Clinical Study Report

A Randomized, Double-blinded (Evaluator, Subject) Matched Pairs, Active-controlled Medical device pivotal study to Evaluate the Efficacy and Safety of Injection with JUVEGEL as Compared to RESTYLANE® in Correction of Nasolabial Fold

Sponsor	BNC KOREA, Inc.
Investigational Device (Test Device)	JUVEGEL (Classic 01)
CSR Version	1.0
Protocol No.	NPT-MD-01
Phase	Medical Device Pivotal Study
Start Date	27 Mar. 2019
End Date	26 Dec. 2019
CSR Written Date	07 May 2020

1. Title Page

<table>
<tr><td>Study Title</td><td>A Medical Device Pivotal Study to Evaluate the Efficacy and Safety of Injection with JUVEGEL as Compared to RESTYLANE® in Correction of Nasolabial Fold</td></tr>
<tr><td>Investigational Device</td><td>- Test Device: JUVEGEL (Sodium polynucleotide 5mg/mL, Cross-linked hyaluronic acid 15mg/mL)
- Reference Device: RESTYLANE® (Cross-linked hyaluronic acid 20mg/mL)</td></tr>
<tr><td>Protocol No.</td><td>NPT-MD-01</td></tr>
<tr><td>Subject</td><td>Those who want to improve nasolabial folds on both sides of the face</td></tr>
<tr><td>Sponsor</td><td>BNC KOREA, Inc.</td></tr>
<tr><td>Clinical Study Phase</td><td>Medical Device Pivotal Study</td></tr>
<tr><td>Clinical Study Design</td><td>A Randomized, Double-blind (Evaluator, Subject), Matched Pairs, Active-controlled, Medical Device Pivotal Study</td></tr>
<tr><td>MFDS Approval and Amendment</td><td><table>
<tr><th>Approval/Amendment</th><th>Protocol Version</th><th>Approval Date (Report Date)</th></tr>
<tr><td>Initial Approval</td><td>3.0</td><td>12 Sep. 2018</td></tr>
<tr><td>Amendment Report</td><td>4.1</td><td>07 Jan. 2019</td></tr>
<tr><td>Amendment Approval</td><td>4.2</td><td>15 Mar. 2019</td></tr>
<tr><td>Amendment Approval</td><td>5.1</td><td>09 Sep. 2019</td></tr>
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<tr><td>Start Date of Study</td><td>27 Mar. 2019</td></tr>
<tr><td>End Date of Study</td><td>26 Dec. 2019</td></tr>
<tr><td>Coordinating Investigator</td><td>None</td></tr>
<tr><td>Compliance with Good Clinical Practice (GCP)</td><td>This clinical study and retention of essential documents were conducted in accordance with the Good Clinical Practice (GCP) for Medical Devices.</td></tr>
<tr><td>CSR Written Date</td><td>07 May 2020</td></tr>
</table>

2. Synopsis

<table>
<tr><td colspan="2">Name of Sponsor: BNC KOREA, Inc.</td><td rowspan="3">CSR Volume
: Total 78 pages</td></tr>
<tr><td colspan="2">Product Name: JUVEGEL</td></tr>
<tr><td colspan="2">Active Ingredient: Sodium polynucleotide 5mg/mL, Cross-linked hyaluronic acid 15mg/mL</td></tr>
<tr><td colspan="3">Study Title:
A Medical Device Pivotal Study to Evaluate the Efficacy and Safety of Injection with JUVEGEL as Compared to RESTYLANE® in Correction of Nasolabial Fold</td></tr>
<tr><td>Study Site and Principal Investigator:</td><td colspan="2">Beom-jun Kim, Professor of Dermatology, Chung-Ang University Hospital</td></tr>
<tr><td>Publication:</td><td colspan="2">None</td></tr>
<tr><td colspan="2">Study Period: 27 Mar. 2019 ~ 26 Dec. 2019</td><td>Clinical Study Phase: Medical Device Pivotal Study</td></tr>
<tr><td colspan="3">Study Objective:
The objective of the study was to prove that JUVEGEL is non-inferior to RESTYLANE® as the comparator in terms of the safety and improvement effect on the nasolabial fold on the face.</td></tr>
<tr><td colspan="3">Study Method:
This study was conducted as a randomized, double-blind (evaluator, subject), matched pairs, active-controlled clinical study.
Once a subject who met the inclusion/exclusion criteria and voluntarily signed the informed consent form was enrolled in this study, the subject was finally selected at the time of initial treatment (0D). Through randomization, which side of the nasolabial fold would receive the test device or the reference device was decided, and the investigational device was applied to each nasolabial fold. An investigator in charge of the treatment was designated, and the subject maintained blinding during the treatment by covering eyes with a light eyepatch or cotton to prevent from knowing which investigational device was being applied.
After applying the investigational device, the subject was observed for local adverse events for 30 minutes, received the subject diary, and recorded the occurrence and resolution of the adverse event in the subject diary until the next visit. The subject visited the site at week 2 after application of the investigational device and returned the subject diary. Based on the judgement by the investigator on whether or not repeat (touch-up) treatment was necessary, a maximum of one touch-up was planned, but there were no subjects who received touch-up during this study. After the final treatment with the investigational device, a 24-week follow-up was conducted.
All subjects underwent photography and efficacy evaluation (Wrinkle Severity Rating Scale) for the investigational device application site at visit 1 (before application of the investigational device), visit 3, visit 4, visit 5, and visit 6. Safety was evaluated at every visit after application of the investigational device.</td></tr>
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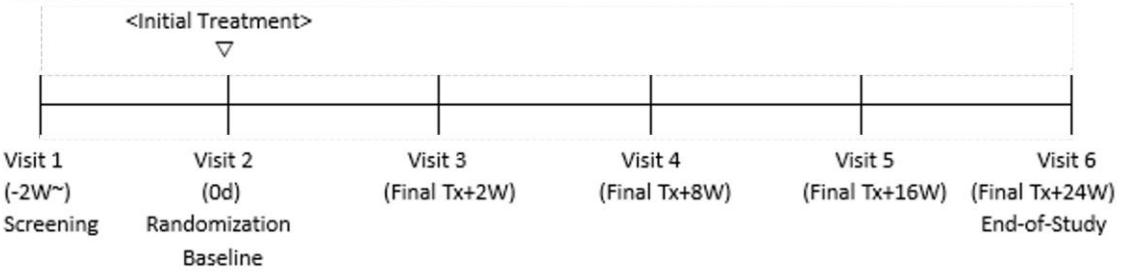
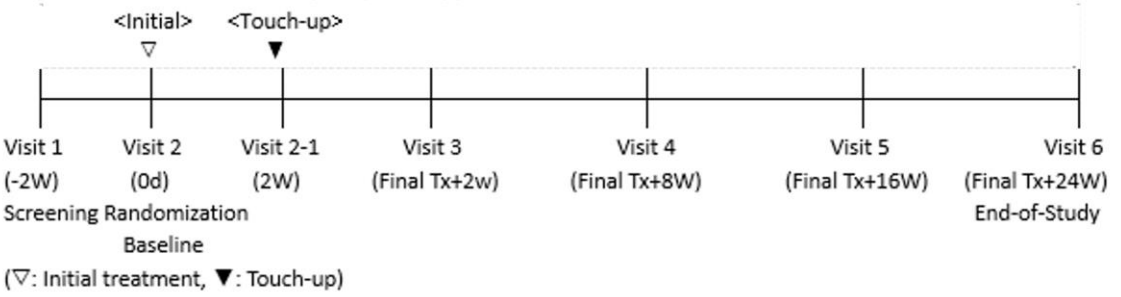
As for the subject's photographs of the medical device application site, a new number was randomly assigned to each photographs by an independent data manager regardless of the assigned group and the shooting timing, and then the photographs were sent to three independent evaluators without information on the subject and the shooting timing, etc. Independent evaluators proceeded with the evaluation based on the primary endpoint, Wrinkle Severity Rating Scale (WSRS), by looking at only the photographs.

<Study Flow>

-Implementation of one-time initial treatment



-Implementation of one-time repeat (touch-up) treatment



(▽: Initial treatment, ▼: Touch-up)

Number of Subjects (Planned and Analyzed):

This clinical study was planned with a matched pairs design, and at least 65 subjects were required to prove the non-inferiority of the test device compared to the reference device, and 81 subjects were required considering the dropout rate of 20%.

The number of subjects included in the three types of analysis was 80 each for SS (Safety Set), FAS (Full Analysis Set), and PPS (Per Protocol Set).

Indication: Nasolabial folds on the face

Inclusion/Exclusion Criteria:

<Inclusion Criteria>

1. Men and women aged 20 years or older as of the date of consent
2. Those whose both nasolabial folds are visually symmetrical at screening and fall under WSRS (Wrinkle

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Severity Rating Scale) Grade 3 (moderate) or Grade 4 (severe)

3. Those who agreed not to undergo any treatments for wrinkle improvement (filler treatment, laser or chemical peeling, Botox, facial wrinkle removal surgery, etc.) other than this investigational device during the study period
4. Those who can understand and follow instructions and participate over the entire study period
5. Those who voluntarily gave written consent to participate in the study

<Exclusion Criteria>

1. Those with a history of allergic disease, autoimmune disease, sarcoid granulomatous pathology, and Osler's endocarditis
2. Those with a history of anaphylaxis or severe complex allergy symptoms
3. Those with a history of hypertrophic scars or keloids, or those who are susceptible to hyperpigmentation
4. Those who have taken anticoagulants (excluding low-dose aspirin 100mg and max. 300mg/day), aggregation inhibitors, immunosuppressants, or NSAIDs within 2 weeks before screening
5. Those who have used topical agents (steroids, retinoids) or wrinkle improvement cosmetics on the face within 4 weeks before screening or who plan to continue using them during the study period
6. Those who are hypersensitive to the components of the investigational device (hyaluronic acid, sodium polynucleotide, etc.)
7. Those who have skin diseases such as inflammation, infection, or tumor, or have scars or wounds at the investigational device application site
8. Those who have or have a history of herpetic eruption
9. Those with hemorrhagic disease
10. Those who have experienced wrinkle improvement treatment or soft tissue augmentation (including filler), laser or chemical peeling, or facial plastic surgery (including Botox) on the nasolabial fold within 6 months before screening
11. Those who have received permanent implant treatment (PMMA, silicone, Gore-Tex, etc.) in the investigational device application site
12. Those who have a clinically serious disorder in the cardiovascular, digestive, respiratory, endocrine, immune, or central nervous system, or those who had or currently have a mental illness that significantly affects this study
13. Drug addicts or alcoholics
14. Smokers who smoke more than 20 cigarettes per day

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15. Those who participated in other clinical studies within 30 days before screening
16. Among women of childbearing potential during the study period, those who do not agree to use contraception* by medically acceptable methods, or those who are pregnant, breast-feeding, or planning to become pregnant

    *Medically acceptable methods of contraception: condoms, oral contraceptives, injectable or implantable contraceptives, intrauterine devices
17. Those who are judged by the investigator to be ineligible for participation in the study

Dosage and Administration of Investigational Device, Lot No.:

<Investigational Device>

- Test device: JUVEGEL (Sodium polynucleotide 5mg/mL, Cross-linked hyaluronic acid 15mg/mL)
- Reference device: RESTYLANE® (Cross-linked hyaluronic acid 20mg/ mL)

<Dosage and Administration>

1) Initial treatment (0D): According to the randomization method, subjects received the test device and the reference device in each of both nasolabial folds with a test device maximum dose of 1.0mL and a reference device maximum dose of 1.0mL. The subject's eyes were covered with an eyepatch or light cotton, and the investigational devices were applied using a linear threading technique and/or a serial puncture technique. Prior to treatment, 0.1 mL of each investigational device was injected into the skin of the forearm. It was then observed whether an acute allergic reaction (swelling, erythema, pruritus, injection site pain, etc.) occurred for about 2 minutes. Following the observation, treatment was administered.
2) Repeat (Touch-up) treatment (2-week): Two weeks after the initial treatment, the investigator assessed the Global Aesthetic Improvement Scale (GAIS) of both nasolabial folds. Repeat treatment (touch-up) was performed on the side that was not assessed as much improved or higher. During the touch-up, the same investigational device used in the initial treatment was applied to the repeat treatment site, with a maximum dose of 1.0 mL.

<Lot No.>

- JUVEGEL: HDG0.5-1-1801
- RESTYLANE®: 15690-1

Treatment/Follow-up Period:

After screening, the investigational device was applied once, and a 24-week follow-up was conducted after the final treatment with the investigational device.

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Endpoints and Evaluation Methods:

<Efficacy Evaluation>

1) Primary Endpoint

: Mean WSRS score evaluated by independent evaluators at week 24 after the final treatment with the investigational device

Based on the evaluation of the Wrinkle Severity Rating Scale by independent evaluators, the nasolabial fold was classified into five stages: 'Absent', 'Mild', 'Moderate', 'Severe', and 'Extreme'.

2) Secondary Endpoint

① Mean WSRS score evaluated by independent evaluators at weeks 2, 8, and 16 after the final treatment with the investigational device

② Mean WSRS score evaluated by the investigator at weeks 2, 8, 16, and 24 after the final treatment with the investigational device

③ Changes from screening in the mean WSRS score evaluated by independent evaluators at weeks 2, 8, 16, and 24 after the final treatment with the investigational device

④ Changes from screening in the mean WSRS score evaluated by the investigator at weeks 2, 8, 16, and 24 after the final treatment with the investigational device

⑤ Mean GAIS (Global Aesthetic Improvement Scale) score evaluated by subjects at weeks 2, 8, 16, and 24 after the final treatment with the investigational device

⑥ Mean GAIS score evaluated by the investigator at weeks 2, 8, 16, and 24 after the final treatment with the investigational device

⑦ Proportion of subjects who improved from screening by at least one grade in WSRS evaluated by independent evaluators at week 24 after the final treatment with the investigational device

⑧ Proportion of subjects who improved from screening by at least one grade in WSRS evaluated by the investigator at week 24 after the final treatment with the investigational device

<Safety Evaluation>

1) Adverse Event (AE)

① Evaluation immediately after application of the investigational device

- Local adverse events (swelling, erythema, injection site pain, pruritus, injection site nodule, bruising, tenderness, etc.) occurring for 30 minutes after application of the investigational device were observed and recorded.

② Subject diary

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- After applying the investigational device, the type, intensity, and duration of all adverse events that occurred for 14 days were recorded, and they were also recorded for 14 days after repeated treatment (touch-up).

③ Adverse events that occurred from the time of the initial treatment with the investigational device to 24 weeks after the final treatment were checked.

2) Laboratory test: hematology, blood chemistry, blood coagulation, urinalysis

3) Vital signs: blood pressure, pulse, body temperature

Statistical Analysis Method:

Analyses were conducted for PPS and FAS, and the PPS analysis result was used as the main analysis.

<Efficacy Evaluation>

1) Primary Endpoint

For the mean WSRS score, a non-inferiority test was performed for the test device compared to the reference device. The test device was evaluated to be non-inferior when the lower limit of the one-sided 97.5% confidence interval of the difference between the mean WSRS scorers of the two groups (control group-study group) was greater than -0.29.

2) Secondary Endpoint

Basic statistics were presented for the secondary endpoints. To determine if there was a statistically significant difference between the two groups ($p<0.05$), categorical data were analyzed by the Chi-square test if the number of cells with an expected frequency of < 5 was ≤ 20% of the total cells and by the Fisher's exact test if the number of cells with an expected frequency of < 5 was > 20% of the total cells. Continuous data were analyzed by the two-sample t-test when the assumption of normality was satisfied and by the Wilcoxon's rank sum test when the assumption of normality was not satisfied.

<Safety Evaluation>

For the safety set, adverse events and their incidence rates and the subjects who were in a normal or clinically insignificant abnormal state before application of the investigational device but showed a change to clinically significant abnormal after application of the investigational device were summarized. The difference between the treatment groups in local adverse events was compared by the Chi-square test if the number of cells with an expected frequency of < 5 was ≤ 20% of the total cells and by the Fisher's exact test if the number of cells with an expected frequency of < 5 was > 20% of the total cells.

For the results of laboratory tests and vital signs, to determine if there was a difference before and after the

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application of the investigational device, within-group comparison of continuous data was performed by the paired t-test if the assumption of normality was satisfied and by the Wilcoxon's signed rank test if the assumption of normality was not satisfied. Within-group comparison of categorical data was performed by the McNemar's test regardless of the expected frequency cell ratio or assumption of normality.

Summary and Conclusion:

This report summarized the study results prepared after completion of the 24-week follow-up period following the application of the investigational device.

<Efficacy Evaluation Results>

In the PPS, the mean Wrinkle Severity Rating Scale (WSRS) score evaluated by independent evaluators at week 24 after the final treatment with the investigational device was 1.79±0.69 in the study group and 1.75±0.70 in the control group, with a mean difference of the two groups (control group-study group) of -0.04 and the lower limit of the one-sided 97.5% confidence interval of -0.25, which was higher than the non-inferiority range of -0.29, proving non-inferiority. As the FAS and PPS subjects were the same, the results of the FAS were also the same.

The results of secondary endpoints of this study are as follows.

(1) Mean WSRS score evaluated by independent evaluators at weeks 2, 8, and 16 after the final treatment with the investigational device

After the final treatment with the investigational device, the mean WSRS score evaluated by independent evaluators was 1.59±0.61 in the study group and 1.53±0.59 in the control group at week 2, 1.68±0.67 in the study group and 1.63±0.70 in the control group at week 8, and 1.84±0.72 in the study group and 1.71±0.73 in the control group at week 16. There were no statistically significant differences between the two groups at all time points (week 2 p=0.5130; week 8 p=0.5625; week 16 p=0.2561).

(2) Mean WSRS score evaluated by the investigator at weeks 2, 8, 16, and 24 after the final treatment with the investigational device

After the final treatment with the investigational device, the mean WSRS score evaluated by the investigator was 2.23±0.45 in the study group and 2.21±0.44 in the control group at week 2, 2.23±0.48 in the study group and 2.23±0.48 in the control group at week 8, 2.28±0.50 in the study group and 2.29±0.51 in the control group at week 16, and 2.30±0.51 in the study group and 2.30±0.51 in the control group at week 24. There were no statistically significant differences between the two groups at all time points (week 2 p=0.8585;

week 8 p>0.9999; week 16 p=0.8628; week 24 p>0.9999).

(3) Changes from screening in the mean WSRS score evaluated by independent evaluators at weeks 2, 8, 16, and 24 after the final treatment with the investigational device

After the final treatment with the investigational device, the change in the mean WSRS score evaluated by independent evaluators was -0.73±0.73 in the study group and -0.89±0.71 in the control group at week 2, -0.64±0.73 in the study group and -0.79±0.72 in the control group at week 8, -0.48±0.69 in the study group and -0.70±0.77 in the control group at week 16, and -0.53±0.69 in the study group and -0.66±0.69 in the control group at week 24. There were no statistically significant differences between groups at all time points except for week 16 (week 2 p=0.1908; week 8 p=0.1322; week 16 p=0.0481; week 24 p=0.2002), and there were statistically significant differences within groups at all time points in both groups (all time points p<0.0001 for both groups).

(4) Changes from screening in the mean WSRS score evaluated by the investigator at weeks 2, 8, 16, and 24 after the final treatment with the investigational device

After the final treatment with the investigational device, the change in the mean WSRS score evaluated by the investigator was -1.23±0.42 in the study group and -1.24±0.43 in the control group at week 2, -1.23±0.45 in both the study and control groups at week 8, -1.18±0.47 in the study group and -1.16±0.49 in the control group at week 16, and -1.15±0.45 in the study group and -1.15±0.48 in the control group at week 24. There were no statistically significant differences between groups at all time points (week 2 p=0.8538; week 8 p>0.9999; week 16 p=0.8896; week 24 p=0.9798). There were statistically significant differences within groups at all time points in both groups (all time points p<0.0001 for both groups).

(5) Mean GAIS (Global Aesthetic Improvement Scale) score evaluated by subjects at weeks 2, 8, 16, and 24 after the final treatment with the investigational device

After the final treatment with the investigational device, the mean GAIS score evaluated by subjects was 2.38±0.68 in the study group and 2.40±0.69 in the control group at week 2, 2.13±0.89 in the study group and 2.15±0.89 in the control group at week 8, 1.81±1.03 in the study group and 1.84±1.02 in the control group at week 16, and 1.55±1.07 in the study group and 1.58±1.04 in the control group at week 24. There were no statistically significant differences between the two groups at all time points (week 2 p=0.7903; week 8 p=0.8544; week 16 p=0.8884; week 24 p=0.8834).

(6) Mean GAIS score evaluated by the investigator at weeks 2, 8, 16, and 24 after the final treatment with

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the investigational device

After the final treatment with the investigational device, the mean GAIS score evaluated by the investigator was 2.50±0.50 in the study group and 2.51±0.50 in the control group at week 2, 2.09±0.84 in the study group and 2.13±0.85 in the control group at week 8, 1.75±0.97 in the study group and 1.79±0.96 in the control group at week 16, and 1.46±0.98 in the study group and 1.49±0.97 in the control group at week 24. There were no statistically significant differences between the two groups at all time points (week 2 p=0.8765; week 8 p=0.7588; week 16 p=0.8184; week 24 p=0.8638).

(7) Proportion of subjects who improved from screening by at least one grade in WSRS evaluated by independent evaluators at week 24 after the final treatment with the investigational device

The proportion of subjects was 48.75% (39/80) in the study group and 58.75% (47/80) in the control group, and there was no statistically significant difference between the two groups (p=0.2046).

(8) Proportion of subjects who improved from screening by at least one grade in WSRS evaluated by the investigator at week 24 after the final treatment with the investigational device

The proportion of subjects was 96.25% (77/80) in the study group and 95.00% (76/80) in the control group, and there was no statistically significant difference between the two groups (p>0.9999).

<Safety Evaluation Results>

In the safety set of 80 subjects, a total of 20 local adverse events (AEs) occurred in 12 subjects, with 8.75% (7/80 subjects, 12 events) in the study group and 6.25% (5/80 subjects, 8 events) in the control group. There was no statistically significant difference (p=0.5483). The incidence rate of non-local adverse events was 3.75% (3/80 subjects, 4 events).

As a result of reviewing a total of 20 local adverse events with MedDRA PT, in the study group, 'Injection site swelling' was 6.25% (5/80 subjects, 5 events), 'Injection site erythema' and 'Injection site pain' were 2.50% each (2/80 subjects, 2 events), and 'Injection site nodule', 'Injection site pruritus', and 'Injection site warmth' were 1.25% each (1/80 subject, 1 event). In the control group, 'Injection site swelling' was 5.00% (4/80 subjects, 4 events), and 'Injection site erythema' and 'Injection site pain' were 2.50% each (2/80 subjects, 2 events). The local adverse events were all confirmed to be local adverse device effects (ADEs).

As a result of reviewing a total of 4 non-local adverse events with MedDRA PT, 'Haemothorax', 'Hyperventilation', 'Nasopharyngitis', and 'Rib fracture' were 1.25% each (1 event in 80 subjects). There were no adverse device effects (ADEs) among non-local adverse events.

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In this study, there was 1 serious adverse event, 'Rib fracture', which occurred due to the subject's careless fall and recovered after inpatient treatment at another hospital. The result was 'recovered/resolved', and the causality with the investigational device was 'definitely not related'.

As a result of vital signs measurement (blood pressure, pulse, body temperature) and laboratory tests, there were some statistically significant items within groups, but no clinically significant changes were identified in relation to the changes from baseline. In addition, there were no adverse events reported as clinically significant abnormalities related to vital signs and laboratory tests.

<Conclusion>

The primary endpoint of this study was the mean WSRS score evaluated by independent evaluators at week 24 after the final treatment with the investigational device. The difference between the mean scores of the two groups (control group-study group) was -0.04, with the lower limit of one-sided 97.5% confidence interval of -0.25%, which was higher than the non-inferiority margin of -0.29%, proving non-inferiority.
In secondary endpoints, there were no statistically significant differences between the two groups at all endpoints and at all time points, except for the change from screening in the mean WSRS score evaluated by independent evaluators at week 16.

In this study, there were no statistically significant differences between the two groups in local adverse events and local adverse device effects (ADEs), and no non-local ADEs occurred. During the study period, 1 serious adverse event occurred in non-local adverse events (rib fracture), but it recovered during the study, and no serious ADEs occurred. There were no clinically significant issues among the other safety evaluation items. Accordingly, JUVEGEL is considered safe for use by subjects who desire to improve the nasolabial fold.

Through this pivotal study, it was confirmed that JUVEGEL is effective in improving the nasolabial fold and can be used safely.

CSR Written Date: 07 May 2020