Report on Human Patch Study for Sensitive Skin

【Jevie Lotion】

<Sponsor> Biolink Corporation

Study Number:	2023-A015
Study Period:	Mar. 7, 2023～Mar. 9, 2023
Final Report Submission date:	May 10, 2023
Contracted Testing Facility:	701 Research, Inc. Oak Otsuka Building 4F,1-13-4 Kita Otsuka, Toshima-ku, Tokyo 170-0004, Japan

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1. OBJECTIVE

The human patch test is a test in which test materials (test and control materials) are applied to human skin and absorbed transdermally to evaluate whether they cause artfitial contact dermatitis. This 24-hour closed patch study was conducted to assess the potential of the test material to produce primary skin irritation in adult subjects who have self-perceived sensitive skin.

2. SPONSOR AND CONTRACT RESEARCH ORGANIZATION

2-1. Sponsor

Company name: Biolink Corporation

Address: 1-11-7-2001 Tsukuda, Chuo-ku, Tokyo 104-0051, Japan

Phone: +81-3-5726-9696

Spomsor's representative: Shahram Mesri, Managing Director

Sponsor's primary point of contact: Ikeda, Business Department

2-2. Contract Research Organization (CRO)

Company name: 701 Research, Inc.

Address: Oak Otsuka Building 4F,1-13-4 KitaOtsuka, Toshima-ku, Tokyo 170-0004, Japan

Phone: +81-3-5832-9875

Study Physician: Shinichi Watanabe, MD (Dermatologist)

Study Investigator: Hiroshi Kakishima

Study Leader: Miyuki Ikeda

Study Staff: Miyuki Ikeda

3. MATERIAL INFORMATION

3-1. Test material and control materials

Material Name	Storage Condition	Concentration	Properties	Application Quantity	
Jevie Lotion	Room Temperature	100% (Neat)	Liquid	30μL	Test Material
Purified Water	Room Temperature	-	Liquid	30μL	Control
White Petrolatum	Room Temperature	-	White solid	30μL	Control

3-2. Test material characteristic and safety information

The sponsor guarantees the chemical stability and safety of the test material. CRO confirmed the safety of the test material using the preliminary test information, all ingredients list disclosed by the sponsor.

3-3. Test material storage condition

The test material was stored at room temperature.

3-4. Destruction of test materials

After the test completion, the test materials, both used and unused, were destroyed by CRO.

4. STUDY CALENDAR

March 7-9, 2023

5. SUBJECTS

5-1. Subject disposition and demographics

A total of 23 healthy Japanese male and female subjects aged between 22 and 58 years who met the inclusion criteria and did not meet the exclusion criteria were enrolled in this study. The tables for subject disposition and demographics information are presented in Appendix I. (see p.12).

5-2. Subject identification code

Each subject was assigned a multiple-digit number in addition to the study number. This number was used by the subjects throughout the study.

5-3. Inclusion criteria

A subject who met all of the following inclusion criteria was selected for this study:

1) Japanese men or women with normal skin between 20 and 60 years of age who did not meet any of the exclusion criteria.
2) Individuals with self-perceived sensitive or slightly sensitive facial skin.
3) Individuals who have previously experienced skin irritation or skin problems on the body or face when using skincare products or body care products.
4) Individuals who were willing to participate in this study and provided informed consent after understanding the study contents.

5-4. Exclusion criteria

A subject was excluded if they met any of the following exclusion criteria:

1) Individuals who were undergoing dermatological treatment at a doctor's office.
2) Individuals who had atopic dermatitis or any other allergic skin disease.
3) Individuals with any skin disease or damage at the test site
4) Individuals who had psoriasis or previously had psoriasis
5) Women who were known to be pregnant, nursing, or planning to become pregnant within the test period.
6) Individuals who, the study physician deems, are not suitable for study participation due to a disease

or use of medications, such as anti-inflammatory medications.

7) Individuals who had not rested for more than 4 weeks after completion of any other patch study they had participated in.
8) Individuals with skin that is sensitive to adhesive tape.
9) Individuals who were judged ineligible by the study physician, or principal investigator
10) Individuals who were able to read, write, and communicate in Japanese.

6. INFORMED CONSENT

Before conducting the study, staff members educated the prospective subjects on the nature of the study. After confirming that the prospective subjects fully understood the study contents, each of them consented and signed the informed consent form voluntarily. Furthermore, each subject received a signed copy of the informed consent form (including the consent document). The subjects were informed that they were free to revoke their consent at any time during the study; however, this did not happen.

7. STUDY METHOD AND PROCEDURE

7-1. Study design

The subjects visited the CRO three times on three consecutive days. During the first visit, the test materials were applied to the test sites. On the second visit the next day, the applied patches were removed, and the test sites were clinically evaluated for reactions by the study physician. The test sites were also evaluated on the third visit.

7-2. Study method

The study was conducted according to the method of "Hifusigekisei・kansaseishiken no jisshihou to hifuseijoukeisoku oyobi hyouka"[1].

1) Informed consent
   After the candidate subjects had been educated on this study, the subjects signed an informed consent form.
2) Questionnaires
   Questionnaires on sensitive skin were administered.
3) Verification of test site
   Each subject's back skin, where the test materials were patched, was evaluated for existing problems.
4) Test material applying method
   The application sites were assigned using the circuit method to prevent the effects when assessing skin irritation. After wiping the test site with distilled water, a patch test unit (hereinafter referred to as "patch"), manufactured by Torii Pharmaceutical Co. Ltd., was applied to the back of the subject. The cotton portion

of the patch was pre-filled with the test or control material.

5) Removal

The patches were removed approximately 24 h after patch application, and the test sites were gently wiped with purified water and marked with indelible ink.

6) Grading

Approximately 30 min after patch removal (which was indicated as 24 hours after patch application: "24-hour judgment") and 24 hours after patch removal (which was indicated as 48 hours after patch application: "48-hour judgment"), the test material and control sites were evaluated by the study physician for reactions, as described in section 7-3.

7-3. Grading Method

7-3-1. Visual grading scale

The visual grading was based on the standard evaluation scale (Table 1) of the Japan Patch Test Research Group.

Table 1.

Japan Patch Test Research Group Grading Scale and corresponding skin irritation score[1), 2), 3)]

Code	Response	Skin irritation score
-	None	0
±	Faint macular erythema only	0.5
+	Definite erythema	1
++	Erythema and edema, or papules	2
+++	Erythema + papules + edema, or vesicles	3
++++	Bullous reaction	4

7-3-2. Evaluation Timing

The designated test sites (including control sites) were clinically graded by the study physician at the "24-hour judgment" and "48-hour judgment" according to the standard evaluation scale of the Japan Patch Test Research Group (Table 1). In addition, photographs were taken of the test site of the subjects who observed skin reactions due to the test material at the time of the "24-hour judgment".

7-3-3. Classification of Skin Irritation Index Score

Irritation was graded, as shown in Table 2, based on the skin irritation index. The skin responses at the "24-hour and 48-hour judgments" after the patch application were numerically scored based on the scale in Table 1. The highest among the two grading scores was used for each subject's skin irritation score, and the skin irritation index of the test material was determined using the following formula:

Skin irritation index = (total sum of skin irritation scores) / (total number of subjects) × 100

Table 2. Classification of Skin Irritation Index[1),2)]

Skin Irritation Index	Classification
5.0 or lower	Safe material
5.0-15.0	Acceptable material
15.0-30.0	Material that needs improvement
30.0 or higher	Harmful material

7-4. Follow-up of skin reactions at test sites

7-4-1. Reaction follow-up procedure

If a subject's test site response was "grade 1 (+)" or higher at the time of the "48-hour judgment," the CRO followed the subject until the study physician confirmed that the subject's skin reaction had satisfactorily resolved. However, even if the judgment at the time of the "48-hour judgment," was "0.5 (±)", at the discretion of the study physician, the CRO might carry out a follow-up survey until the study physician confirmed that the subject's skin reaction had satisfactorily resolved. However, follow-up of subjects was not performed when subjects developed hypopigmentation or hyperpigmentation.

7-4-2. Status of reaction follow-up

There was no case in this study.

8. COMPLIANCE INSTRUCTIONS FOR SUBJECTS

The subjects were required to adhere to the following rules and prohibitions:

1) Keep the patch dry.
2) If the patch is coming off, use medical tape or bandages. The CRO should be contacted when the patch is completely removed.
3) Bathing should be avoided. Showers are allowed, but care should be taken to avoid getting the application sites wet. However, long showers that can cause sweating should be avoided. After removing the patch, bathing in a bathtub is allowed up to the waistline, but bathing for a long time, which can cause sweating, should be avoided.
4) Sweating is prohibited, and vigorous exercises, sporting activities, sauna, or swimming, among others, during the study should be avoided.
5) The application site should not be exposed to direct sunlight.
6) Physical stimulation of the application site, such as rubbing and massage, should be avoided.
7) Compresses, acupuncture, moxibustion, and magnetic induction therapy, among others involving the upper half of the body are prohibited.
8) Applying moisturizing products, such as body cream or oil, to the application site and its surroundings is prohibited.

9) Disclosing the information obtained by participation in this study to third parties without permission is prohibited.
10) Make prompt contact with the CRO when taking a new medicine or changing the dosage/usage of the medicine.
11) If dietary supplements are regularly used, they should be continued without a change in the dosage/usage.
12) Be careful not to erase the mark of the application sites.

9. STATUS OF ADVERSE EVENTS

9-1. Definition of adverse events

An adverse event (AE) is any unfavorable or unintended sign, symptom, or disease resulting from participation in a study, irrespective of any causal relationship with the investigated item. However, the following symptoms that can be generally expected to occur due to the application of the test product are excluded. Symptoms including mild to moderate redness, swelling, slight pimples, acne, itching, burning, peeling, cracks, rare papules, vesicles and small blisters at the patch application site are excluded. If there is a strong reaction, hypopigmentation or hyperpigmentation may occur. In addition, for some subjects, mild inflammation due to the tape adhesive and, rarely, allergic symptoms are also included in the expected symptoms. In addition, if an event was observed before the application of the test item and the symptoms and findings did not worsen after participating in the study, it was not considered an AE. Furthermore, if an event was predicted to occur due to the subject's previous daily activities or state before the start of the study, it was not regarded as an AE. The study physician had the final authority to determine whether the reaction was an AE.

9-2. Occurrence of adverse events

No AE occurred or was reported in this study.

10. STATUS OF WITHDRAWAL OR CANCELLATION

10-1. Withdrawal/ cancellation criteria

A subject was dropped out or discontinued from the study if the following criteria were met:

1) The subject did not comply with the study instructions (dropout).
2) It became difficult for the subject to continue the study due to illness and injury, among others, during the study period (dropout).
3) During the study period, a subject was found to meet the above-mentioned exclusion criteria (dropout).
4) The subject requested to discontinue the study due to personal reasons (dropout).
5) The study physician or sponsor realized that the discontinuation of the study was necessary.
6) The sponsor requested to discontinue the study.

10-2. Dropout or cancellation status

There was no case in this study. (See Appendix I (p.12))

11. STATUS OF HEALTH HAZARD

11-1. Response to health hazards

In the event of a health hazard, the following actions shall be taken.

In the event of a health hazard arising from participation in the study, the sponsor shall ensure that compensation and treatment are provided appropriately. In such cases, the CRO will compensate if the treatment costs, etc. are borne by the CRO; otherwise, the sponsor will compensate. If it is not clear which party is responsible, the sponsor and the CRO shall discuss and resolve the issue in good faith.

11-2. Status of health hazards

No health hazards were reported in this study.

12. STATUS OF SCHEDULE, CONTENT CHANGES, AND CANCELLATIONS

In the event of a natural disaster, such as an earthquake, flood, fire, epidemic, and accidents, which was not the responsibility of the sponsor or CRO, both parties could change the study schedule, study content, or cancel the study after consultation.

However, there was no change in this study.

13. DEVIATIONS OR MODIFICATIONS OF THE STUDY PROTOCL

13-1. Procedure for deviation or modifications of the study protocol

Modifications of the study protocol that could affect study conduct, participation requirements, data management, and reporting, among others, were recorded as protocol modifications. Violations of protocol during the study (such as enrollment of ineligible subjects, missing data, or deviations from the study procedures specified in the protocol) were documented as protocol deviations. Modifications that did not affect the conduct of the study, participation requirements, data management, and reporting, among others (such as typos, proposed start and end date changes), were recorded as notes.

13-2. Status of protocol deviations or modifications

There were no deviations or modifications of the original study protocol in this study.

14. ETHICAL COMPLIANCE

The study was conducted in compliance with the Declaration of Helsinki (2013 edition), the Japanese Ethical Guidelines for Medical and Biological Research Involving Human Subjects (Reiwa 4th year Ministry of Education, Culture, Sports, Science and Technology, Ministry of Health, Labor and Welfare, Ministry of Economy, Trade and Industry Notification No. 1), and the study protocol.

15. MANAGEMENT OF PERSONAL INFORMATION

The personal information obtained through this study included the signed informed consent, name and contact information, and subject number and name correspondence table. These data were properly stored and managed in a locked cabinet in accordance with the CRO regulations. When using the information obtained in this study for academic presentations, promotions, and regulatory applications, among others, the privacy protection of subjects was and will be fully considered to prevent the identification of individuals using their subject numbers.

The subject number was used in this report with due consideration of the protection of the privacy of the subjects.

16. DATA MANAGEMENT

The original data and recorded documents (including personal information data such as study plan documents, study result reports, judgment result records, and signed informed consent forms) obtained in this test were properly stored for 3 years after the study was completed based on the regulations of the CRO. After the retention period, the personal information has to be destroyed following the CRO regulations. Other data and documents obtained in this study will be destroyed after the end of the retention period. However, if the sponsor requests data transmission before the end of the retention period, this will be granted. In addition, requests for extension of the storage period by the sponsor, the extension deadline, and other conditions will be discussed.

17. RESULTS

17-1. Handling of results

Since there were no dropouts or discontinuations in this study, the data of all subjects were treated as report preparation data.

17-2. Results

As a result of the grading based on the Japan Patch Test Research Group Grading Scale, the skin irritation index was identified for each test material, as shown in Table 3. The individual results are shown in Appendix II. (See p.13)

Table 3. Grading Results

Test material	24 hours after patch application						48 hours after patch application						Skin Irritation Index and Classification	
	-	±	+	++	+++	++++	-	±	+	++	+++	++++		
Jevie Lotion	22	1	0	0	0	0	23	0	0	0	0	0	2.2	Safe Material
Purified Water	23	0	0	0	0	0	23	0	0	0	0	0	0	Safe Material
White Petrolatum	23	0	0	0	0	0	23	0	0	0	0	0	0	Safe Material

18. DISCUSSION AND CONCLUSION

For the test material, "Jevie Lotion", faint macular erythema only (score 0.5) was observed in one subject (subject 007) at the time of "24-hour judgement", but the finding disappeared at the time of "48-hour judgement".

For the control materials, which included purified water and white petrolatum, no response was observed for any subject at the "24 hour-judgment" and the "48 hour-judgment" after the patch application.

Based on the above results, the test material, "Jevie Lotion", was classified as an "Safe Material" under the test conditions.

19. REFERENCES

1) Hifushigekisei/kansaseishiken no jisshihou to hihuseijoukeisoku oyobi hyouka (The methods for dermal irritation/sensitization study, and the skin properties measurements and evaluation), Gijutsu jouhou kyoukai ed. p. 29-33, 1999 (in Japanese).
2) Tetsuro Sugai. Kousyouhin no anzensei (Cosmetic safety), Journal of Japanese Cosmetic Science Society, 19 (enl.), 49-56, 1995 (in Japanese).
3) Masatoshi Ito et al. Sessyokuhifuensinryou gaidorain (Japanese guideline for care of contact dermatitis), The Japanese Journal Of Dermatology, 119 (9), 1757-1793, 2009 (in Japanese).

REPORT APPROVAL

We declare that this report was elaborated based on the test result.

Shinichi Watanabe 5/10/2023

Study Physician Date

Shinichi Watanabe, M.D. (Dermatologist)

Hiroshi Kakishima 5/8/2023

Study Investigator Date

Hiroshi Kakishima

Appendix I

Subject Demographic

No	Gender	Age
001	Female	41
002	Female	28
003	Female	47
004	Female	42
005	Female	34
006	Female	43
007	Female	55
008	Female	29
009	Female	49
010	Female	40
011	Female	30
012	Male	57
013	Male	22
014	Female	38
015	Female	53
016	Female	47
017	Male	35
018	Female	47
019	Female	58
020	Female	49
021	Female	51
022	Female	32
023	Female	38

Subject Disposition

	N
Enrolled Subjects	23
Completed Subjects	23
Discontinued Subjects	0

Appendix II

Individual Patch Test Results

No	Test Material		Control		Control	
	Jevie Lotion		Purified Water		White Petrolatum	
	24H	48H	24H	48H	24H	48H
001	–	–	–	–	–	–
002	–	–	–	–	–	–
003	–	–	–	–	–	–
004	–	–	–	–	–	–
005	–	–	–	–	–	–
006	–	–	–	–	–	–
007	±	–	–	–	–	–
008	–	–	–	–	–	–
009	–	–	–	–	–	–
010	–	–	–	–	–	–
011	–	–	–	–	–	–
012	–	–	–	–	–	–
013	–	–	–	–	–	–
014	–	–	–	–	–	–
015	–	–	–	–	–	–
016	–	–	–	–	–	–
017	–	–	–	–	–	–
018	–	–	–	–	–	–
019	–	–	–	–	–	–
020	–	–	–	–	–	–
021	–	–	–	–	–	–
022	–	–	–	–	–	–
023	–	–	–	–	–	–