An Open-label Pilot Study to Investigate the Efficacy of Apremilast in the Treatment of Central Centrifugal Cicatricial Alopecia (CCCA)

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Brief Summary of Research (250-400 words):

Central centrifugal cicatricial alopecia (CCCA) is a type of scarring alopecia commonly seen in women of African American descent. Clinically, hair loss starts at the vertex of the scalp and progresses circumferentially. The etiology is incompletely understood, but likely results from a combination of hair-grooming practices, a pro-inflammatory state within the hair follicles, and genetic factors.
This will be a single-center, open-label clinical study to determine the efficacy of apremilast in the treatment of mild to moderate central centrifugal cicatricial alopecia. A total of 20 subjects (ages 18 years and older, female, CHLG <4) are expected to complete this study, which will run for a total of up to 30 weeks.
The study consists of two periods: Screening (from 1 to 4 weeks); Open label treatment period (24 weeks). Follow-up for suture removal will occur 2 weeks after discontinuation only in patients who have undergone punch biopsy. Those who meet all of the inclusion/exclusion criteria and are enrolled in the study will receive apremilast for the entire treatment period.

Objectives

The purpose of this study is to evaluate the efficacy of apremilast in the treatment of mild to moderate CCCA. We hypothesize that the anti-inflammatory properties of apremilast may play a role in the decreasing scalp inflammation in patients with CCCA and will prevent further hair loss and potentially induce hair regrowth in patients with mild to moderate disease.

Background

Central centrifugal cicatricial alopecia (CCCA) represents the most common type of scarring alopecia in women of African American descent (1,2). Clinically, hair loss starts at the vertex of the scalp and progresses circumferentially. Microscopically, in the early stage, it is characterized by an inflammatory, lymphocytic perifollicular infiltrate and perifollicular fibroplasia (3,4).

The etiology of CCCA remains incompletely understood, but appears to be multifactorial. Hair-grooming practices involving heat, chemical processing, extensions and braids have largely been implicated, however with inconsistent supporting data (5-8). More recent literature highlights a possible metabolic dysregulation (8). A baseline pro-inflammatory state in afro-texture natural hair has been documented. Pro-inflammatory cytokine IL-1α was found to be 18 times higher in scalp sebum than anti-inflammatory cytokine IL-1R antagonist in a study of women with afro-texture natural hair (9). Genetics have also shown significance (8).

The management of CCCA remains a challenge as there are no published treatment guidelines. Current therapies aim to decrease inflammation in order to prevent further hair loss. Common clinical practice includes encouraging modification of hair-grooming techniques in addition to the use of topical corticosteroids, topical immunomodulators (tacrolimus and pimecrolimus), intralesional corticosteroids, anti-inflammatory antibiotics (tetracycline and doxycycline) and antimalarials (hydroxychloroquine) (4,7,10). The use of cyclosporine, mycophenolate mofetil and hair transplantation have also been described in the literature (4). Treatment success has largely been reported in anecdotal reports, as there are no published case-controlled studies documenting effective treatment.

Apremilast, an oral PDE4 inhibitor, has been shown to be effective in the treatment of moderate to severe plaque psoriasis and psoriatic arthropathy (11). In vitro studies have demonstrated anti-inflammatory properties, with inhibition of inflammatory mediators TNF, IFN, CXCL9, IL-2, IL-12, IL-23, macrophage inflammatory protein (MIP)-1a, monocyte chemoattractant protein (MCP)-1 and granulocyte macrophage-colony stimulating factor (GM-CSF) (12). CCCA is described as an inflammatory condition consistent with the characteristic lymphocytic infiltrate on histopathology in early stages (3,4). While the literature on inflammatory cytokines specific to CCCA is sparse, the anti-inflammatory properties of apremilast offer a possible therapeutic option for CCCA.

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 Coordinators. 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. Females of African ancestry >18 years of age at the time of screening
3. Clinical diagnosis of mild to moderate vertex-predominant CCCA as defined by CHLG stages 1B, 2B, 3B
4. Punch biopsy at screening, or punch biopsy of the scalp within six months prior to screening visit, consistent with CCCA.

5. Females of childbearing potential (FCBP) must have a negative pregnancy test at Screening and Baseline. 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.

6. Must be in general good health as judged by the Investigator, based on medical history and physical examination. (NOTE: The definition of good health means a subject does not have uncontrolled significant co-morbid conditions).

Exclusion:

1. Systemic or intralesional treatment of CCCA for 4 weeks prior to baseline visit, including but not limited to corticosteroids (systemic, intralesional), oral tetracycline antibiotics, and oral anti-inflammatory medications
2. Topical corticosteroid or calcineurin inhibitor treatment of CCCA for 2 weeks prior to baseline visit.
3. Topical minoxidil for 4 weeks prior to baseline visit.
4. Severe or end-stage CCCA with CHLG as defined as CHLG >3
5. CCCA with frontal accentuation pattern as defined as CHLG 1A to 5A.
6. Diagnosis of other dermatologic diagnosis or condition that, in the opinion of the investigator, would interfere with diagnosis, examination, or treatment of the studied condition (i.e. lichen planopilaris*, systemic lupus, cutaneous lupus) or would require treatment with systemic steroids, topical or intralesional steroids on the scalp, or systemic tetracycline antibiotic therapy during the duration of the study.

   *based on clinico-pathologic correlation

7. Other than the disease under study, any clinically significant (as determined by the Investigator) cardiac, endocrinologic, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, immunologic disease, or other major disease that is currently uncontrolled.
8. Malignancy or history of malignancy, except for:
   - treated [ie, cured] basal cell or squamous cell in situ skin carcinomas;
   - treated [ie, cured] cervical intraepithelial neoplasia (CIN) or carcinoma in situ of cervix with no evidence of recurrence within the previous 5 years.

9. Any condition, including the presence of laboratory abnormalities, which would place the subject at unacceptable risk if he/she were to participate in the study.
10. Use of systemic immunosuppressive drugs (including, but not limited to, cyclosporine, corticosteroids, mycophenolate mofetil, azathioprine, methotrexate, or tacrolimus) within four weeks prior to Baseline/Randomization (Visit 2).
11. Prior history of suicide attempt at any time in the subject's life time prior to screening or randomization, or major psychiatric illness requiring hospitalization within the last 3 years.
12. Pregnant or breast feeding.
13. Subjects not willing to implement the following suggested hair care practices and/or maintain the same or similar hair style for the duration of study:
    - Shampoo hair every 7 days with a conditioning shampoo
    - Condition hair every 7 days with a deep or reconstructive conditioner
    - Towel-dry hair before exposing it to a dryer to minimize excessive heat
    - Comb hair daily with a wide-toothed comb; gently pass the comb through hair starting from the ends and working your way up to the roots
    - Avoid heavy pomades and hair oils to scalp; opt for silicone based products or light pomades to hair shafts
    - Limit use of styling gels
    - Limit traction-associated hair styles (e.g. tight braids, tight weaves, tight cornrows) as determined by investigator
    - Avoid chemical or thermal injury to scalp during hair styling process
    - Chemical relaxer treatments can be used as long as there is no associated scalp injury (i.e. tingling, burning, pain)
    - Maintain the same hair style throughout the study i.e. weave or braids present at baseline must be maintained through the end of the study; weaves or braids may be redone during the study if needed, but should resemble the subject's hair style at baseline, if possible.
14. Use of any investigational drug within 4 weeks prior to randomization, or 5 pharmacokinetic/pharmacodynamics half-lives, if known (whichever is longer).
15. Prior treatment with apremilast
16. History of allergy to any component of the IP
17. Active substance abuse or a history of substance abuse within 6 months prior to Screening.

c) Number of Subjects

Up to 40 patients with CCCA 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 8 to 10 visits over up to 30 weeks (4 week screening period, 24 weeks enrolled in study, optional 2 week follow-up for suture removal). Study visits will be conducted at Screening (Visit 1), Baseline (Visit 2, Week 0), Week 4 (Visit 3), Week 8 (Visit 4), Week 12 (Visit 5), Week 16 (Visit 6), Week 20 (Visit 7), Week 24/Discontinuation (Visit 8). For subjects undergoing punch biopsy, additional suture removal visits (Visits 1a and 8a) may also occur 2 weeks after the baseline and week 24/discontinuation visits.

Enrollment will occur over a 12 month period from May 2018 to May 2019.

e) Endpoints

Primary Endpoint:

1. **Physician Global Assessment of Improvement (PGA-I) at week 24**
   At baseline, week 12, and week 24, trained study personnel will take standardized photos of the scalp. These photographs will be provided to a panel of three dermatologists with expertise in CCCA, each of whom will review the photographs at baseline, week 12 and week 24. Investigators will assess the improvement in hair loss severity using PGA-I. PGA-I will range from -3 (significant worsening) to 3 (significant improvement). Treatment response will be considered no change (0) or improvement (+1 to +3) in CCCA.

Secondary Endpoints:

1. **Change in CCCA Investigator Global Severity Score (IGSS) at week 24 compared to baseline**

   Blinded investigators will review standardized photographs of the scalp and assess change in hair loss severity using a CCCA Investigator Global Severity Score (IGSS). Treatment response will be considered no change or improvement in IGSS.

   CCCA Investigator Global Severity Score (IGSS):
   0 (no hair loss), 1 (subtle features of CCCA, e.g. early loss of follicular ostia, <5% involvement of vertex scalp), 2 (mild features of CCCA, e.g. 5-10% involvement of vertex), 3 (mild to moderate features of CCCA, e.g. 11-25% involvement of vertex), 4 (moderate features of CCCA, e.g. >25 and <50% involvement of vertex), 5 (moderate to severe CCCA e.g. 50-75% involvement of vertex), 6 (severe CCCA, e.g. >75% involvement of vertex)

2. **Change in Central Hair Loss Grade (CHLG) at week 24 compared to baseline**

   The change in central scalp alopecia will be determined using a standardized visual scale called Central Hair Loss Grade (CHLG) that has been found to be reliable in dermatologists experienced in hair disorders (13). The photographic scale grades pattern and severity of central hair loss in African American women, wherein hair loss is characterized by either frontal (A) or vertex (B) predominant. Degree of severity of hair loss is graded on a 6-point visual scale

(pattern 0: no hair loss, pattern 1-2: mild hair loss, pattern 3-5: more severe hair loss). Treatment response will be considered no change or decrease (improvement) in CHLG.

3. **Change in subject VAS of hair loss severity at weeks 12 and 24 compared to baseline**

   The VAS is a numerical scale used to assess patients' perception of hair loss severity. Subjects will be asked to complete the VAS scale at all scheduled visits. The evaluation is a 10cm long line on which the subjects indicate the severity of their condition from "0" (complete loss of hair in affected area – ie no visible hairs on central scalp) to "10" (full growth/regrowth in affected area—ie no visible hair loss on central scalp). Treatment response will be defined as no change or improvement in VAS.

4. **Global Assessment of Improvement (PaGA-I) at 24 weeks**
   At week 12 and week 24, subjects will be asked to assess the improvement in hair loss severity on a PaGA-I patient questionnaire. PaGA-I will range from -3 (significant worsening) to 3 (significant improvement). Treatment response will be defined as no change (0) or improvement (+1 to +3) in CCCA.

5. **Change in subject rating of symptom severity (pruritus, burning, pain) at weeks 12 and 24 compared to baseline**

   Subjects will complete a symptom severity questionnaire consisting of 3 numeric rating scales (NRS) measuring severity of pruritus, burning, and pain (14). The NRS will range from 0 (no symptoms) to 10 (severe symptoms). Patients indicate the intensity of each symptom (pruritus, burning, or pain) by choosing a number from 0 to 10 that corresponds to the severity of that symptom. Subjects will complete the 3 NRS' at all scheduled visits.

6. **Change from baseline in Dermatology Life Quality Index (DLQI) total score at week 24**
   Subjects will complete a DLQI at baseline, week 12, and week 24. Change in DLQI total score between baseline and week 24 will be assessed.

b) Procedures Involved in the Human Research

Table 1: Assessment Schedule

Visit	1	*1a*[1]	2	3	4	5	6	7	8	*8a*[2]
Week	-4 to BL	*-2 to BL*	0 (BL)	4	8	12	16	20	24 ET/ EOT	*26*
Visit Window (days)		±3		±3	±3	±3	±3	±3	±3	*±3*
Assessment										
Informed Consent	X									
Demographics	X									
Inclusion/Exclusion	X		X							
Medical History	X									
AE/SAE assessment	X	*X*	X	X	X	X	X	X	X	*X*
Hair care practice history	X									
CCCA treatment history	X									
Concomitant medications	X	*X*	X	X	X	X	X	X	X	*X*
Vital Signs	X		X	X	X	X	X	X	X	
Height and Weight	X		X						X	
Physical Examination	X		X			X			X	
Scalp Examination	X		X			X			X	
Photography	X		X	X	X	X	X	X	X	
Punch Biopsy	X[3]								X[4]	
Suture Removal		*X*[5]	X							*X*
Dermatoscopic examination of scalp	X								X	
Urine Pregnancy Test			X	X	X	X	X	X	X	
Serum pregnancy test	X									
Investigator CCCA Investigator Global Severity Score (IGSS) - Photograph			X			X			X	
Physician Global Assessment of Improvement (PGA-I) – Photograph						X			X	
Investigator grading using CHLG - In Person Exam	X		X			X			X	
Patient grading of pruritus, burning, pain severity, and overall CCCA severity			X	X	X	X	X	X	X	
Patient Global Assessment of Improvement (PaGA-I)						X			X	
Dermatology Life Quality Index (DLQI)			X			X			X	
Study Drug Training			X							
Study Drug Dispensation and Return			X	X	X	X	X	X	X	
Hair care diary distribution/collection			X	X	X	X	X	X	X	

[1] *Visit 1a will only be performed in subjects requiring a screening period of >2 weeks such that suture removal can occur within 2 weeks after punch biopsy. Visit 1a will be performed 2 weeks (+/- 3 days) after screening visit.*

[2] *Visit 8a will only be performed in subject who undergo a punch biopsy at visit 8 such that sutures can be removed.*

[3] *May be omitted in subjects who have undergone a punch biopsy confirming a diagnosis of CCCA within 6 months prior to the screening visit, at the discretion of the investigator.*

[4] *optional post-treatment biopsy*

[5] *Suture removal will either occur at visit 1a or 2*

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. After providing informed consent, subjects will be assessed for study eligibility at the Screening visit (day -28 to day -1). 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. At this Baseline visit, subjects will receive the first oral dose of study drug (apremilast). All subjects will receive study drug training. Study drug will be dispensed at baseline and then every 4 weeks. Un-used drug will be returned to the site at each visit.

Subjects will return for visits every four weeks through Week 24 (Weeks 4, 8, 12, 16, 20 and 24) so that a review of concomitant medications and adverse events can be assessed. The PI or designee will interview the subjects to collect and record any adverse events (AEs) or changes to health/concomitant medications that may have occurred since the previous visit. Additional procedures and assessments will be performed as outlined in table 1.

If a subject terminates early or chooses to discontinue the study, he/she will be asked to return for a final visit, at which time the procedures for visit 24 will be performed. Whether optional punch biopsy will be offered and performed is at the discretion of the investigator.

Apremilast will be provided as 10-, 20-, or 30-mg tablets. Apremilast will be taken orally twice daily, approximately 12 hours apart. Apremilast can be administered without regard to meals, and tablets should not be crushed, split, or chewed.

When subjects first start to take apremilast, the dose will be titrated in 10-mg/day increments. Following the 5-day titration, the recommended maintenance dosage is 30 mg twice daily taken orally starting on Day 6. This titration is intended to reduce the gastrointestinal symptoms associated with initial therapy.

Day 1: 10 mg in morning
Day 2: 10 mg in morning and 10 mg in evening
Day 3: 10 mg in morning and 20 mg in evening
Day 4: 20 mg in morning and 20 mg in evening
Day 5: 20 mg in morning and 30 mg in evening
Day 6 and thereafter: 30 mg twice daily

The procedures and assessment performed during this study are described in detail below:

Informed Consent: 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 the ICF. The subjects will retain one original copy and one photocopy will be kept in the study file. The subjects who sign an ICF will be assigned a screening number.

Demographics: Subjects will be asked to complete a questionnaire about their demographics at the screening visit.

Eligibility Assessment (Inclusion/Exclusion): After providing informed consent, subjects will be assessed for study eligibility at the Screening visit (day -28 to day -1), which includes limited physical examination, scalp examination, vital signs, height and weight, investigator severity ratings, clinical photography, pre-treatment punch biopsy of an area affected by CCCA (if not performed within 6 months prior to screening visit), review of medical history and concomitant medications as well as prior medications/treatments, and serum pregnancy test (if applicable). These assessments will be described below. 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. Eligibility will be assessed at Screening and Baseline visits.

Medical History and Concomitant Medications: At the screening visit, subjects will be asked about current medical conditions or history of any medical conditions. Subjects will be asked about history of systemic or discoid lupus, lichen planus, other autoimmune disorders, severe acne, hidradenitis suppurativa, keloids, syphilis, sarcoidosis, alopecia areata, female pattern alopecia, frontal fibrosing alopecia, acne keloidalis nuchae, liver disease, and recurrent infections, in addition to other significant medical problems. Subjects will also be asked about current medication use and use of medications for 1 month prior to screening. Concomitant medications will be reviewed and recorded at every scheduled visit.

Hair Care Practice History and CCCA Treatment History: At the screening visit, subjects will be asked about their current or past hair care practices and use of treatments for CCCA based on the NAHRS workshop guidelines (15).

Vital Signs: Vital signs will be assessed at all scheduled study visits. Whether action needs to be taken regarding abnormal vital signs (as defined below) will be at the investigator's discretion. After the subject has been sitting for at least five minutes with back supported and both feet on the ground, systolic and diastolic blood pressure (BP) will be measured using an appropriately sized cuff. Pulse will also be measured using either an automated machine or manually. Normal Blood pressure will be defined as systolic 90 to <120mmHg and diastolic 60 to <80mm Hg. Notable blood pressure will be hypertension (systolic ≥140 mmHg and/or diastolic ≥100 mmHg). A normal pulse rate will be defined as 60 to 100 beats per minute. Notable pulse rates will be defined as bradycardia (<50bpm) and tachycardia (>100bpm).

Height and Weight: Height and weight will be measured by a designated site individual at screening, baseline, and week 24 visits.

Physical examination: Physical examination will be performed by the investigator, sub-investigator, or other qualified individuals at screening, baseline, week 12, and week 24. This will include examination of the heart, lungs, abdomen, extremities, and skin, as well as any additional body systems as deemed necessary by the investigator.

Scalp Examination: A scalp examination will be performed based on the NAHRS workshop physical examination checklist (15) at screening, baseline, week 12, and week 24. The scalp examination will include the following parameters:

- Extent of hair loss (graded from 0- none to 3 - severe)
    - Percent of scalp surface involved
    - Smallest dimension
    - Largest dimension
    - Most representative dimension
- Erythema, scale/crusting, pustules, absence follicular markings, anagen/total pulls (pull test), perifollicular hyperkeratosis, telangiectasia, atrophy, pigmentary changes, keratosis pilaris graded from 0- none to 3-severe.
- Number of follicular openings and hair count within a $1cm^2$ representative region of CCCA (at the active border of the lesion on scalp). The exact location will be recorded using distance from the screening visit punch biopsy site.

Photography: Standardized photographs will be taken of the frontal and central scalp. The photograph will be taken such that the entire vertex of the scalp is included in the picture, at a distance of 3 feet. Photographs will be taken at all scheduled visits.

Punch biopsy: A 4mm punch biopsy of the scalp into and including the subcutaneous tissue will be performed at the screening visit for diagnosis of CCCA. The biopsy will be performed at the active border of the lesional scalp after dermatoscopic examination; if there are multiple distinct area of alopecia, dermoscopy and biopsy will be performed at the largest area (greatest diameter) affected by CCCA. If peripilar white/gray halos are identified on dermoscopy, an area that demonstrates peripilar white/gray halo(s) will be chosen, as this dermatoscopic finding is associated with 100% specificity and 94.12% sensitivity for CCCA (16,17). The site of biopsy will be marked with a marker and a photograph will be taken to record the location. In addition, the site of the biopsy will be recorded using distance from bilateral top of the pinna. This biopsy specimen will also be used as a comparison for the optional post-treatment biopsy. If performed, the post-treatment biopsy will be obtained at the same site as the original biopsy, as identified via picture and distance from anatomic landmarks.
The biopsy specimens will be evaluated based on the NAHRS Pathology Evaluation for Cicatricial Alopecia flowsheet. The post-treatment biopsy will be evaluated for changes in inflammation compared to the pre-treatment biopsy. Changes in hair follicle structure and density (vellus and terminal), adnexal structures, epithelium, fibrous tissue, and interstitial will also be evaluated.

If a punch biopsy of the affected area of the scalp was performed within 6 months of the screening visit, this may replace the pre-treatment punch biopsy. In this case, the initial biopsy report will be obtained to confirm a diagnosis of CCCA by clinicopathologic correlation. In addition, unstained slides and biopsy block may be obtained from the initial pathology lab, if available, for evaluation by the pathologist in this study. The biopsy specimen will be evaluated based on the NAHRS Pathology Evaluation for Cicatricial Alopecia flowsheet. If the unstained slides or biopsy block cannot be obtained, or the obtained specimen is insufficient for analysis using the NAHRs

flowsheet, a new punch biopsy may be performed at the screening visit as deemed necessary by the investigator.

Dermatoscopic evaluation of the scalp: Dermoscopy will be used to assist in determining the anatomic location of the scalp biopsy as described above.

Suture Removal: In those who have undergone punch biopsy at screening, sutures will be removed at visit 1a (for those requiring a screening period of >2 weeks) or visit 2 (for those requiring a screening period of ≤ 2 weeks). Suture removal may occur as early as 1 week after screening and as late as 2 weeks (+ 3 day window) after screening. For those who undergo optional punch biopsy at the end of study visit (visit 8), sutures will be removed 2 weeks later (+/- 3 day window) at visit 8a. Visit 8a will only be performed in subjects requiring suture removal and will not be performed in subjects who forego the end of study biopsy.

Investigator CCCA Investigator Global Severity Score (IGSS): Standardized photographs will be provided to a panel of three dermatologists with expertise in CCCA, each of whom will review the photographs at baseline, week 12 and week 24. Blinded investigators will assess change in hair loss severity using a global severity scale. The same blinded investigators will evaluate the baseline and week 24 photographs.
CCCA Investigator Global Severity Score:

- 0 (no hair loss)
- 1 (subtle features of CCCA, e.g. early loss of follicular ostia, <5% involvement of vertex scalp)
- 2 (mild features of CCCA, e.g. 5-10% involvement of vertex)
- 3 (mild to moderate features of CCCA, e.g. 11-25% involvement of vertex)
- 4 (moderate features of CCCA, e.g. >25 and <50% involvement of vertex)
- 5 (moderate to severe CCCA e.g. 50-75% involvement of vertex)
- 6 (severe CCCA, e.g. >75% involvement of vertex)

Investigator Determination of CHLG: The change in central scalp alopecia will be determined using a standardized visual scale called Central Hair Loss Grade (CHLG) that has been found to be reliable in dermatologists experienced in hair disorders (13). The photographic scale grades pattern and severity of central hair loss in African American women, wherein hair loss is characterized by either frontal (A) or vertex (B) predominant. Degree of severity of hair loss is graded on a 6-point visual scale (pattern 0: no hair loss, pattern 1-2: mild hair loss, pattern 3-5: more severe hair loss). CHLG will be determined at screening, baseline, week 12 and week 24.

Investigator Global Assessment of Improvement (PGA-I): A panel of three blinded investigator will be provided with photographs at baseline, week 12, and week 24. The investigator will determine the PGA-I at weeks 12 and 24 compared to baseline, which will allow the investigator to rate improvement or worsening in the overall clinical condition. The scale will range from -3 (significantly worse) to 3 (significantly improved), with 0 being no change.

Subject VAS of hair loss severity: The VAS is a numerical scale used to assess patients' perception of hair loss severity. Subjects will be asked to complete the VAS scale at all scheduled visits. The evaluation is scored from 0 (complete loss of hair in affected area – i.e. no visible hairs on central scalp) to 10 (full growth/regrowth in affected area—i.e. no visible hair loss on central scalp).

Patient Global Assessment of Improvement (PaGA-I): Patient will complete a PaGA-I questionnaire at weeks 12 and 24 to ask about improvement or worsening in their overall clinical condition. The scale will range from -3 (significantly worse) to 3 (significantly improved), with 0 being no change.

Subject grading of symptom severity (pruritus, burning, and pain severity): Subjects will complete a questionnaire containing 3 distinct numeric rating scales (NRS). Patients with indicated the intensity of (1) pruritus, (2) burning, and (3) pain by choosing a number from 0 to 10 that corresponds to their symptoms. A number 0 refers to no symptoms (pruritus/burning/pain) and a 10 refers to the most severe symptoms (14). Subjects will complete the NRS of symptom severity at all scheduled visits.

Dermatology Life Quality Index (DLQI): DLQI is a validated 10-question questionnaire developed to address quality of life in patients with dermatological disorders. It has previously been used with success to assess the impact of scarring and non-scarring alopecia on quality of life (18,19). Patients will be asked to fill out a DLQI at baseline, week 12, and week 24.

Hair Care Diary: Subjects will be provided with a diary for the duration of the study during which they will be asked to record hair care practices (use of shampoo, conditioner, straightening, weaves, braids, etc.). They will also record symptoms of the scalp, including itching, burning, and pain. Additional medications taken and adverse events will be recorded.

Urine and Serum Pregnancy tests: Venipuncture will be performed at screening visit in order to perform serum pregnancy test as required by local IRB. Urine pregnancy test will be performed at all subsequent study visits for women of child-bearing potential. A woman is considered post-menopausal if she has not had a menstrual period in >12 months.

Adverse Events and Serious Adverse Events: An adverse event (AE) is any noxious, unintended, or untoward medical occurrence occurring at any dose that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any medical condition that was present prior to study treatment and that remains unchanged or improved should not be recorded as an AE. If there is a worsening of that medical condition this should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the Case Report Form rather than the individual signs or symptoms of the diagnosis or syndrome.

All AEs will be recorded by the Investigator(s) from the time of signing the informed consent through the end of the designated follow-up period.

Serious adverse event: A serious adverse event (SAE) is any AE which:

- Results in death
- Is life-threatening (i.e., in the opinion of the Investigator(s) the subject is at immediate risk of death from the AE)

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Constitutes an important medical event

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events not considered to be SAEs are hospitalizations which: were planned before entry into the clinical study; are for elective treatment of a condition unrelated to the studied indication or its treatment; occur on an emergency outpatient basis and do not result in admission (unless fulfilling other criteria above); are part of the normal treatment or monitoring of the studied indication and are not associated with any deterioration in condition.

If an AE is considered serious, both the AE pages of the CRF and the SAE Report Form must be completed.

For each SAE, the Investigator(s) will provide information on severity, start and stop dates, relationship to study drug, action taken regarding study drug, and outcome.

Classification of severity

For both AEs and SAEs, the investigator(s) must assess the severity of the event. The AEs will be evaluated for severity according to the following scale:

Grade 1 = Mild

Grade 2 = Moderate

Grade 3 = Severe

Classification of Relationship/Causality of adverse events (SAE/AE) to study drug

The Investigator(s) must determine the relationship between the administration of study drug and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	The temporal relationship of the adverse event to study drug administration makes **a causal relationship unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event
Suspected:	The temporal relationship of the adverse event to study drug administration makes **a causal relationship possible,** and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

Immediate reporting of serious adverse events

Any AE that meets the any criterion for a SAE requires the completion of an SAE Report Form in addition to being recorded on the AE pages of the CRF. The Investigator(s) is required to ensure that the data on these forms is accurate and consistent. This applies to all SAEs, regardless of relationship to study drug, that occur during the study, those made known to the Investigator(s) within 30 days after a subject's last dose of study drug, and those made known to the investigator(s) at anytime that are suspected of being related to study drug.

The SAE must be reported immediately (i.e., within 24 hours of the Investigators' knowledge of the event) to Amgen Safety by facsimile. A written report (prepared by the Investigator(s) using an SAE Report Form or a 3500A Medwatch form is to be faxed to Safety (see below for contact information).

Amgen Drug Safety Contact Information:

Fax: 888-814-8653

The SAE report should provide a detailed description of the SAE. If a subject has died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Amgen as soon as these become available. Any follow-up data will be detailed in a subsequent SAE Report Form or Medwatch form and sent to Amgen.

The Investigator(s) is responsible for informing the Institutional Review Board/Ethics Committee (IRB/IEC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator(s) must keep copies of all SAE information, including correspondence with Celgene and the IRB/IEC, on file. All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until either the event resolves completely, stabilizes/resolves with sequelae, or returns to baseline (if a baseline value is available).

Pregnancy: 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 Amgen Safety immediately facsimile using the Pregnancy Report form provided by Amgen.

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 Amgen Safety of the outcome of the pregnancy as a follow-up on the follow up Pregnancy Reporting form.

If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the Investigator(s) should follow the procedures for reporting SAEs (i.e., report the

event to Amgen Safety by facsimile within 24 hours of the Investigator's knowledge of the event).

In the case of a live "normal" birth, Amgen Safety should be advised by facsimile within 24 hours of the Investigator's knowledge of the event.

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator(s) suspects is related to the in utero exposure to the study drug should also be reported to Amgen Safety by facsimile within 24 hours of the Investigators' knowledge of the event.

If the female is found not to be pregnant, any determination regarding the subject's continued participation in the study will be determined by the Investigator.

Overdose: Abuse, withdrawal, sensitivity, or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported as an AE. Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE.

If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form but should not be reported as an SAE itself.

In the event of an overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for apremilast overdose.
Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

Overdose for this protocol, on a per dose basis, is defined as ingestion of any more than the amount prescribed of apremilast tablets in any 24 hour period whether by accident or intentionally.

c) Specimen Banking

The skin biopsy specimens (Screening and optional biopsy at Week 24) will be sent to, processed, and stored at the designated pathology facility according to standard operating procedures. The specimens will be identified with subject ID number and time of biopsy.

Since this study is designed to gain basic knowledge rather than to yield information directly related to patient care, the results are not entered in the participants' medical records. If, at a later date, correlations of in-vitro tests and the patients' clinical situation suggest that the results do bear on the patients' health, an amended protocol will be submitted to the IRB so that results can be made available to the medical record. As all tissue is obtained for research purposes and not for routine clinical tests, the above outlined skin samples may be stored until used. Skin cells will be studied and de-identified samples may be shared with collaborating investigators at Mount Sinai in the future for further histology and immunochemistry. The samples will be stored indefinitely and will primarily be used for the scope of this study.

Subjects will have the option to request destruction of their samples at any time, unless the samples have already been destroyed by the study team, and will not be used for any future studies. Samples will be stored at Mount Sinai indefinitely. Stored samples will be linked back to subjects via an ID#. Only clinical staff will have the link. Pathology personnel will not have access to the link, and will not have any identifiable information.

d) 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, pathology reports, source 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.

e) 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]
Phone*:* 212-523-3812
Fax: 212-523-6293
E-mail*:* Saakshi.khattri@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]
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 data 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. All data captured in this project will be reviewed for accuracy by the principal monitor and the additional monitor.

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

f) 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
- 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

<u>Risks of Apremilast:</u>

As of 30 Nov 2016, apremilast has been given to more than 6700 subjects (people) in studies conducted by Celgene/Amgen. The following are the most commonly seen risks, discomforts and side effects in subjects who have taken apremilast: headache including tension headache, stuffiness

or infections of the nose and throat (upper respiratory tract infections including nasopharyngitis), stomach upset (nausea), vomiting and diarrhea. Most of these side effects were mild to moderate in intensity and resolved with continued treatment. Similar side effects have been observed in studies that are running now. About 8 out of every 100 subjects treated have discontinued the study drug because of side effects.

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

- **Very common:** Diarrhea, Nausea (stomach upset), Vomiting
- **Common:** Upper abdominal (stomach) pain, Indigestion, Frequent bowel movement, Heartburn, Fatigue, Bronchitis (infection of the tubes to the lungs), Redness/swelling/pain in the sinuses, Inflammation or infections of the nose and throat, Weight loss, Decreased appetite, Back pain, Headache (including tension and migraine), Difficulty sleeping, Depression, Cough, Rash, Dizziness, Weakness, Flu, Muscle pain, Numbness, Itchiness
- **Uncommon:** Allergic reaction.

Reports of various types of cancers, heart problems, and serious infections have been found from apremilast studies. However, these events in patients being treated with apremilast happened as often as those being treated with placebo (sugar pill). Drugs in the same family as apremilast have been shown to produce inflammation around the vessels of the skin (vasculitis) in rats and mice. Skin vasculitis has been rarely reported equally in patients taking apremilast or placebo.

Depression and weight loss have been reported with the use of apremilast, thus, subjects will be questioned about any mood changes and weight loss at each visit.

Blood Draws:

Possible risks from needle puncture include fainting, pain, bruising, discomfort, tingling, bleeding, redness or formation of blood clots at the needle puncture site. In rare cases infections can occur.

Biopsy Collection:
Possible risks from a biopsy include the following: bleeding from the biopsy site, pain, local reaction to the anesthetic (lidocaine), infection or healing problems such as the possibility of a scar at the site.

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

Amgen, the manufacturer of the study drug will provide the study drug. Amgen also provided a grant toward 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 visit, with the exception of the screening visit, for a total of $175.00 upon completion of the study. 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 one original copy of the ICF. They 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 is single site project.

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.

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