Protocol Title: Comparison of the cosmetic effects of bakuchiol and retinol

Protocol Version Date: 31 August 2017

1) Objectives

We are looking to compare Bakuchiol and Retinol in reducing the appearance of photodamage.

2) Background

Retinoids are widely used in the treatment of wrinkles; however, the use of retinoids is associated with side effects such as skin dryness, redness, and peeling.

Bakuchiol is a purified meroterpene of natural origin from the leaves of *Psoralea Corylifolia*. This compound acts as a retinoid analog. Clinical studies have shown significant improvement in the appearance of wrinkles, as well as skin firmness and photo-damage in patients using Bakuchiol without the side effects associated with the use of Retinoids(1).

The aim of this study is to compare the cosmetic effects of Bakuchiol to Retinol over a 12-week period.

3) Inclusion and Exclusion Criteria

Inclusion criteria:

- Individuals aged 30-55

Exclusion Criteria:

- Adults unable to consent
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant or breast feeding women
- Prisoners
- Those with visible signs in the area of application of or on active treatment for acne, eczema, seborrheic

dermatitis, papulopustular rosacea or polycystic ovarian syndrome.
- Those who have used isotretinoin in the last 6 months
- Those who have used products containing salicylic acid, beta hydroxyl acids or vitamins A, C, or E in the last 14 days
- Those who have used topical antibiotics or topical retinoids in the last 30 days
- Those who are currently smoking or have smoked within the past 3 years.
- Those who have had a recent surgical or cosmetic procedure in the last 3 months that can affect facial wrinkles or facial hyperpigmentation, such as botulinum toxin injections, chemical peels, laser based therapies to the face, or face lift surgeries

4) Study Timelines

The duration of each subject's participation is as follows:

- Healthy volunteers –12 weeks

This study will be conducted over the course of one year.

5) Study Endpoints

Primary study endpoints include:
- Change in appearance of skin pigmentation
- Change in wrinkle appearance

Secondary study endpoints:
- Change in photographically measured skin texture and roughness

6) Procedures Involved

Subjects meeting the inclusion criteria without any of the exclusion criteria will be enrolled into this study.

Subjects will be randomized (double blind) to two groups:

- Retinol Group (n= 25)
- Bakuchiol group (n=25)

The following procedures will be conducted:

Procedures related to research:

Bakuchiol
Bakuchiol 0.5% applied to face twice daily

Retinol
0.5% retinol applied to face nightly

Facial Photography:
This will be conducted using digital visible light photography with no UV exposure of the face and neck. These photographs will be taken at all visits. After completion of all study visits, a dermatologist blinded to study group assignment will grade pigmentation, redness or wrinkles.

Assessments:
There will be a tolerability assessment of the skin performed by study staff to assess for subject based grading of facial redness, stinging, scaling, itching, and burning, as well as assessments by a board-certified dermatologist regarding facial erythema, scaling, hyperpigmentation, and hypopigmentation.

Schedule of visits:

Prescreening:

1. Informed consent
2. Review concomitant medication, topical agents and medical history

Visit 1:

1. Pregnancy test for all female subjects, excluding females with hysterectomy.
2. Facial photographs
3. Randomization to either Bakuchiol or Retinol
4. Study agent log given to each subject for the next 4 weeks
5. Study agent will be weighed prior to being given to subjects
6. Assessment: tolerability assessments
7. In person application

(Pre-screening and Visit 1 may take place on the same day)

Visit 2 (week 4):

1. Pregnancy test for all female subjects, excluding females with hysterectomy.
2. Facial Photographs
3. Previous diary card collected
4. New diary card issued
5. Study agent weighed
6. Assessment: Tolerability assessments

Visit 3 (week 8):

1. Pregnancy test for all female subjects, excluding females with hysterectomy.
2. Facial Photographs
3. Previous diary card collected
4. New diary card issued
5. Study agent weighed
6. Assessment: Tolerability assessments

Visit 4 (week 12):

1. Facial Photographs
2. Previous diary card collected
3. Study agent weighed and collected
4. Assessment: Tolerability assessment

Subject compensation is outlined as follows:

- $100 for completion of the whole study. If the subject leaves the study early, this amount will be pro-rata:
  Visit 1: $20
  Visit 2: $20
  Visit 3: $30
  Visit 4: $30

Protocol Activity	**Screening**					
	Pre-Screen	**Visit 1** (Day 0)	**Visit 2** (4 weeks +/-1 week)	**Visit 3** (8 weeks +/- 1 week)	Visit 4 (12 weeks +/- 1 week)	
Informed Consent	X					
Medical and Surgical History	X					
Review concomitant Medication	X					
Pregnancy test		X	X	X		
Facial photography		X	X	X	X	
Tolerability assessments		X	X	X	X	
Study agent dispensed		X	X	X		
Application of study agent		X				
Sunscreen dispensed		X		X		

Study agent returned			X	X	X	
Weighing of study agent and sunscreen		X	X	X	X	

7) Data and/or Specimen Management and Confidentiality

All data will be coded for the safety of the study subjects. Research data will only be available to the listed research personnel. The research site will maintain appropriate medical and research records for this study in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects.

All of the study data will be coded and stored within a locked cabinet within a locked room with two levels of keyed entry required to gain access. Furthermore, data files will either be stored in password-protected files within a locked room that will require two levels of keyed entry for access.

Precaution will be taken to maintain the privacy of the participants. These include the following: All subjects will be assigned a subject ID number after signing the consent form. This will be their only form of identification throughout the remaining of the study period. Each subject's name, age, medical record number, and group assignment will be recorded. The consent forms will be kept in a binder. The subjects will be entered into the data analysis sheets as subject ID numbers and a separate password-protected file will contain the key for these codes. All of the files will be saved on password-protected computers within locked rooms. All study related material will be kept in a locked cabinet within a locked room at UC Davis Department of Dermatology. Only the research team personnel will have access to study- related materials. Participant information will not be disclosed to third party individuals except for those authorized to oversee the research project.

Samples that are already collected will not be destroyed but will be stored in a codified format that will not allow linkage to identifying information. If the subject withdraws from the study, we will destroy their entry in the code key. We will make subjects aware that any

collected material/samples will not be destroyed during the consent process but that their identifying code entry in the code key will be deleted if they withdraw from the study.

The facial photographs are immediately stored after capture into a password-protected computer that will be stored in a locked room within the UC Davis Clinical Trials unit. These photographs will not have any associated names or other identifiers with them and will be stored with coded file names.

Each of the subjects' signed consents will be filed in a locked cabinet within a locked room. All of the subjects' data will be entered into the data analysis sheets as codes and a separate password protected file will contain the key for these codes. All of the files will be saved on computers that will be within locked rooms. The research team will follow the UC Davis Institutional Policy for data security to ensure that all subjects and collected data are protected. The coded images will not have any link to identifying information except through the subject code that will be stored in a password protected document that will be stored on password protected computers within a locked room. At the end of the study, the code key files will be deleted such that there will be no way for the study team to link the codes with any identifiable information.

We will also utilize StudyPages for recruitment. StudyPages is a secure cloud-based clinical research recruitment solution. Study coordinators can set up a dedicated webpage for a research study, share over email and social media with target communities, and collect contact information from potential participants.

StudyPages listings are intended to be consumer-facing, with an emphasis on the use of plain language combined with educational materials and a clear call to action for interested visitors. The goal is to provide a simple way for people to discover and participate in research.

StudyPages is an additional tool for researchers to maximize the success of a human subject study; reaching a more diversified audience, compressing recruitment timelines, and reducing costs.

Privacy and Security

Yuzu Labs does not sell data to third parties. User data collected is only provided to the study coordinator and optionally to Yuzu Labs, if a user chooses to be notified of future research. The full policy is located here: http://studypages.yuzulabs.com/privacy_terms

StudyPages meets applicable 21 CFR Part 11 requirements. The StudyPages platform consists of a network of cloud servers and any data transfer in/out of the system is encrypted using SSL. It is hosted on Amazon Web Services (AWS) using Heroku. Both AWS and Heroku have implemented robust security tracking and monitoring procedures to ensure secure transactions and data protection in the cloud. Additional information about the security and compliance of our hosting infrastructure can be found at
http://aws.amazon.com/security,
http://aws.amazon.com/compliance, and
http://policy.heroku.com/security

All StudyPages data is stored in the Application Database and Yuzu Labs maintains daily backups to ensure data integrity and provide disaster recovery protection.

8) Data and/or Specimen Banking

All patient information will be only accessible to authorized research personnel only, and otherwise personalized information will be locked in a cabinet and password protected electronic drive at the UC Davis Department of Dermatology during the trial. After the study has completed and analyzed, all patient information will be discarded. The code keys will be stored in a secure file in a password-protected

computer in a locked room and this code key will be deleted upon completion of the analysis.

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

The records and study materials will be maintained in a locked cabinet. Subjects will be asked about their health and any adverse events that may have occurred. Adverse effects will be related to the treating physician if it is deemed to be study agent related. All subjects will receive a number to contact if they note any side effects. Noted and serious adverse effects will be relayed to the IRB within 24 hours of the occurrence.

10) Withdrawal of Subjects

The subjects may withdraw consent at any time and they will be reassured that their clinical care will not be compromised if a subject were to withdraw. Subjects will be withdrawn from the study if they develop adverse side effects. The investigator can remove the subject from the study. Possible reasons for removal include:

- Noncompliance with the protocol
- Significant protocol deviation

11) Risks to subjects

The two randomized treatments have certain risks. Subjects will be counseled that the physical risks from retinoid based topical agent (if they are randomized into this group) may include skin redness, dryness, peeling, or irritation. The physical risks from bakuchiol topical (if subject is randomized into this group) may include mild itching or redness with sensitive skin. Subjects will be advised to inform the research team if they experience any side effects.

Additionally, some subjects may feel uncomfortable during the photographic process. Although provisions are put in place to protect identifiable data, we cannot guarantee absolute protection of the data

and photographs collected from each subject. Accordingly, the subjects will be informed of this risk.

12) Potential Benefits to Subjects

There are no direct benefits to the subjects. Subjects may see improvements in wrinkles and/or photo-damage.

This study will help us add to the general scientific knowledge that may benefit individuals in the future.

13) Sharing of Results with Subjects

Any peer reviewed manuscripts that result from the study will be made available to the subjects on request.

14) Provisions to Protect the Privacy Interests of Subjects

Steps will be taken to protect subjects' privacy interests. Subjects will only interact with approved study personnel who have successfully completed human subjects training. This includes those involved in the study visits, consent, and in any study related procedures. We will do our best to make sure that the personal information in the subject's medical record is kept private. However, no study can guarantee 100% protection of private information despite all of our measures to protect each subject's privacy. Subjects will be made aware of this during the consent process.

15) Compensation for Research-Related Injury

If a subject is injured as a result of being in this study, the University of California will provide necessary medical treatment. Depending on the circumstances, the costs of the treatment may be covered by University or the study sponsor or may be billed to the subjects' insurance company just like any other medical costs. The University and the study sponsor do not normally provide any other form of compensation for injury. For more information about compensation, call the IRB

administration at (916) 703-9151 or email at IRBAdmin@ucdmc.ucdavis.edu.

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16) Economic Burden to Subjects

Standard of care and other routine costs will be billed to the patient or the patient's insurance carrier, Medicare, or Medi-Cal where appropriate. Only the costs of research and experimental procedures will be paid by the sponsor/department. Subjects may incur a cost in relation to travel needed to get to the UC Davis Dermatology Department for each visit.

17) Drugs or Devices

☒ I confirm that all investigational drugs will be received by the IDS pharmacy, which will store, handle, and administer those drugs so that they will be used only on subjects and be used only by authorized investigators.

☒ I confirm that all investigational devices will be labelled in accordance with FDA regulations and stored and dispensed in such a manner that they will be used only on subjects and be used only by authorized investigators.

There are no investigational drug or devices used in this topical cosmetic study.

References:

1. Chaudhuri RK, Bojanowski K. Bakuchiol: a retinol-like functional compound revealed by gene expression profiling and clinically proven to have anti-aging effects. Int J Cosmet Sci. 2014;36(3):221-30.