A 24-Week, Randomized, Double-blind, Placebo-controlled Clinical Study to Evaluate the Efficacy and Safety of Proso Millet and Wheat Extract(Keranat™) on Hair Health

Brief Title	Evaluate the Efficacy and Safety of Proso Millet and Wheat Extract(Keranat™) on Hair Health
Protocol Number	NC07-NOVA-2022
Study Design	Randomized, Double blind, Parallel Assignment
Name of product(s)	Keranat™(proso millet and wheat extract) 300 mg/capsule, and respective matched Placebos.
Indication	Hair health / Dietary supplement
Phase	Interventional- Dietary supplement
Enrollment:	100 (50 Experimental, 50 Placebo Comparator)
How to eat	Take 1 capsules 2 times daily for 24 weeks
Sponsor/CRO	Novarex / Nutracore
Site	Korean Skin Research Center(KSRC) Seongnam-si, Gyeonggido, South Korea, 11234

1. Background

Millet (Panicum miliaceum) and its main compound, miliacin, arouse a lot of interest in dermatological research, especially for its tissue repair and wound healing properties. Miliacin, also called Panicol or Prosol, belongs to the class of organic compounds known as triterpenoids. Miliacin is a white odorless solid crystal practically fat- and water-insoluble. Cellular studies using thymocyte and splenocyte cultures have revealed a protective effect of miliacin from DNA fragmentation and apoptosis. Animal and clinical studies with suppurating wounds in different physiopathological conditions have confirmed and deepened these first results. Thanks to its strong anti-inflammatory properties, topical application of millet oil promoted rapid cleansing of the wounds and significantly activated the reparative processes. More recent studies focusing on miliacin have showed that it improved cellular renewal and proliferation and promoted the process of hair growth. When normal human keratinocytes derived from the foreskin were exposed to miliacin (6 mg/mL), the metabolic capacity of these cells was increased (+162%) and their proliferation was also stimulated (215%). Miliacin, the main triterpenoid from millet, is known to stimulate keratinocyte metabolism and proliferation. Polar lipids are able to form vesicles with active compounds and to improve their bioavailability.

2. Trial objective and endpoint

2.1. Objectives

The purpose of this randomized, double-blind, placebo-controlled study will be to evaluate whether the daily intake of Keranat™ for 24 weeks can promote the gloss and elasticity of hairs, improve their density and strength, and reduce hair loss.

2.1.1. Primary Objective

- To evaluate the change in hair elasticity between the Keranat™ and placebo group at baseline and 24 weeks, as measured by Expert 7601Tension Testing System.
- To evaluate the change in hair gloss between the Keranat™ and placebo group at baseline and 24 weeks, as measured by Skin-Glossy meter GL200.

2.1.2. Secondary Objective

- To evaluate the change in hair thickness improvement between the Keranat™ and placebo group at baseline and 24 weeks, as measured by microscope and ToupLite software.
- To evaluate the change in the ratio of anagen hair between the Keranat™ and placebo group at baseline and 24 weeks, as measured by Image-Pro® 10 program.
- To evaluate the change in the number of hair loss between the Keranat™ and placebo group at baseline and 24 weeks. Collected and counted the number of lost hair.
- To evaluate the change in the number of hairs per unit area between the Keranat™ and placebo group at baseline and 24 weeks, as measured by Folliscope PS.
- To evaluate the change in hair distribution score through clinical photography between the Keranat™ and placebo group before and after intake. This evaluates improvement and deterioration on a 7-point scale, with higher scores meaning improvement. By comparing photos before and after intake, if there is no change, 0 points, improvement is a maximum of 3 points, and worsening is a minimum of -3 points.
- To evaluate the change in Hair health improvement between the Keranat™ and placebo group at baseline and 24 weeks. The evaluation was conducted through Patient Report Outcome(PRO) using a standardized survey form. Survey allowing for participant-report changes in hair health because of intervention using a 7-point scale.
- To evaluate the change in serum levels of cytokines through clinical photography between the Keranat™ and placebo group at baseline and 24 weeks.

2.2. Trial Endpoints

2.2.1. Primary Endpoints

- The change of hair elasticity: Change of the week 24 from baseline
- The change of hair gloss: Change of the week 24 from baseline

2.2.2. Secondary Endpoints

- The change of hair thickness: Change of the week 24 from baseline
- The change of anagen hair ratio(%): Change of the week 24 from baseline
- The change in hair loss amount: Change of the week 24 from baseline
- The change of number of hair per unit area: Change of the week 24 from baseline
- The change of hair distribution score through clinical photography: Change of the week 24 from baseline
- Self-reported Hair health assessments: Change of the week 24 from baseline
- The change of serum levels of cytokines (IL-1, TNF-α, PGE2): Change of the week 24 from baseline

2.3.3. Safety Endpoints

- Incidence and severity of adverse events (clinical, laboratory measurements, hormone measurement, hCG)

  Safety will be assessed through routine monitoring of adverse events, evaluation of hematological and blood chemistry values, regular measurement of vital signs, and physical examination at selected trial visits (according to the trial schedule).

3. Selection of Patients

3.1. Inclusion Criteria

- Age 19 and 60
- Hair gloss score of 3 or less and a hair damage score of less than 18 according to the visual evaluation classification method.
- Willing to maintain the same hairstyle, hair color, hair length, and hair regimen throughout the study period.
- Subject must be able to comprehend and voluntarily sign study procedures and consent forms.

3.2. Exclusion Criteria

- Those diagnosed with and receiving treatment for the alopecia within 3 months before screening (androgenetic alopecia, alopecia areata, Telogen effluvium, etc.)
- Use of that may affect hair or hair loss symptoms treatment medicine, dietary

supplements, or treatments containing herbal medicine ingredients within 3 months before screening.

- Any active scalp or skin disease that may interfere with the study treatment and evaluations.
- Pregnancy or breastfeeding or planning pregnancy.
- Case of abnormal values at creatinine (excess at the upper limit of the reference range)
- Case of abnormal values at ALT or AST (2 times excess at the upper limit of the reference range)

4. Randomization

A random number will be assigned during visit 1 (week 0) in the order in which the subject is enrolled according to the inclusion and exclusion criteria. Subjects will be assigned to the study group, based on a random list prepared by a third party independent of the study before the study begins. Study participants will be allocated to the control group, and the test group (Keranat^{TM}) at a 1:1 ratio using a block randomization method. The study will be double-blind and group assignments will not be disclosed to investigators or subjects until the end of the study.

5. Study setting and design

This randomized controlled study will be conducted at the Korean skin research center(KSRC) in South Korea.

This will be a 24-week, randomized, double-blind, parallel group, placebo-controlled trial with two arms, as summarized below:

- Arm 1 (Placebo arm): placebo; 300 mg capsule twice a day
- Arm 2 (Test group 1): Keranat^{TM}; proso millet and wheat extract; 150 mg/capsule twice a day

Study subjects who voluntarily consent to the study at visit 1 (week 0) will be judged for eligibility according to inclusion and exclusion criteria. Selected subjects will be randomly assigned to study groups and tested for functional biomarkers after ingesting the experimental or control foods for 24 weeks.

6. Schedule of Events

Item	Screening	Pre-V1	V1	V2	V3	V4	V5
	-21~-D1	D-3	D0	8w±7	16w±7	24w-3	24w±7
Medicine takes history	●		●	●	●	●	●
Physical measurement	●	X	X	●	●	X	●
Drinking and smoking history	●	X	X	●	●	X	●
Hair damage assessment	●	X	X	X	X	X	X
Clinical photography (DSLR)	X	X	●	●	●	X	●
Hair elasticity	X	X	●	X	X	X	●
Hair gloss	●	X	●	●	●	X	●
Hair thickness	X	X	●	X	X	X	●
Hair loss amount	X	X	●	X	X	X	●
Self-reported Hair health assessments	X	X	●	X	X	X	●
anagen hair ratio(%)	X	X	●	X	X	X	●
IL-1, TNF-α, PGE2	X	X	●	X	X	X	●
Laboratory measurements	●	◐	X	X	X	X	●
Adverse reaction	X	X	X	●	●	●	●
Vital sigh	●	X	●	●	●	X	●
Dietary intake	X	X	●	X	X	X	●
Physical activity	X	X	●	X	X	X	●
Life habits	X	X	●	X	X	X	●
Compliance check	X	X	X	●	●	X	●

7. Treatments

7.1. Investigational Products

Investigational products supplied for this will include:

Keranat™ 300mg capsules or matching placebos in PTP packaging are going to be supplied to Subjects.

Keranat™ capsules are containing 150mg of proso millet and wheat extract.

7.2. Dosage

All treatment arms consider the regimens in fixed doses. Keranat™ 300mg and placebo are administered in two separate daily doses for 24 weeks.

8. Statistical Analysis Plan

The Statistical Analysis Plan will be written after the protocol finalization and definitely finalized before breaking the blind mode, prior to the first database lock. These specifications will detail the implementation of all statistical analyzes planned according to the main features reported in the protocol.

8.1. Sample size determination

This study hypothesizes that the use of Keranat™ will improve hair health. Therefore, a primary comparison will be conducted between the placebo arm and the test arm(Keranat™).

To calculate the number of test subjects, based on a 24-week intake study similar to this clinical trial, the change in hair count per unit area (Mean ± SD) of the test group was assumed to be 16.9 ± 15.6 and the control group was 4.5 ± 14.9. (d=12.4)

(1) $H_0 : \mu t = \mu c$ VS $H_1 : \mu t \neq \mu c$

(2) At the 5% significance level, the type 2 error is 0.2, maintaining 95% power. (α = 0.05, β = 0.2, statistical power =95%)

(3) test group : placebo group = 1:1(k=1)

(4) Calculation program: G*power 3.1.9.2

As a result of calculating the number of subjects using G*power 3.1.9.2, the number of subjects was calculated to be 41 per group and a total of 82. After considering the dropout rate of 20%, the number of subjects was calculated to be 50 per group and a total of 100.

8.2. Definition of trial populations included in the analysis

- The efficacy analyses will be performed on the PPS(Per protocol set), defined as all randomized subjects by their assigned treatment arms.
- The PPS(Per protocol set) will be defined as subjects receiving randomized treatment, who meets entry criteria, have not permanently discontinued treatment administration and had no major protocol deviation
- Additionally, efficacy analyses will be performed on a FAS(Full Analysis Set).
- All safety analyses will be performed on the Safety Set, defined as all patients who received at least one dose of the treatment.
- Tests of normality will be performed to evaluate the data distribution. Test group of continuous variables will be compared to the placebo group using Independent T-

test, analysis of covariance, and the Wilcoxon rank-sum test. Comparison between groups according to changes in time will be analyzed using Paired T-test. Categorical data will be analyzed using the chi-square test or Fisher's exact test. A two-sided test will be considered significant when the p value <0.05.

9. Confidentiality

Records confirming the subject's identity will be kept confidential. Monitoring staff and officers involved in the study may access subject records for the purpose of monitoring, reviewing, or managing the progress of the study, but such information will also be kept confidential. All documents related to the study, such as case records, will be recorded and distinguished using a subject identification code, not subject name. The collected information will be kept in the document storage room of the research institute for 3 years after the end of the study and will be discarded after 3 years according to the standards and procedures prescribed by the Personal Information Protection Act. During or after the study, research data, including medical records, may be reviewed to verify the conduct of the study and the reliability of the data, but this access is limited to the extent to which confidentiality of each subject's identity is protected.