Efficacy and Safety of Duobrii in the Management of Acne Keloidalis Nuchae (AKN)
PI: Emma Guttman-Yassky, MD, Ph.D
NCT05608499
Document Date: 8/1/2023

Title: **Efficacy and safety of Duobrii in the management of Acne Keloidalis Nuchae (AKN)**

Principal Investigator: Emma Guttman-Yassky, MD, Ph.D

Investigators: Marguerite Mearimán, MD
Mark Taliercio, MD
Anusha Pasumarthi, MD

Study Site: Icahn School of Medicine at Mount Sinai
Department of Dermatology
5 East 98th Street - 5th Floor, Box 1048
New York, NY 10029
Tel: 212-241-3288

Protocol Version Date: August 15, 2022

Amendment #1 Version: 03 October 2022

Amendment #2 Version: 26 October 2022

INTRODUCTION:

Acne keloidalis nuchae (AKN) is one of the chronic forms of scarring folliculitis, affecting predominantly the occipital scalp, seen mostly in men of African descent. It has been reported in a few Caucasians and other ethnic groups. The reported prevalence in African Americans ranges from 0.5% to 13.6%[1]. The pathogenesis is yet to be elucidated. However, inflammation is central to its pathogenesis. Standard dermatologic recommendations for early or mild disease with non keloidal lesions include potent topical steroids which may be combined with topical retinoids. Early to mild disease, for the purpose of this study, includes class I and Class II AKN as defined by Lullo et al.[2]

Combining a topical corticosteroid with a topical retinoid allows for dual mechanistic action in the management of AKN; the topical corticosteroid, provides a primarily anti-inflammatory effect and the vitamin A derivative, impairs keratinocyte proliferation. Duobrii has the advantage of being the only high potency topical steroid-retinoid combination approved by the FDA with dermatologic indication. We are, thus, proposing, the off-labeled use, of Duobrii for the management of early-mild AKN.

HYPOTHESIS:

Primary Hypothesis:

1. Subjects treated with Duobrii will experience significant clinical improvement in lesion counts, symptoms associated with AKN as well as minimal dyspigmentation when compared to patients receiving placebo.

STUDY OBJECTIVE

Evaluate the efficacy and safety of Duobrii in the management of early to mild AKN

ENDPOINTS:

Primary Endpoint

- The primary endpoint will be clinical improvement as assessed by lesion counts and captured by photography.

Secondary Endpoint

- Patient reported outcome, improvement in severity of AKN associated symptoms as well as degree of dyspigmentation.

STUDY DESIGN OVERVIEW:

Following IRB approval, we will conduct a single center, prospective, double-blinded placebo vs. active-control trial assessing the efficacy of the vehicle vs. Duobrii, respectively, in the management of AKN over 3 months.

Blinding will be performed by pharmacy and research staff. In addition, different investigators will do the clinical enrollment and follow up vs. statistical analysis.

Patients with class I and class II AKN (Appendix C) from our various clinics at our Skin of Color Center will be screened with plan to enroll 30 participants after obtaining written informed consent. In addition, flyer announcement of our trial will be distributed and active patient recruitment will be conducted at various local barber shops and social media platforms (instagram, twitter and facebook) to increase patient recruitment.

Enrolled participants will be instructed to apply placebo (n=10) vs. active (n=20) to affected area of the occipital scalp for 4 weeks once a day (label use). Each application will be approximately 1g. Following the 4 weeks, participants will be instructed to increase application to twice daily (BID; off-label; at least 8 hours apart) for one week. Investigators will conduct a phone visit on week 5 to discuss any potential side effects with this increased dose. If tolerated, this BID regimen will be carried throughout the length of the study. If BID is not tolerated (if irritation occurs), then Bryhali will be used as a "rescue treatment" once daily for 1 week before the subject returns to BID treatment with Duobrii. If irritation recurs, subjects will be instructed to alternate Duobrii and Bryhali (ie Duobrii BID one day, followed by Bryhali QD the next day, Duobrii BID the next, and so on). Alternating topical steroid use and stepping down topical steroid strength have been known to reduce lesion count in AKN.[3] If irritation continues to persist, then participants will be instructed to use Bryhali QD for five days a week and Duobrii BID two days a week. If participants still experience irritation with this regimen, then subjects will be transitioned entirely to Bryhali QD for the remainder of the study. In case of clearance earlier than the end of the study, participants will be instructed to continue their respective regimen to completion of the study. Gentle hair care regimen will be recommended for duration of the length of the study; with unscented shampoo & conditioner (such as Head & shoulder) and Vaseline to scalp as moisturizer to minimize risk of contact dermatitis. In addition, patients will be instructed to postpone any form of hair coloring or chemical hair processing until after the study is over.

Participants will be followed with visits scheduled at baseline, 4 weeks, 8 weeks and 12 weeks. At each visit, participants will complete surveys regarding the severity of AKN's associated symptoms (pain, pruritus, burning etc.) as well as the dermatology quality of life index (DLQI) and numerical rating scale (NRS) surveys (Appendix B&D). In addition, photographs will also be obtained for global assessment and lesion count will be performed. The investigator will assess the treatment area for any dyspigmentation and document the % area affected within the treatment area at each visit. Tape strips will also be collected from lesional (occipital scalp) and non-lesional (frontal scalp) at Baseline and Week 12. There will be a phone call visit at week 5 to assess tolerance of medication increase and a safety follow-up visit at Week 14. Statistical analysis will be performed. Throughout the length of the study, any adverse events (AEs) related to the treatment will be recorded.

PATIENT POPULATION:

Prior to enrollment, all subjects must meet the following inclusion and exclusion criteria:

Inclusion criteria:

1. Male or female subject at least 18 years of age
2. Subject is able to provide written informed consent and comply with the requirements of this study protocol
3. Subjects have AKN class I or II (less than 6.5 cm in width)
4. Subjects who are women of childbearing potential (WOCBP) must have a negative urine pregnancy test at screening and must be practicing an adequate and medically acceptable method of birth control for at least 30 days prior to Day 0 and at least 6 months after the last dose of study. Acceptable methods of birth control include intrauterine device (IUD) oral, transdermal, implanted or injected hormonal contraceptives (must have been initiated at least 1 month before entering the study); tubal ligation; abstinence; barrier methods with spermicide. If not of child-bearing potential, subjects must have a sterile or vasectomized partner; have had a hysterectomy, a bilateral oophorectomy or be clinically diagnosed infertile; or be in a menopausal state for at least a year.
5. Subject is judged to be in good general health as determined by the principal investigator.

Exclusion criteria:

1. Unable to understand and provide written consent
2. Have received prior intralesional steroids for AKN within the past 6 months
3. Are using topical steroids or topical medications on their scalp within 4 weeks
4. Have used Duobrii on the scalp for AKN or other scalp disorders
5. Subject is pregnant or breastfeeding
6. Use of prior systemic medication for AKN or acne (doxycycline or isotretinoin) or hair loss in the last 6 months
7. Currently using topical minoxidil or prior use within the past 3 months
8. Have a history of other or other active scalp/hair disease or other forms of or other forms of alopecia
9. Are on systemic steroids or other immunosuppressants
10. Have a history of auto-immune disease, thyroid disorder, or hypersensitivity to steroids.

FUTURE TAPE-STRIP ANALYSIS:

Tape strips will be obtained to characterize the differential gene expression profile of affected areas with AKN before and after treatment. Comparative gene-expression profiling of the treated and untreated sides will then be performed to characterize the exact molecular pathogenesis of AKN. These samples will be frozen and stored until additional funding sources are obtained to cover the expenses associated with the processing and analyses of the tape strips.

RANDOMIZATION:

Once a subject meets all the inclusion and exclusion criteria, they will be assigned a randomization number on day 0/baseline. Enrolled subjects will be randomized in a 2:1 ratio of Duobrii to placebo.

The randomization will be performed by designated research staff/personnel at the Icahn School of Medicine using a randomization generator. The subjects and assessors (sub-investigators) will remain blinded to individual treatment assignment during the study. Research staff will also be responsible for blinding of the medication.

INVESTIGATIONAL DRUG SUPPLY:

Study medication will be given to subjects at their baseline visit and subsequent visits as needed. All study medication will be stored in a secured area at 20° to 25°C.

Unblinded research personnel will dispense study drug in an opaque bag to the subject. Individuals will be instructed not to reveal the study drug to anyone except the unblinded research staff.

Investigators will instruct subjects on how to approximately measure 1g per application.

Amount of product requested:
Duobrii = (2 x 100 g tube) or 200g/subject x 20 subjects
Bryhali = (2 x 100 g tube) or 200 g/subject x 20 subjects
Vehicle= (3 x 60 g tube) or 180 g/subject x 10 subjects

DATA ANALYSIS:

Sample Size Considerations

A sample size of n=20 Duobrii-treated subjects allows 80% power at 5% significance to detect a minimum reduction of 35% in the median number of lesions at week 12 with the one-sided Wilcoxon nonparametric test. This calculation assumes an average count of 15 AKN lesions at baseline and a standard deviation of 7 lesions around the mean difference at week 12, and a drop-out rate of 30%. These numbers are based on data reported by Okoye et al. (2014), who compared lesion counts at week 16 to baseline in a set of 11 UVB-treated subjects. The sample size calculation is based on the asymptotic relative efficiency of the Wilcoxon test compared to paired Student's t-test. A sample size of n=20 treated subjects compared to n=10 placebo-treated ones allows 80% power at 5% significance to detect a minimum 50% difference between proportions of patients with a reduced number of AKN lesions. This calculation is based on the application of a one-sided Z-test for the difference between two independent proportions and also assumes a maximum 30% dropout rate within each arm.

Primary Endpoint

The primary analysis for the primary endpoint will test for a reduction in lesion counts after 12 weeks of treatment. We will apply the two-sided Wilcoxon test to assess the significance of the difference between pre- and post-treatment median numbers of lesion counts. The secondary analysis will compare the reduction in lesion counts between active and placebo groups after 12 weeks. For this purpose, we will apply the Z-test to verify the hypothesis that the proportions of patients with reduced AKN lesions differ between active and placebo groups. A more comprehensive analysis will adjust a generalized linear mixed-effects model, based on Poisson distribution, including time and treatment group as fixed factors and a random intercept for each subject. This model will include the whole time-course and contrasts of interests will be estimated.

Secondary Endpoints

We will compare the improvement in the severity of AKN symptoms, degree of dyspigmentation, and patient-reported outcomes (DLQI and NRS) between time points (Baseline, 4, 8, and 12 Weeks) and groups (placebo and active) with the nonparametric tests described for the primary endpoint. We will also adjust, for each outcome, a generalized linear mixed-effects model including time, treatment group, their interaction as fixed effects, and a random intercept for each participant. This modeling strategy will decide each outcome's probabilistic distribution and link function based on goodness-of-fit criteria. The Spearman correlation coefficient will measure the association between reduction in lesion counts and improvement in patient-reported outcomes. In addition, we will compare the percent area of the treatment area affected with dyspigmentation (hypo- or hyperpigmentation) at each visit.

SAFETY MONITORING

The study will be conducted in accordance with our department's Standard Operating Procedures, which are based on US FDA Title 21 Code of Federal Regulations and ICH Good Clinical Practice guidelines.

An investigator will review all laboratory results and assess for adverse events. The principal investigator will be informed of all adverse events. In the event that a subject's safety is compromised, the investigator will discontinue the subject immediately.

POTENTIAL RISKS

Duobri:

Participants will be advised to avoid a severe sunburn and/or prolonged periods of sunlight exposure. If a sunburn does occur, subjects will be instructed to consult with their

healthcare provider and discontinue Duobrii until sunburn is healed. Hats or other head coverings will be strongly encouraged if direct sunlight exposure is unavoidable.

The following side effects are grouped by likelihood and severity.

Serious Reactions:

- HPA axis suppression (prolonged use)
- Cushing syndrome (prolonged use)
- Hyperglycemia (prolonged use)
- Cataracts (prolonged use)
- Glaucoma (prolonged use)
- Intracranial HTN (prolonged use in pediatric patients)

Common Reactions:

- Allergic contact dermatitis
- Application site pain
- Folliculitis
- Skin atrophy
- Excoriation
- Burning
- Pruritus
- Irritation
- Dryness
- Hypertrichosis
- Acneiform dermatitis
- Hypopigmentation
- Perioral dermatitis
- Maceration
- Secondary infection
- Striae
- Milaria
- Photosensitivity

Bryhali:

- URI (lotion form)
- Stinging
- Burning
- Pruritis
- Irritation
- Dryness
- Skin atrophy
- Folliculitis
- Hypertrichosis
- Aceneiform dermatitis

- Hypopigmentation
- Perioral dermatitis
- Allergic contact dermatitis
- Maceration
- Secondary infection
- Striae
- Miliaria

For further safety information on Duobrii and Bryhali, refer to the respective package inserts.

CONTRAINDICATIONS/CAUTIONS:

Duobrii: 1) Hypersensitivity to drug/class/compound 2) Pregnancy 3) Breastfeeding if applied on nipples 4) Female patients of reproductive potential 5) Pediatric patients 6) Skin infection 7) Photosensitivity 8) Sunburn 9) History of skin cancer

Bryhali: 1) Hypersensitivity to drug/class/compound 2) Pediatric patients 3) Skin infection

Definition of an AE: Any untoward medical occurrence in a subject administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the investigational medicinal product.

Investigational Medicinal Product (IMP) includes the drug under evaluation and the comparator drug(s) if specified as part of the research objective, given at any time during the study. Medical conditions/diseases present before starting the drug of interest are only considered adverse events if they worsen after starting the drug of interest.

The occurrence of adverse events will be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All adverse events will be recorded in the study database including the following information:

1. the severity grade (mild, moderate, severe)
2. its relationship to the drug(s) of interest (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a serious adverse event (SAE)

A SAE is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity

- is a congenital anomaly/birth defect
- is otherwise a significant medical event

This includes any SAEs likely to arise from the trial indication or progression of underlying/concomitant illness(es) (e.g. progression of cancer in oncology trials), unless specified in the protocol as study specific exemptions.

Any SAE, irrespective of causality, occurring after the subject has provided informed consent and until four weeks after the subject has stopped study participation must be reported unless otherwise stated in the protocol. SAEs occurring after four weeks from ending study participation should only be reported if considered by the Investigator attributable to the exposure to the investigational drug(s) during the trial period. This includes the period in which the study protocol interferes with the standard medical treatment given to a subject, even if study treatment has not yet started (e.g. withdrawal of previous treatment during washout period, change in treatment to a fixed dose of concomitant medication).

Timelines: All serious adverse events (SAEs) from interventional clinical trials must be reported by the sites to the Lead PI within 24 hours of occurrence of the SAE and to the site's own IRB as required. The Lead PI will then report to the manufacturer and any other authorities.

Follow-up reports: All related SAEs will be followed until resolution or until it is judged to be permanent, and an assessment will be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the drug of interest, the interventions required to treat it, and the outcome.

Pregnancies: Any occurrences of a pregnancy in a patient (or a patient's partner) during study participation will be collected. All pregnancies will be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Should a temporary or permanent suspension occur, we would report the occurrence to all appropriate authorities.

DISCONTINUATION OF TREATMENT AND WITHDRAWAL OF SUBJECTS:

The reasons why a subject may discontinue or be withdrawn from the study by the investigator include, but are not limited to the following: subject request, protocol violation, loss to follow up, subject non-compliance, study termination by investigators, and a confirmed grade 3 or higher adverse event, which is suspected to be related to test article administration.

Participants will be given a standard calendar dosing diary that will allow them to place checkmarks each day that study drug was taken. Investigators will assess diary at all in-person visits (weeks 4, 8, and 12). Subjects will be terminated from study if they do not maintain ≥50% dosing compliance.

REFERENCES:

1. Olsen EA, Bergfeld WF, Cotsarelis G, et al. Summary of North American Hair Research Society (NAHRS)-sponsored Workshop on Cicatricial Alopecia, Duke University Medical Center, February 10 and 11, 2001. *J Am Acad Dermatol*. 2003;48(1):103-110. doi:10.1067/mjd.2003.68

2. Umar S, Lee DJ, Lullo JJ. A Retrospective Cohort Study and Clinical Classification System of Acne Keloidalis Nuchae. *J Clin Aesthetic Dermatol*. 2021;14(4):E61-E67.

3. Ogunbiyi A. Acne keloidalis nuchae: prevalence, impact, and management challenges. *Clin Cosmet Investig Dermatol*. 2016;9:483-489. doi:10.2147/CCID.S99225

4. Okoye, G. A., Rainer, B. M., Leung, S. G., Suh, H. S., Kim, J. H., Nelson, A. M., Garza, L. A., Chien, A. L., & Kang, S. (2014). Improving acne keloidalis nuchae with targeted ultraviolet B treatment: a prospective, randomized, split-scalp comparison study. *British Journal of Dermatology*, *171*(5), 1156–1163. https://doi.org/10.1111/bjd.13119.

Appendix A.

Schedule of Events

	Screening	Baseline	W4	W5[c]	W8	W12	W14[d]	ET
Visit number	1	1[a]	2	3	4	5	6	TBD
Informed consent	X							
Medical History	X							
Demographics	X							
Inclusion/Exclusion	X	X						
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X
Pregnancy Test[b]	X	X	X		X	X		X
Administer IP		X						
Assess IP Compliance			X	X	X	X		
Return IP						X		X
DLQI		X	X		X	X		X
NRS		X	X		X	X		X
AKN severity		X	X		X	X		X
Clinical Photographs		X	X		X	X		X
Clinical Assessment/ Lesion Count		X	X		X	X	X	X
Tape strips (lesional & non-lesional)		X						
Tape strips (lesional only)						X		

a. If screening is successful, patient will continue into their Baseline visit on same day.
b. Where applicable, a urine pregnancy test with high sensitivity to HCG will be performed at screening and at all other visits, prior to dosing female participants of childbearing potential with Investigational Product (IP).
c. Phone call visit
d. Follow up visit

Appendix B.

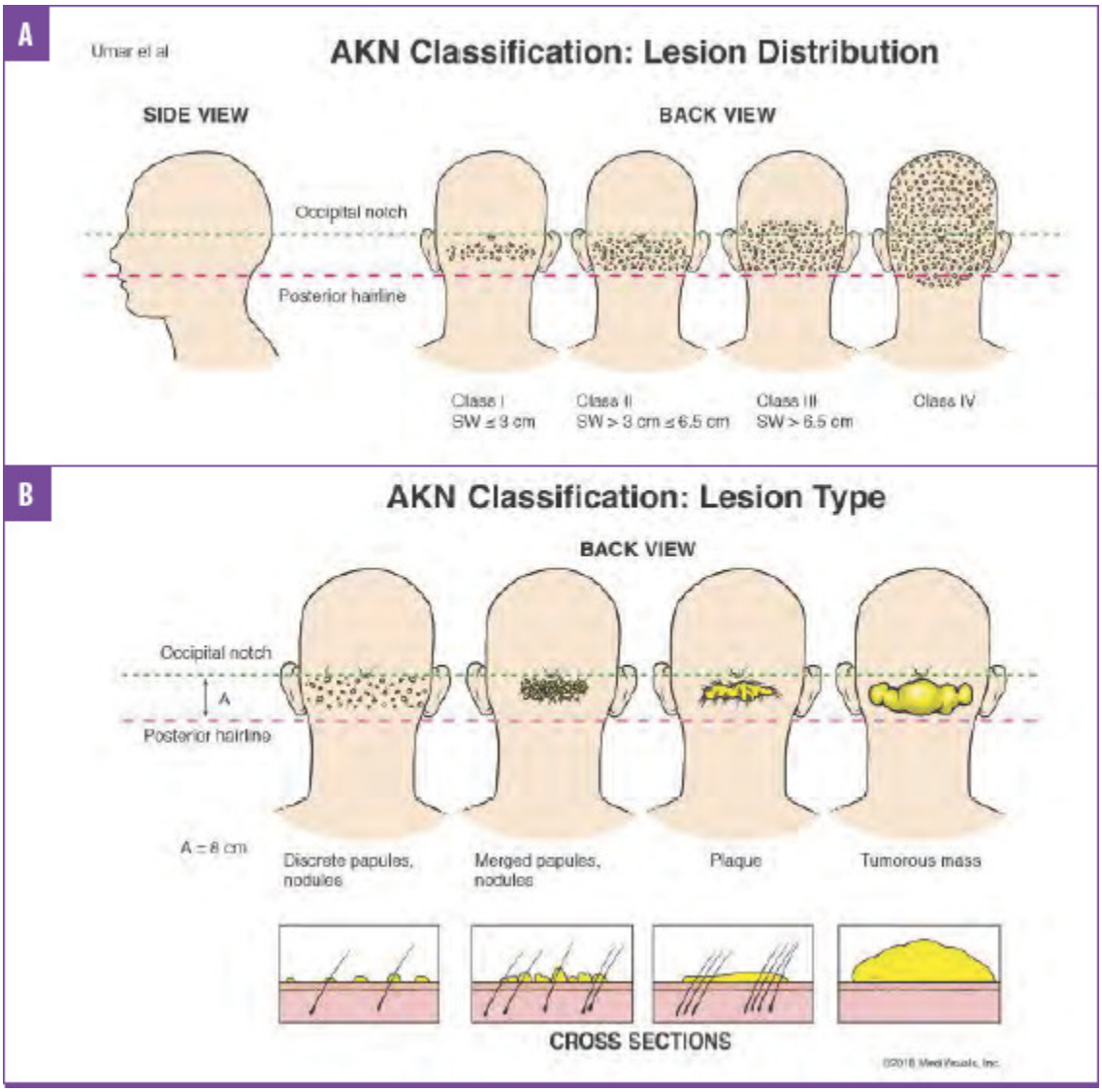
DERMATOLOGY LIFE QUALITY INDEX (DLQI)

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please check one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden?**	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	yes no	☐ ☐	Not relevant ☐

	If "**No**", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
10	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐

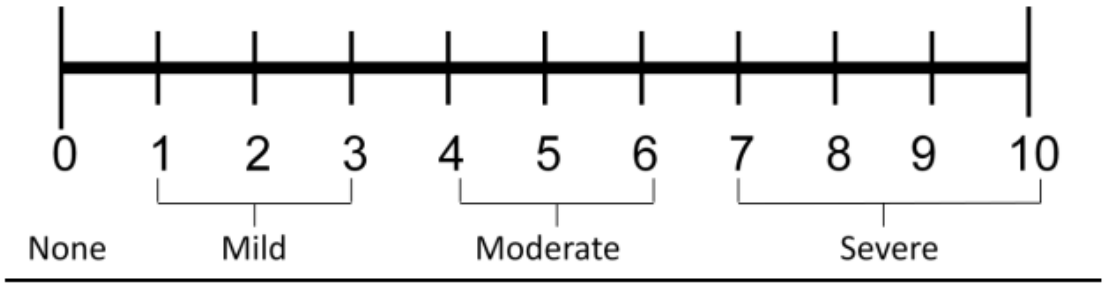
Appendix C.



Appendix D.

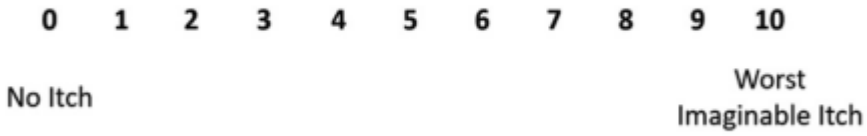
The Numeric Pain Rating Scale Instructions

Please indicate the intensity of current, best, and worst pain levels over the past 7 days on a scale of 0 (no pain) to 10 (worst pain imaginable).



The Numeric Itch Rating Scale Instructions

Please indicate the intensity of current, best, and worst itch levels over the past 7 days on a scale of 0 (no itching) to 10 (worst itching imaginable).



Appendix E.

Amendment # 1 Dated 03 Oct 2022 List of Revisions

Page 1 Title page: Added: Amendment #1 Version:03 October 2022

Page 2 Primary Hypothesis: added "as" **…**symptoms associated with AKN as well **as** minimal dyspigmentation when compared to patients receiving placebo.

Page 3 Study Design Overview 2nd paragraph added: …recruitment will be conducted at various local barber shops and social media platforms (instagram, twitter and facebook) to increase patient recruitment.

Page 3 Study Design Overview last paragraph: added **"**The investigator will assess the treatment area for any dyspigmentation and document the % area affected within the treatment area at each visit."

Page 4 Exclusion Criteria Revised criterion # 6: Use of prior systemic medication for AKN or acne (doxycycline or isotretinoin) or hair loss in the last 6 months.

Page 6 Data Analysis / Secondary Endpoints, added: In addition, we will compare the percent area of the treatment area affected with dyspigmentation (hypo- or hyperpigmentation) at each visit.

Page 10 References – moved ahead of all Appendices.

Page 16 Appendix E – Amendment # 1 list of Revisions added

Amendment # 2 Dated 26 Oct 2022 List of Revisions

Page 1 Title page: Added: Amendment #2 Version:26 October 2022

Page 11 Appendix A: Deleted "Where applicable, serum BHCG at screening, urine tests at all other visits to be performed prior to dosing female participants of childbearing potential with Investigational Product (IP) Two negative pregnancy tests are required before receiving IP (1 negative Serum Pregnancy Test at Screening and 1 negative Urine pregnancy test at the baseline visit before IP administration).

Added… "Where applicable, a urine pregnancy test with high sensitivity to HCG will be performed at screening and at all other visits, prior to dosing female participants of childbearing potential with Investigational Product (IP). "

Page 17 – Amendment # 2 list of Revisions added