Confirmatory Study: Assessing the Efficacy and Safety of the AcusMu Microneedle Patch in Treating Periorbital Wrinkles

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Study Protocol

1. Objective

We have developed a microneedle patch infused with Argireline, with the aim of providing a user-friendly, effective, and safe at-home treatment for under-eye wrinkles. Despite the potential benefits, the efficacy and safety of this novel patch have not yet been investigated in patients with mild to moderate under-eye wrinkles. Therefore, we conducted a split-face, double-blind, randomized, placebo-controlled clinical trial to evaluate the effectiveness and safety of this product in improving under-eye wrinkles.

2. Design

This trial was designed as a prospective, randomized, controlled, double-blinded, single-center study. A split-face design was employed to compare the effects of microneedle patches with and without anti-wrinkle ingredients on patients with under-eye wrinkles. Subjects applied the test products daily, using either product A (microneedle patches containing active anti-wrinkle ingredients) or product B (placebo patches), to the under-eye area. The patches were pressed onto the skin with fingers 5-10 times and left in place for 8 hours before removal. The treatment was continued for 14 days.

Subjects visited the clinic at four time points: baseline (week 0), week 1, week 2, and week 4 (±2 days). During each visit, two independent and blinded dermatologists evaluated the under-eye wrinkles using photographs based on the wrinkle grading scale, calculating the wrinkle improvement index. These evaluations were complemented by the subjects' self-assessment questionnaires to understand the efficacy of the microneedle patches with anti-wrinkle ingredients compared to the placebo patches over two weeks (assessments at weeks 0, 1, 2, and 4). Throughout the study period, subjects were advised to continue using their usual cosmetics and avoid changing any products. Any discomfort or adverse events experienced by the subjects were reported during the study.

3. Methods

3.1 Subjects

This prospective study was approved by the Institutional Review Board (IRB) of Taipei Medical University (TMU-JIRB No. N202308044). Informed consent was voluntarily and appropriately obtained from all subjects. The inclusion criteria for subjects were individuals aged between 18 and 99 years with clinician-assessed under-eye wrinkles of grade 2 or higher (mild or above). Exclusion criteria included subjects with open or infected wounds on the test skin area, participation in other studies that might interfere with this trial, pregnancy or breastfeeding, plans to become pregnant during the trial period, and major illnesses such as cancer, liver disease, diabetes, kidney disease, or cardiovascular disease. Subjects who had undergone other treatments for periorbital fine lines (e.g., laser, radiofrequency) within the past six months or who were concurrently undergoing such treatments were also excluded.

3.2 Microneedle patch

The microneedle (MN) patch applied to the under-eye area consisted of an adhesive hydrocolloid pad and

needles with a length of 300 μm. The experimental group's patches contained microneedles infused with Argireline at concentrations of 45 μg/g (high concentration) and 15 μg/g (low concentration). The control group's microneedles did not contain any active ingredients.

3.3 Grading of under-eye wrinkles

To evaluate under-eye wrinkles, a modified photonumeric grading scale developed by Jang et al. was utilized. [19] This scale, based on the number of fine, moderate, and deep wrinkles, ranges from 0 to 4 (0: no wrinkles, 4: numerous distinct fine and moderate wrinkles with numerous deep wrinkles). The grading details are as follows: **Grades 0 (GR 0)**: no wrinkles; **Grade 1 (GR 1)**: a few distinct fine wrinkles; **Grade 1.5 (GR 1.5)**: a few distinct fine wrinkles with one or two moderate wrinkles; **Grade 2 (GR 2)**: numerous distinct fine wrinkles with a deep wrinkle confined to the medial side; **Grade 2.5 (GR 2.5)**: numerous distinct fine wrinkles with a few moderate wrinkles; **Grade 3 (GR 3)**: numerous distinct fine wrinkles with a deep wrinkle on both medial and lateral sides and/or indistinct under-eye bags; **Grade 3.5 (GR 3.5)**: numerous distinct fine wrinkles with three or four deep wrinkles and/or distinct under-eye bags; **Grades 4 (GR 4)**: numerous distinct fine, moderate, and deep wrinkles.

3.4 Subject Self-Assessment Questionnaire

Subjects self-assessed the improvement of under-eye wrinkles using a Visual Analogue Scale (VAS) at four different time points: week 0 (baseline), week 1, week 2, and week 4. This subjective evaluation aimed to reflect the treatment's efficacy based on the severity of wrinkles. The VAS scores ranged from 0 to 10, with 0 representing smooth, wrinkle-free skin and 10 indicating severe wrinkles. The questionnaire included a series of icons (Figure S1) depicting "very satisfied," "satisfied," "neutral," "dissatisfied," and "very dissatisfied" from left to right. Subjects were asked to answer the question, "Over the past week, how would you rate the severity of your under-eye wrinkles?" and to record separate scores for the left and right sides.

Statistical Analysis Plan

All statistical tests were conducted using R (version 4.3.3) with one-tailed Wilcoxon signed rank tests at a significance level of 0.05. Confidence intervals were calculated at a 95% confidence level, focusing on the intent-to-treat population. Longitudinal comparisons of microneedle patches and placebo patches were made at baseline, 7, 14, and 28 (±2 days) days. Wilcoxon rank sum tests compared different concentrations of active ingredients. Changes during the trial were estimated using Generalized Estimating Equations (GEE). Results were visualized with bar plots using the R-packages ggpubr (version 0.6.0) and tidyverse (version 2.0.0), with standard errors presented as error bars.