aggregation and stratification (e.g., by severity).

Sample Size Considerations

A sample size of n=20 subjects allows >90% power at 5% significance level for a two-sided paired t-test to detect at week 12 a minimum change in GAAS from baseline of 1 grade point. This calculation was performed in G*Power and it assumes a mean GAAS of 3.5 at baseline and a maximal standard deviation of 0.513.

Analysis of primary Endpoint

The primary analysis will apply a two-sided paired t-test to assess the significance of the change in GAAS from baseline to week 12. However, GAAS is an ordinal measurement and, for this reason, we will also apply a Generalized Linear Mixed-effects Model (GLMM) to assess the significance of the changes in GAAS after including potential covariates.

Analysis of secondary Endpoints

At each time point, the changes from baseline in ordinal secondary endpoints GAAS, PAHPI, MI, the proportion of subjects with a score of 0 or 1 on ASIS "dark spot," the proportion of subjects with GAAS <2 will be presented in frequency tables. The (i,j) entries in the tables are counts of subjects in category i at baseline that moved to category j at that time point. A high frequency of counts falling off the main diagonal of the table is evidence in favor of a significant treatment effect. Similarly, to the primary endpoint, we will apply a two-sided paired t-test to assess the significance of changes from baseline in each outcome. We will apply the Bonferroni correction to adjust for the multiplicity of tests. In parallel, we will test pre vs. post differences in these ordinal outcomes with the Wilcoxon Signed Rank test. Discrepancies between the parametric and non-parametric approaches will be discussed on a case basis. In addition to this approach, we will fit an ordinal logit model, including all available time points, age, and gender as covariates.

The changes from baseline in lesion counts (inflammatory, non-inflammatory, and their aggregation) will be assessed with the two-sided paired t-test followed by Bonferroni correction. A Generalized Linear Mixed Model (GLMM) will be fitted to model the count of lesions as the dependent variable, time and inflammation as fixed effects, age, and gender as covariates. In this framework, we will include random intercept and slope for each subject's trajectory. The contrasts will reveal differences between time points and treatment effect in inflammatory vs. non-inflammatory lesions.

Missing Data and Outliers

Missing data in the longitudinal data analysis will be handled by the mixed-effects approach which performs an appropriate adjustment of the coefficients' degrees of freedom for each fitted model. We do not foresee issues with outliers due to the endpoints' measurement level, most of them being ordinal.

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