Received: 19 May 2019 | Revised: 5 September 2019 | Accepted: 4 October 2019

DOI: 10.1111/jocd.13199

ORIGINAL CONTRIBUTION

JCD Journal of Cosmetic Dermatology WILEY

# A randomized, patient/evaluator-blinded, split-face study to compare the efficacy and safety of polycaprolactone and polynucleotide fillers in the correction of crow's feet: The latest biostimulatory dermal filler for crow's feet

Guk Jin Jeong MD | Ga Ram Ahn MD | Su Jung Park MD | Ji Yeon Hong MD | Beom Joon Kim MD

Department of Dermatology, Chung-Ang University College of Medicine, Seoul, Korea

**Correspondence**
Beom Joon Kim, Department of Dermatology, Chung-Ang University Hospital 224-1 Heukseok-dong, Dongjak-gu, Seoul 156-755, Korea.
Email: beomjoon74@gmail.com

## Abstract

**Background:** No data on the clinical results and safety profiles of the polycaprolactone (PCL) -based dermal filler for crow's feet correction have been published.

**Aims:** This study was designed to compare the efficacy and safety of a novel PCL-based dermal filler, DLMR01, with that of RJR, a purified polynucleotide dermal filler.

**Patients/Methods:** A total of 30 subjects with symmetric crow's feet of 2-4 points on the Crow's Feet Grading Scale (CFGS) were enrolled in this randomized, patient/evaluator-blinded, split-face study. Each subject was randomized to receive injections of DLMR01 or RJR in their right or left crow's feet. At 4 and 12 weeks, all participants were evaluated via CFGS, Global Aesthetic Improvement Scale (GAIS), and PRIMOS software system.

**Results:** No significant difference in CFGS, GAIS, and $R_a$ value was detected between DLMR01 side and RJR at 12 weeks (improvement rate in CFGS from baseline at week 12—DLMR01: 48.28% [14/29], RJR: 41.38% [12/29]).

**Conclusion:** The novel PCL-based dermal filler DLMR01 shows suitable efficacy and safety, widening the selection possibilities for clinicians and patients in the treatment crow's feet.

KEYWORDS
biostimulatory, crow's feet, dermal filler, polycaprolactone, polynucleotide

## 1 | INTRODUCTION

Esthetic medicine has moved forward markedly in the past decade with regard to understanding of the cumulative effects of aging and how dermal fillers may be utilized to restore, minimize, and even reverse these age-related changes. Dermal fillers, whose range and constitution has developed dramatically in the last few decades, are composed of a wide group of products that differ in their chemical constitution, mechanism of action, safety, duration, and interaction with host tissues. Crow's feet wrinkles are characterized as laugh lines spreading from the lateral canthus to the temple. Static fine wrinkles around the eyes and dynamic wrinkles caused by movement of the orbicularis oculi muscle develop with aging. Characteristic anatomy of the crow's feet area that has lots of habitual movement, and considerable sunlight exposure, also deteriorates the wrinkles. On histological study, crow's feet show configurational elastic tissue network changes and photoaging phenotypes such as epidermal thinning, compact

  

stratum corneum, perifollicular fibrosis, increased granular layer thickness, and solar elastosis compared to skin with less sun exposure.[1,2] Thus, volumizing the area under the wrinkles and rejuvenating the damaged dermal tissue can improve crow's feet.[3] Biodegradable collagen stimulators are the latest, next-generation dermal fillers with characteristics capable of inducing a process called neocollagenesis.[4] In addition to calcium hydroxylapatite and polynucleotide fillers, which have particular efficacy and longevity profiles, a promising biostimulatory polycaprolactone (PCL)-based dermal filler has been recently introduced in the esthetic market. However, no data on the clinical results and safety profiles of the PCL-based dermal filler for crow's feet correction have been published. This study was designed to compare the efficacy and safety of a novel PCL-based dermal filler DLMR01 (DexLevo; Inc) with that of RJR (Rejuran®; PharmaResearch Products, Inc), a purified polynucleotide dermal filler. RJR is a biostimulatory dermal filler composed of macromolecules with a concentration of 20 mg/mL of highly purified polynucleotides of natural origin. It is known to exert a volumizing and neocollagenic effect on skin and was selected as control due to its similarity to DLMR01 in terms of the mechanism of action.[5]

## 2 | MATERIALS AND METHODS

### 2.1 | Subjects

This randomized, split-face study was conducted at Chung-Ang University Hospital, Seoul, Korea. We included 30 healthy volunteers aged >19 years with symmetric crow's feet of 2-4 points on the Crow's Feet Grading Scale (CFGS). All subjects voluntarily participated in the study and were able to freely terminate their participation at any time. Written informed consent was obtained from all participants after a full explanation of the risks and benefits of the procedure, and the study protocol conformed to the guidelines of the Declaration of Helsinki and Korea Good Clinical Practice guidelines. The study was approved by the Chung-Ang University Hospital institutional review board.

### 2.2 | Study devices

DLMR01 composed of microparticle-free polycaprolactone solubilized in water was the subject of investigation in this study. It was administered via sterile, 1.0-mL, prefilled syringes with 33-gauge needles. RJR composed of a transparent liquid consisting of polynucleotides 20 mg/mL was used as the control.

### 2.3 | Treatment

Participants were randomized using a computer-generated code to determine which crow's feet, right or left, would receive the DLMR01. The contralateral crow's feet area was designated to receive RJR. Digital photography and three-dimensional (3D) analysis using PRIMOS software (PRIMOS Premium, GFMesstechnik GmbH) were performed both in the resting and smiling states at every visit. Subjects and evaluating investigators were blinded, while the injectors were not, as per the study protocol. The injecting investigator was instructed to optimally correct the crow's feet considering the width, length, and depth of the wrinkle. Up to 1 mL of filler was injected for each area of crow's feet using linear threading techniques.

### 2.4 | Efficacy evaluations

The clinical efficacy measurements were made using the CFGS, Global Aesthetic Improvement Scale (GAIS), and PRIMOS software system (Table 1 and Figure 1). The primary efficacy measure was the improvement rate in CFGS at rest at 12 weeks compared with baseline, as determined by blinded evaluators. The secondary efficacy measures included the mean improvement in CFGS, as determined by blinded evaluators, and the changes in GAIS, evaluated by the subjects (self-assessment) and the treating investigators over 12 weeks. In addition, wrinkle parameters were measured using PRIMOS 3D skin photography equipment. The following parameters were calculated: eye wrinkle volume; $R_a$ = arithmetic average value of profile peaks within the total measuring length; $R_{max}$ = maximum of all peak-to-valley values;

**TABLE 1** Crow's Feet Grading Scale (CFGS) and Global Aesthetic Improvement Scale (GAIS)

| CFGS | | | GAIS | | |
|---|---|---|---|---|---|
| **Score** | **Rating** | **Description** | **Score** | **Rating** | **Description** |
| 4 | Extreme | Severe wrinkles | 3 | Very much improved | Optimal cosmetic result for the implant |
| 3 | Severe | Moderate wrinkles | 2 | Much improved | Marked improvement over initial condition but not optimal |
| 2 | Moderate | Fine wrinkles | 1 | Improved | Obvious improvement over initial condition but a touch-up or retreatment is indicated |
| 1 | Mild | Very fine wrinkles | 0 | No change | Essentially the same appearance as the original condition |
| 0 | Absent | No wrinkles | −1 | Worse | Worse than the original condition |

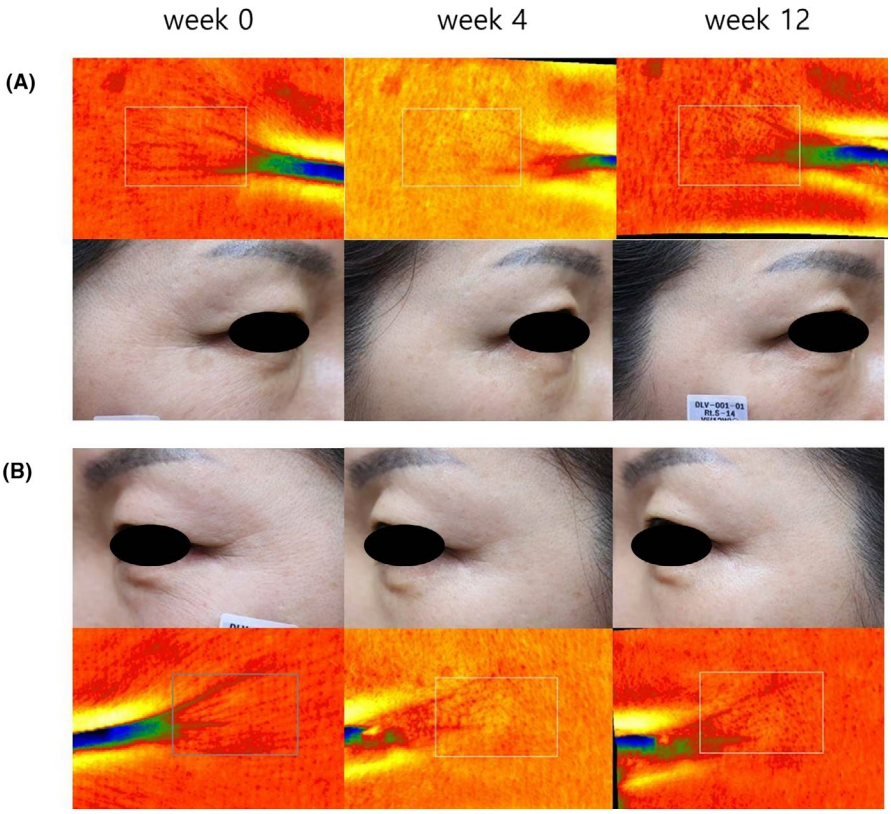


**FIGURE 1** Matched digital photographs and PRIMOS imaging of a representative patient at baseline, 4 wk, and 12 wk. A, The crow's feet on the right side of the subject's face were treated with DLMR01. B, The crow's feet on the left side of subject's face were treated with RJR

$R_p$ = maximum profile peak height; $R_v$ = maximum profile valley depth; and $R_z$ = average maximum height of the profile.

### 2.5 | Safety measures

Adverse effects were evaluated at every visit, including erythema, edema, itching, and induration. Safety was also assessed using laboratory findings and physical examinations during the study period. All abnormal reactions were documented.

### 2.6 | Statistical analysis

Statistical comparisons between the investigational and control groups were made using McNemar's test. Statistical comparisons before and after treatment were performed using a paired *t* test or Wilcoxon's signed-rank test. Data are presented as mean ± SD. *P* values < .05 were considered statistically significant. Safety analysis was performed using the paired *t* test or Wilcoxon's signed-rank test for continuous variables and McNemar's test for categorical variables.

## 3 | RESULTS

### 3.1 | Efficacy outcome

#### 3.1.1 | Changes in resting state wrinkle severity

Based on clinical photography, the improvement rate (compared with baseline) in the resting state at 12 weeks after the treatment of crow's feet was 48.28% (14/29) in the investigational group and 41.38% (12/29) in the control group. The investigational group showed a 6.9% greater improvement rate compared with the control group, though there was no statistically significant difference (*P* = .5637). Two weeks after the final treatment, the investigational group showed 41.38% (12/29) improvement compared with baseline, while the control group showed 37.93% (11/29) improvement. There was no statistically significant difference between the groups (*P* = .7630). Four weeks after the final treatment, the investigational group showed 48.28% (14/29) improvement compared with baseline, while the control group showed 37.93% (11/29) improvement. There was no statistically significant difference between the groups (*P* = .4386) (Figure 2). The changes in average CFGS values compared with baseline for the DLMR01 and RJR were −0.41 ± 0.50 and −0.38 ± 0.62 at week 2 after treatment, −0.45 ± 0.57 and −0.34 ± 0.67 at week 4, and −0.38 ± 0.68 and −0.34 ± 0.72 at week 12, respectively (Figure 3). Details on the CFGS values in the resting state are shown in Table 2.

#### 3.1.2 | Changes in smiling state wrinkle severity

Compared with baseline values, the improvement rate in the smiling state at 2 weeks after crow's feet treatment was 34.48% (10/29) in the investigational group and 6.9% (2/29) in the control group, with the investigational group showing significantly greater improvement than the control group by 27.59% (*P* = .0047). Four weeks after the final treatment, the investigational group showed 20.69% (6/29) improvement and the control group showed 13.79% (4/29)

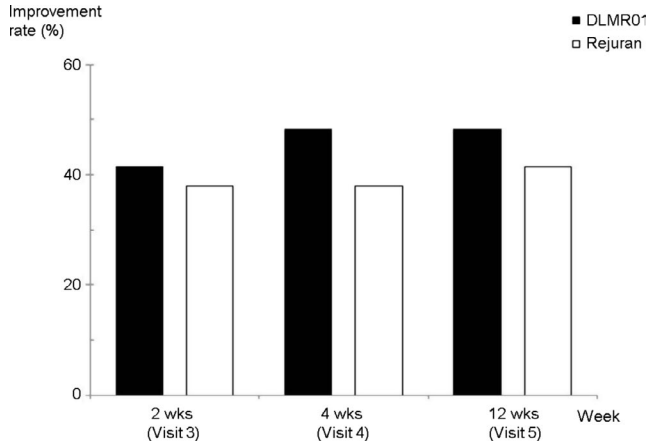


**FIGURE 2** The improvement rate increased by more than 1 CFGS point in the resting state, as evaluated by blinded evaluators

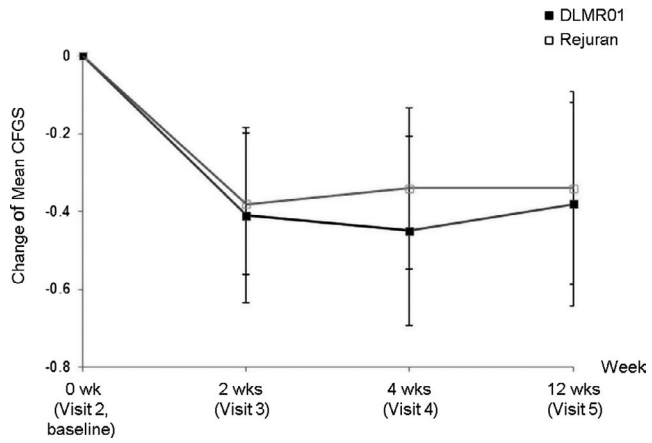


**FIGURE 3** The changes in the average CFGS values compared with baseline, as evaluated by blinded evaluators

improvement. There was no statistically significant difference between the groups ($P$ = .4142). Twelve weeks after the final treatment, both the investigational and control groups showed 17.24% improvement ($P$ = 1.0000) (Figure 4). Details on the CFGS values in the smiling state are shown in Table S1.

### 3.1.3 | Measurement of eye wrinkles using PRIMOS

In the investigational group, the $R_a$ value was significantly decreased at weeks 2 and 4 after treatment compared with baseline ($P$ = .0203, $P$ = .0132). In the control group, the $R_a$ value was significantly decreased at weeks 4 and 12 after treatment ($P$ = .0110, $P$ < .0001). There were no statistically significant differences in the $R_a$ value changes between the groups during the study (Figure 5). Details on the $R_a$ value and other eye wrinkle parameters measured using PRIMOS are shown in Table S2.

## 3.2 | Global Aesthetic Improvement Scale assessments

Global Aesthetic Improvement Scale scores, determined by the injecting investigator or self-assessed by the study subjects, did not show a significant difference between the two groups over 12 weeks. The average GAIS value scores by the injecting investigator for the DLMR01 and RJR were 0.97 ± 0.78 and 0.79 ± 0.62 at week 2 after injection, 1.17 ± 0.76 and 1.07 ± 0.84 at week 4, and 1.03 ± 0.78 and 0.90 ± 0.82 at week 12, respectively. The average GAIS values self-assessed by the study subjects were 1.00 ± 0.80 and 1.03 ± 0.78 at week 2 after injection, 1.59 ± 0.78 and 1.45 ± 0.69 at week 4, and 1.14 ± 0.83 and 1.07 ± 0.65 at week 12, respectively (Figure 6).

## 3.3 | Safety endpoints

Both fillers were well tolerated, and no severe adverse effects were reported by subjects during the study period. No persistent skin abnormalities were observed in the physical examination by the dermatologist. Transient injection site edema (50.00%) was the most common local side effect, followed by injection site pain (23.33%), pruritus (13.33%), and erythema (10.00%). These side effects were detected at a similar frequency in the two groups. No serious systemic adverse events occurred in any subject according to vital signs and laboratory data.

# 4 | DISCUSSION

A PCL-based dermal filler has been recently introduced to the esthetic market, representing a new class of biostimulatory dermal fillers.[6] After injection, the fillers are gradually resorbed over several weeks, during which time the PCL stimulates neocollagenesis. The new collagen replaces the volume of the resorbed portion of the filler. Therefore, after neocollagenesis, a PCL dermal filler may have an elastic modulus almost equal to that of the dermis and is cosmetically more favorable.[7] DLMR01 belongs to the family of microparticle-free PCL-based dermal fillers. The conventional PCL filler is mainly composed of non-cross-linked PCL microspheres (25-50 μm). The aggregation of microspheres can cause a problem by blocking a thin needle during injection. Also, when the microparticles are not uniformly dispersed, they are not uniformly injected into the tissue. DLMR01 is composed of a unique microparticle-free PCL which is homogeneously solubilized in water. Therefore, a gentle injection using a thin needle can be performed without the problem of blockage and it can be uniformly injected into the dermal layer. This also enables the DLMR01 to display a smooth and acceptable extrusion force during procedure.[8] PCL has been used extensively for decades in numerous Conformit Europeene-marked and Food and Drug Administration-approved bioresorbable device applications in the medical and pharmaceutical industries. The PCL dermal filler offers controlled and safe

**TABLE 2** Details on the Crow's Feet Grading Scale values in the resting state, as evaluated by blinded evaluators, and changes in the Crow's Feet Grading Scale values compared with baseline

| Crow's Feet Grading Scale | DLMR01 (N = 29) | RJR (N = 29) | DLMR01—RJR |
|---|---|---|---|
| | n (%) | n (%) | n (%) |
| 0 wk (Baseline) | | | |
| N | 29 | 29 | 29 |
| Mean ± SD | 1.79 ± 0.49 | 1.76 ± 0.64 | −0.03 ± 0.82 |
| Median | 2.00 | 2.00 | 0.00 |
| Min-max | 1.00-3.00 | 1.00-3.00 | −1.00 to 2.00 |
| *P*-value | | | 1.0000 |
| 2 wk | | | |
| N | 29 | 29 | 29 |
| Mean ± SD | 1.38 ± 0.49 | 1.38 ± 0.49 | 0.00 ± 0.53 |
| Median | 1.00 | 1.00 | 0.00 |
| Min-max | 1.00-2.00 | 1.00-2.00 | −1.00 to 1.00 |
| *P*-value | | | 1.0000 |
| 4 wk | | | |
| N | 29 | 29 | 29 |
| Mean ± SD | 1.34 ± 0.48 | 1.41 ± 0.57 | 0.07 ± 0.59 |
| Median | 1.00 | 1.00 | 0.00 |
| Min-max | 1.00-2.00 | 0.00-2.00 | −1.00 to 1.00 |
| *P*-value | | | .7539 |
| 12 wk | | | |
| N | 29 | 29 | 29 |
| Mean ± SD | 1.41 ± 0.57 | 1.41 ± 0.50 | 0.00 ± 0.60 |
| Median | 1.00 | 1.00 | 0.00 |
| Min-max | 1.00-3.00 | 1.00-2.00 | −1.00 to 1.00 |
| *P*-value | | | 1.0000 |
| 2-0 wk (baseline) | | | |
| N | 29 | 29 | 29 |
| Mean ± SD | −0.41 ± 0.50 | −0.38 ± 0.62 | 0.03 ± 0.73 |
| Median | 0.00 | 0.00 | 0.00 |
| Min-max | −1.00 to 0.00 | −2.00 to 1.00 | −2.00 to 1.00 |
| *P*-value | .0005* | .0059* | 1.0000 |
| 4-0 wk (baseline) | | | |
| N | 29 | 29 | 29 |
| Mean ± SD | −0.45 ± 0.57 | −0.34 ± 0.67 | 0.10 ± 0.94 |
| Median | 0.00 | 0.00 | 0.00 |
| Min-max | −1.00 to 1.00 | −2.00 to 1.00 | −2.00 to 2.00 |
| *P*-value | .0010* | .0195* | .6921 |
| 12-0 wk (baseline) | | | |
| N | 29 | 29 | 29 |
| Mean ± SD | −0.38 ± 0.68 | −0.34 ± 0.72 | 0.03 ± 0.94 |
| Median | 0.00 | 0.00 | 0.00 |
| Min-max | −1.00 to 1.00 | −2.00 to 1.00 | −2.00 to 2.00 |
| *P*-value | .0127* | .0296* | .9646 |

Statistical comparisons in this table were performed using a Wilcoxon's signed-rank test: *P*-values.
*Statistically significant.

bioresorption via hydrolysis of the polymer ester linkages, resulting in nontoxic bioresorption products that are resorbed through the normal metabolic pathways and readily excreted.[9] Owing to the characteristic anatomy of the crow's feet area that has relatively little subcutaneous fat, lots of habitual movement, and considerable sunlight exposure, it is very important to choose an appropriate type of dermal filler. In the past, numerous fillers were used to achieve a simple volumizing effect, whereas biostimulatory dermal filler can also stimulate fibroblast growth for skin rejuvenation and is more suitable for skin regeneration. It facilitates the increased production of amorphous extracellular matrix components and fibrillar substances and can reduce fine wrinkles and improve skin roughness, elasticity, and tonicity. The present clinical study was designed as a randomized, split-face study involving the simultaneous injection of DLMR01 and RJR fillers into each crow's feet area. While our results showed a difference in the improvement rate between DLMR01 and RJR of 6.9% in the resting state at 12 weeks, there was no statistical significance ($P$ = .5637). In addition, both the investigational and control groups showed the same 17.24% improvement in the smiling state at 12 weeks. There were no statistically significant differences in the $R_a$ value changes or GAIS between the groups. Therefore, DLMR01 appears to be clinically comparable to RJR in terms of efficacy. No unpredictable serious adverse events were observed during the study period, and only mild transient swelling and pain were reported, which are common local reactions after filler injection. Our results indicate that the administration of DLMR01 is generally safe. Kim et al[7] reported that PCL-based dermal filler is capable of exerting neocollagenesis for more than 13 months after injection in human tissue. Galadari et al[6] revealed that PCL dermal fillers offer longer-lasting cosmetic performance than hyaluronic acid (HA) dermal fillers in nasolabial fold treatment. It is demonstrated that the unique tunable longevity profile of PCL allows the dermal filler to persist up to 4 years.[10] However, polynucleotide group fillers such as RJR showed similar durability to non-cross-linked HA filler in clinical and animal study.[3] Therefore, PCL-based dermal fillers may be more suitable for those who prefer long-lasting effects. Since sufficient comparison studies are not yet available between them, further clinical and histological analyses are required. To our knowledge, this is the first time that a PCL-based dermal filler has been compared with another biostimulatory filler in terms of

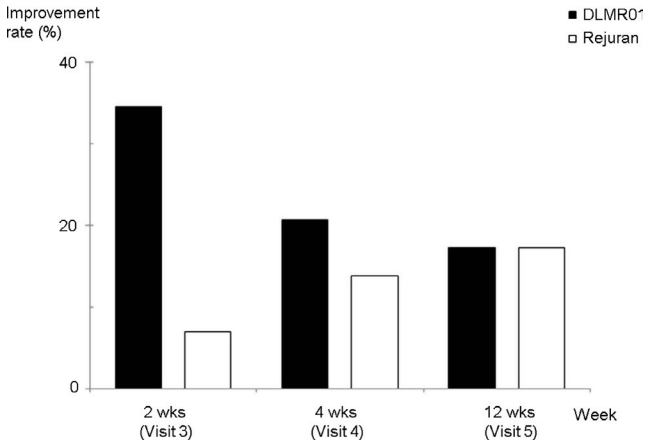


**FIGURE 4** The improvement rate increased by more than 1 CFGS point in the smiling state, as evaluated by blinded evaluators

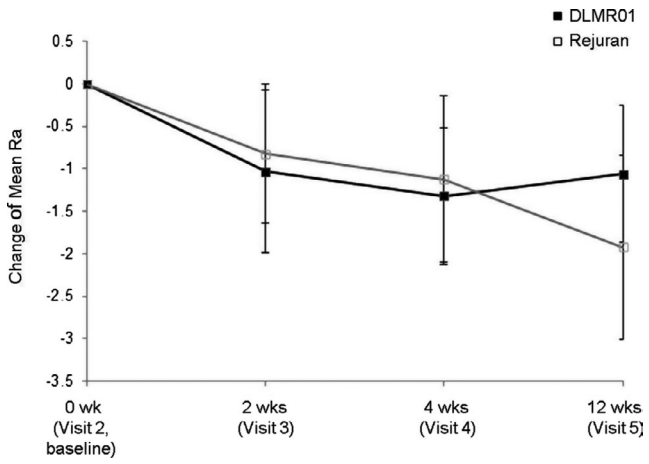


**FIGURE 5** The changes in the average $R_a$ values compared with baseline

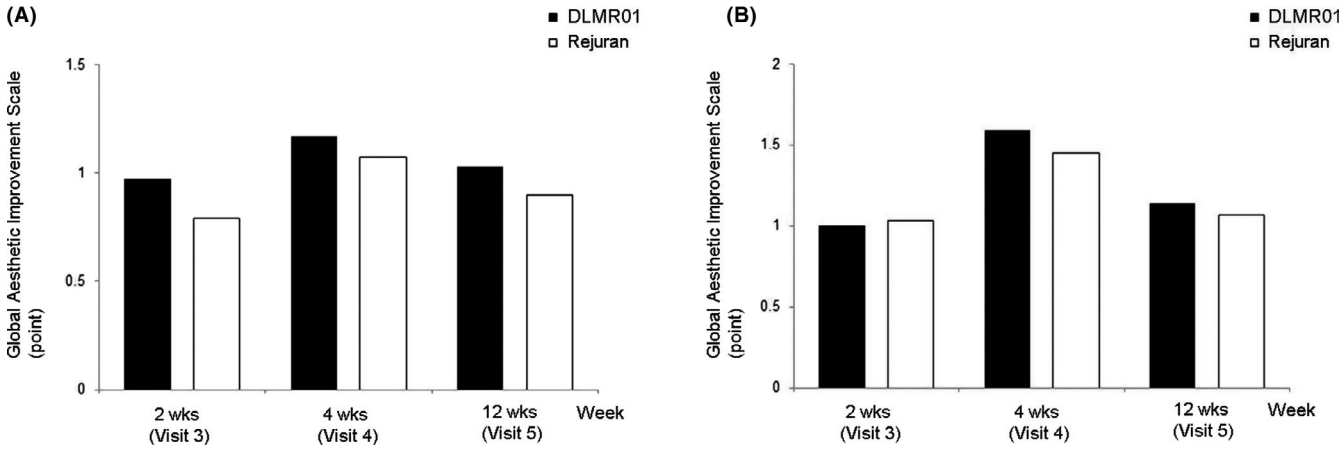


**FIGURE 6** The average GAIS values, as evaluated by the (A) injecting investigator and (B) study subjects

efficacy and safety in the treatment of crow's feet. In this study, we showed that the novel DLMR01 is safe and performs similarly to RJR over 12 weeks. We expect that DLMR01 will widen the available selection of appropriate filler products to treat crow's feet in a variety of patients.

## CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

## ORCID

*Guk Jin Jeong* https://orcid.org/0000-0002-2379-0370
*Ga Ram Ahn* https://orcid.org/0000-0002-5696-4699
*Su Jung Park* https://orcid.org/0000-0001-9314-6401
*Ji Yeon Hong* https://orcid.org/0000-0002-5632-8449

## REFERENCES

1. Avantaggiato A, Palmieri A, Carinci F, Pasin M, Bertuzzi G. Biostimulation and biorevitalization: effects on human skin fibroblasts. *Ann Oral Maxillofac Surg*. 2013;1(2):11.
2. Cavallini M, Papagni M. Long chain polynucleotides gel and skin biorevitalization. *Int J Plast Dermatol*. 2007;3:27-32.
3. Pak CS, Lee J, Lee H, et al. A phase III, randomized, double-blind, matched-pairs, active-controlled clinical trial and preclinical animal study to compare the durability, efficacy and safety between polynucleotide filler and hyaluronic acid filler in the correction of crow's feet: a new concept of regenerative filler. *J Korean Med Sci*. 2014;29(Suppl 3):S201-S209.
4. Kruglikov IL. Neocollagenesis in non-invasive aesthetic treatments. *J Cosmet Dermatol Sci Appl*. 2013;3(1):1-5.
5. Cavallini M. . Biorevitalization ano cosmetic surgery of the face: synergies of action. *J Appl Cosmetol* 2004;22:125-132.
6. Galadari H, van Abel D, Al Nuami K, Al Faresi F, Galadari I. A randomized, prospective, blinded, split-face, single-center study comparing polycaprolactone to hyaluronic acid for treatment of nasolabial folds. *J Cosmet Dermatol*. 2015;14(1):27-32.
7. Kim JA, Van Abel D. Neocollagenesis in human tissue injected with a polycaprolactone-based dermal filler. *J Cosmet Laser Ther*. 2015;17(2):99-101.
8. de Melo F, Marijnissen-Hofste J. Investigation of physical properties of a polycaprolactone dermal filler when mixed with lidocaine and lidocaine/epinephrine. *Dermatol Ther (Heidelb)*. 2012;2(1):13.
9. Moers-Carpi MM, Sherwood S. Polycaprolactone for the correction of nasolabial folds: A 24-month, prospective, randomized, controlled clinical trial. *Dermatol Surg*. 2013;39(3pt1):457-463.
10. Bae B, Lee G, Oh S, Hong K. Safety and long-term efficacy of forehead contouring with a polycaprolactone-based dermal filler. *Dermatol Surg*. 2016;42(11):1256-1260.

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

**How to cite this article:** Jeong GJ, Ahn GR, Park SJ, Hong JY, Kim BJ. A randomized, patient/evaluator-blinded, split-face study to compare the efficacy and safety of polycaprolactone and polynucleotide fillers in the correction of crow's feet: The latest biostimulatory dermal filler for crow's feet. *J Cosmet Dermatol*. 2019;00:1–7. https://doi.org/10.1111/jocd.13199