


## ORIGINAL CONTRIBUTION

# A randomized study showing improved skin quality and aesthetic appearance of dorsal hands after hyaluronic acid gel treatment in a Chinese population

Yan Wu MD, PhD<sup>1</sup> | Yan Tian MD, PhD<sup>2</sup> | Jinhua Xu MD, PhD<sup>3</sup> |  
Shaomin Zhong MD, PhD<sup>1</sup> | Ruiyan Wang MD<sup>2</sup> | Wenyu Wu MD, PhD<sup>3</sup> 

<sup>1</sup>Peking University First Hospital, Beijing, China

<sup>2</sup>Air Force General Hospital PLA, Beijing, China

<sup>3</sup>Fudan University Huashan Hospital, Shanghai, China

## Correspondence

Wenyu Wu, Fudan University Huashan Hospital, No. 12 Middle Wulumuqi Road, Jing'an District, Shanghai, China.  
Email: william88888@139.com

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Galderma

## Abstract

**Background:** Patients are increasingly aware of the aesthetic appearance of aging hands.

**Aims:** To evaluate efficacy and safety of a hyaluronic acid gel for improving skin quality in aged skin of the dorsal hand.

**Methods:** This was a 15-month randomized, multi-center, evaluator-blinded, split-hand, no treatment-controlled study. Three treatments with hyaluronic acid gel were administered in the same hand in adult Chinese subjects with grade 2 or 3 (mild or moderate aging) on the Hand Grading Scale (HGS). The primary objective was to evaluate the difference at 3 months between treated and untreated hands, based on the blinded evaluator's HGS assessment. Secondary assessments included the Global Aesthetic Improvement Scale (GAIS), biophysical measurements (skin elasticity, skin roughness and hydration), and subject satisfaction. Safety was evaluated by incidence of adverse events.

**Results:** A total of 100 subjects were enrolled. Clinically relevant differences in HGS favored HA gel ( $P < .0001$ ). At 15 months, 87%-96% of treated hands were still improved according to GAIS (per evaluator and subject, respectively). Objective measures of skin quality improved, confirmed by evaluators and highly satisfied subjects. Treatment was well tolerated.

**Conclusions:** Hyaluronic acid treatment improved skin quality and reduced the aging appearance of the hand, with high subject satisfaction.

## KEYWORDS

Chinese, hand rejuvenation, hyaluronic acid, Restylane skinboosters, skin quality

## 1 | INTRODUCTION

Although hyaluronic acid (HA) fillers have traditionally been used and studied in the aesthetic rejuvenation and volume enhancement

of aging skin, particularly facial lines and folds,<sup>1</sup> there is a growing interest in ameliorating skin texture itself.<sup>2</sup> Aging skin is characterized by decreased concentrations of HA and collagen, resulting in reduced skin hydration and elasticity and thereby increased fine lines, roughness, and irregular pigmentation.<sup>2-4</sup>

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Compared to the face, reversing the impact of aging on skin quality of the hands has been less extensively studied. Treatment options range from rejuvenation with fillers, microdermabrasion, chemical peels, intense light sources, and laser therapy, to autologous fat injections and fat grafting.<sup>5,6</sup> However, subdermal injections or even surgical intervention to increase volume does not necessarily improve skin texture or dryness.<sup>7</sup> The intradermal use of Restylane® Vital (RES<sub>V</sub>, also known as Restylane Skinboosters; Galderma/Q-Med) was approved for marketing in Europe in 2004 and several other countries since then. RES<sub>V</sub> has been shown to be safe and effective for skin rejuvenation of the aging hand, restoring skin hydrobalance and improving skin structure and elasticity.<sup>4,8,9</sup>

The current study is the first to evaluate RES<sub>V</sub> in a Chinese population and in a larger number of individuals beyond 1 year. In this study, efficacy and safety of RES<sub>V</sub> were evaluated for aged skin of the dorsal hand using both objective and subjective methods.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design

This 15-month randomized, multi-center, evaluator-blinded, split-hand, no treatment-controlled study (Clinicaltrials.gov ID: NCT02545608) enrolled 100 subjects for the efficacy and safety analysis. RES<sub>V</sub> was evaluated on aged skin of the dorsal hand compared to the untreated control hand. Three treatment sessions with RES<sub>V</sub> were administered in the same hand to improve structure, hydration, and elasticity of the skin. The study was conducted at three clinics in China from October 19, 2015, to March 15, 2017. All subjects provided informed consent. The study protocol was approved by independent ethics committees and conformed to the ethical principles in the Declaration of Helsinki.

### 2.2 | Eligibility criteria

Eligible subjects were Chinese males or females aged 18 years or older, with a grade 2 or 3 on the Hand Grading Scale (HGS) (mild loss of fatty tissue and slight visibility of veins, or moderate loss of fatty tissue and mild visibility of veins and tendons), with the same grade in both hands.

Subjects were excluded if they had active skin disease, inflammation or related conditions in the hand, if they had undergone any previous nonpermanent or permanent implant/filler in the hands (including autologous fat), or if they had an aesthetic treatment/procedure in the hands within the previous 6 months. Subjects with previous hand surgery (including sclerotherapy), fibrosis, scarring or deformities, or a disease that may have affected peripheral circulation were also excluded. Females who were pregnant or breastfeeding were ineligible to participate. Drugs known to increase coagulation time were withdrawn for 2 weeks prior to study treatment.

### 2.3 | Treatment procedure

Subjects were randomized using an electronic case report form system. One hand was randomly assigned to be treated with RES<sub>V</sub> and the opposite hand to no treatment. Subjects were offered topical anesthesia prior to injection. A volume of 0.5-1 mL RES<sub>V</sub> per hand and treatment session was allowed. The product was administered into the intradermal layer of the skin (deeper part of dermis was recommended) using a thin-gauge needle (30G), distal to the dorsal wrist crease and proximal to the metacarpophalangeal joints. The micropuncture technique (injections approximately 0.5 – 1 cm apart) or the short linear technique was used. Massage and ice application could be performed after treatment.

All subjects were administered RES<sub>V</sub> (in the same hand), with the first treatment on day 1, followed by two additional treatment sessions at 1 and 2 months. Subjects were offered optional treatment of the control (untreated) hand with RES<sub>V</sub> at 6 months, followed by one to three additional treatment sessions at a 4-week interval to obtain the same treatment result in both hands.

### 2.4 | Biophysical measurements of skin quality

Biophysical measurements were performed in an air-conditioned room under standardized climate conditions, following acclimatization for 30 minutes. Subjects were asked to avoid physical exercise and sauna 12 hours prior to the visit, and to avoid drinking coffee or smoking 2 hours prior to the visit. Measurements were performed pretreatment at the baseline visit and at all follow-up visits (up to 15 months) for the RES<sub>V</sub>-treated hand, and at follow-up visits up to 6 months for the control hand.

#### 2.4.1 | Skin elasticity

Elastic properties of the skin were evaluated using a suction-based method with the Cutometer MPA 580® (Courage + Khazaka electronic GmbH). The parameter R2 (gross elasticity) was calculated from the curves.

#### 2.4.2 | Skin surface roughness

Silicon Replicas (Repliflo, Cuderm Corp) were used for in vitro assessment of skin surface roughness. A silicon rubber impression material was applied on the skin surface, and the replica was evaluated using 3D digital fringe projection (PRIMOS Lite 3D Sensor 45x30, GF Messtechnik GmbH). The skin surface roughness parameter R<sub>z</sub> (mean depth of roughness) was evaluated.

#### 2.4.3 | Skin Hydration

A MoisturemeterEpiD (Delfin Technologies Ltd) was used to assess skin hydration. The value increases with increasing water content.

The dielectric constant value was converted into tissue water content in percentage.

## 2.5 | Outcome assessments

The primary objective of this study was to evaluate the within-subject difference at 3 months between the RES<sub>v</sub>-treated hand and the untreated hand, based on the blinded evaluator's live assessment of the severity of hand aging using a validated HGS photograph scale.<sup>10</sup> Secondary and exploratory objectives were to evaluate the severity of hand aging as measured by HGS, aesthetic improvement of the dorsal hands for live assessment by both blinded evaluator and subject using the 5-grade Global Aesthetic Improvement Scale (GAIS), improvement of skin elasticity, skin surface roughness and skin hydration as evaluated by biophysical measurements, the blinded evaluator's judgment by live assessment of which hand had the best skin quality at 3 and 6 months, and subject satisfaction. Safety objectives were the evaluation of adverse events (AEs) throughout the study and anticipated injection-related reactions using subject diaries. The blinded evaluator remained blinded throughout the study by not being allowed to be present during injections or to discuss treatments with the treating investigator or the subjects.

## 2.6 | Statistical methods

A difference of 1 in hand grading score at Week 12 as assessed by the blinded evaluator was assumed to be meaningful when comparing the RES<sub>v</sub>-treated hand with the untreated control hand. Assuming a standard deviation of 2.6, a power of 90% and a paired t test with significance level 0.05, a sample size of 73 subjects would be needed for the primary efficacy evaluation. It was estimated that approximately 100 subjects would provide a reasonable amount of safety data of RES<sub>v</sub> in a split-hand study design. Three analysis populations were defined for the study: the safety population and intention-to-treat (ITT) population (all subjects who were injected at least once), and per protocol (PP) population (all ITT subjects who completed the 3-month visit without major deviation and had available data at 3 months for the primary and secondary variables). All statistical analyses were performed using the SAS<sup>®</sup> system version 9.4.

All efficacy analyses were performed on the ITT population. The primary analysis was also performed on the PP population. For HGS scores and the continuous variables, p-values were obtained using

**TABLE 1** Demographic data and baseline characteristics

	n (%)
Gender	
Male	4 (4.0%)
Female	96 (96.0%)
Age (y)	
Mean ± SD	48.5 ± 11.2
Min, Max	23, 74
Ethnicity	
Han Chinese	93 (93.0%)
Other Chinese	7 (7.0%)
Baseline Hand Grading Scale score	
Score 2	71 (71.0%)
Score 3	29 (29.0%)

paired t tests. For the categorical variables (GAIS and skin quality), p-values were obtained using McNemar's tests. A post hoc analysis was performed regarding change from baseline in the HGS score and biophysical measurements in order to include visits between 9 and 15 months. Safety data were analyzed descriptively.

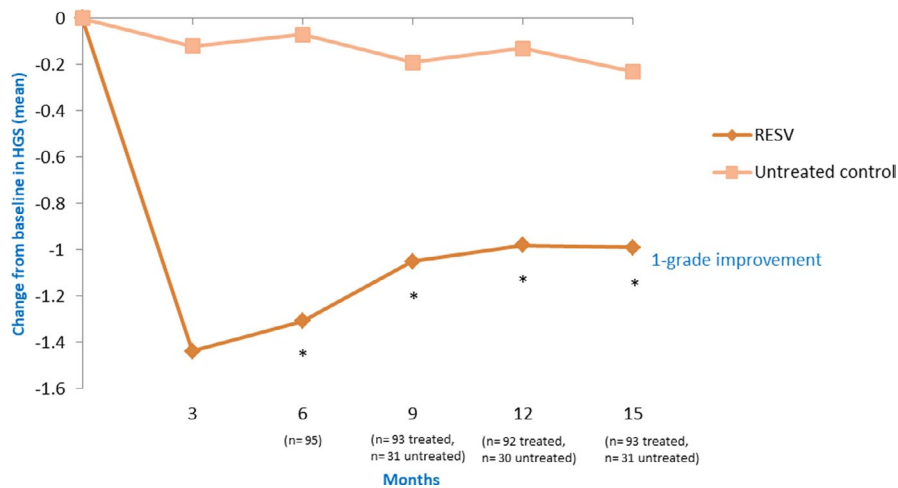
## 3 | RESULTS

### 3.1 | Subject disposition, demographic, and injection data

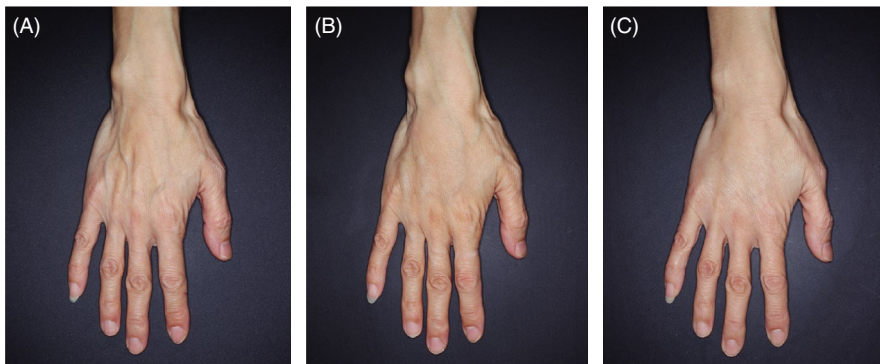
A total of 100 subjects were enrolled and 7 withdrew from the study (5 by the subject's request, 1 lost to follow-up, and 1 due to wrong inclusion). The ITT and safety populations both comprised the 100 subjects enrolled, and the PP population included 91 subjects. Demographic and baseline data are presented in Table 1, and injection details are presented in Table 2. Patients were 49 years of age on average (ranging from 23 to 74 years) and were mainly of Han Chinese background (93%). The majority (71%) had a HGS of 2 (moderate) and the rest had a score of 3 (severe). None of the subjects had previously experienced surgeries or revitalization treatments of their hands. The mean total volume of RES<sub>v</sub> injected over the 3 treatment sessions was 2.88 mL. The micropuncture injection technique was used for the majority (95%) of treatments in the RES<sub>v</sub> hand and for all optional treatments of the control hand. The alternative injection technique was the short linear technique with or without

**TABLE 2** Volume (mL) injected per treatment session (safety population)

	RES <sub>v</sub> hand			
	Session 1	Session 2	Session 3	Total
N	100	97	95	100
Mean ± SD	1.00 ± 0.01	0.98 ± 0.07	0.98 ± 0.09	2.88 ± 0.38
Median	1.00	1.00	1.00	3.00
Range	0.9-1.0	0.5-1.0	0.5-1.0	1.0-3.0



**FIGURE 1** Mean change from baseline in blinded evaluator HGS (ITT)<sup>†</sup>. \* $P < .0001$  for RES<sub>V</sub> vs baseline. <sup>†</sup> Some subjects received optional treatment on the control hand after 6 mo; therefore, data shown from 9 to 15 mo refer to those who did not receive optional treatment



**FIGURE 2** Photographs of a 57-y-old female subject treated with 1 mL RES<sub>V</sub> in the right hand at baseline, 1 mo, and 2 mo, using the micropuncture technique: A, baseline, B, 6 mo, and C, 15 mo

the micropuncture technique. The majority of subjects chose to use topical local anesthesia prior to treatment.

### 3.2 | Efficacy

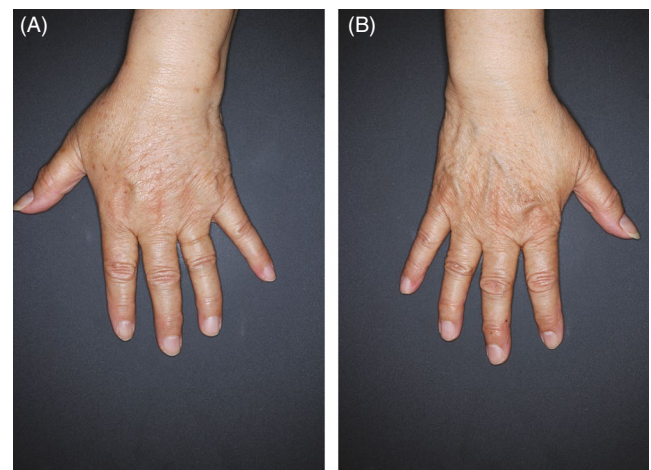
#### 3.2.1 | Primary objective: Severity of hand aging (HGS score)

The primary objective of the study was met according to live assessments of the severity of hand aging performed by the blinded evaluator. The within-subject difference in HGS score between the RES<sub>V</sub> hand and control hand was statistically significant at 3 months (mean HGS score difference of  $-1.32$  between hands,  $P < .0001$ ). Furthermore, a significant improvement in HGS score was maintained throughout the whole study period ( $P < .0001$  compared to baseline at all visits), with a sustained 1-grade (0.99) improvement in HGS compared with baseline at 15 months for the RES<sub>V</sub> hand (Figure 1). Photographs of representative subjects' treated hands are shown in Figures 2-4.

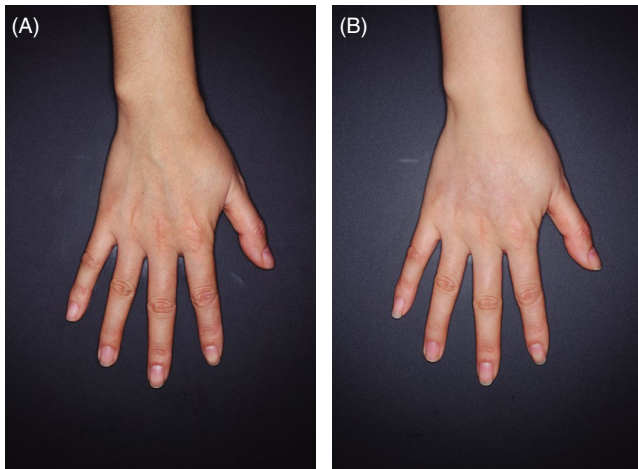
#### 3.2.2 | GAIS

According to the blinded evaluator, treatment with RES<sub>V</sub> also resulted in improvement in GAIS (defined as at least "somewhat improved")

in 96% of subjects at 3 months (Figure 5). Inversely, improvement of GAIS in the untreated control was observed in only 1% of subjects ( $P < .0001$ ). This significant difference in favor of RES<sub>V</sub> was also found at 6 months ( $P < .0001$ ). The GAIS improved for the RES<sub>V</sub> hand throughout the study, particularly at 9 months (approximately 98%). At the last study visit at 15 months, 87% of hands treated with RES<sub>V</sub> were still assessed to be improved. The subject's own evaluation of



**FIGURE 3** Photographs of a 74-year-old female subject treated with 1 mL RES<sub>V</sub> in the left hand at baseline, 1 mo, and 2 mo, using the micropuncture technique: A, 3 mo (treated hand) and B, 3 mo (control hand)



**FIGURE 4** Photographs of a 27-y-old female subject treated with 1 mL RES<sub>V</sub> in the right hand at baseline, 1 mo, and 2 mo, using the short linear technique (baseline and 1 mo) and micropuncture technique (2 mo): A, baseline and B, 3 mo

GAIS for the RES<sub>V</sub> hand was similar to that of the blinded evaluator; at least 96% reported improvement throughout the study. The highest improvement rate was reached at 3 months (99% of subjects), and at 15 months, 96% were still improved.

### 3.2.3 | Skin elasticity

Skin elasticity measured by Cutometer was improved in the RES<sub>V</sub>-treated hand compared to the untreated control hand based on the change from baseline at 3 months in the skin elasticity variable R2 (gross elasticity). The mean difference in change from baseline between hands at 3 months was statistically significant ( $P = .0193$ ), but no difference was found at 6 months. A significant difference in terms of change from baseline in R2 for the RES<sub>V</sub> hand was observed at 12 months ( $P = .0016$ ), but not at other visits. R2 mean values are illustrated in Figure 6.

### 3.2.4 | Skin surface roughness

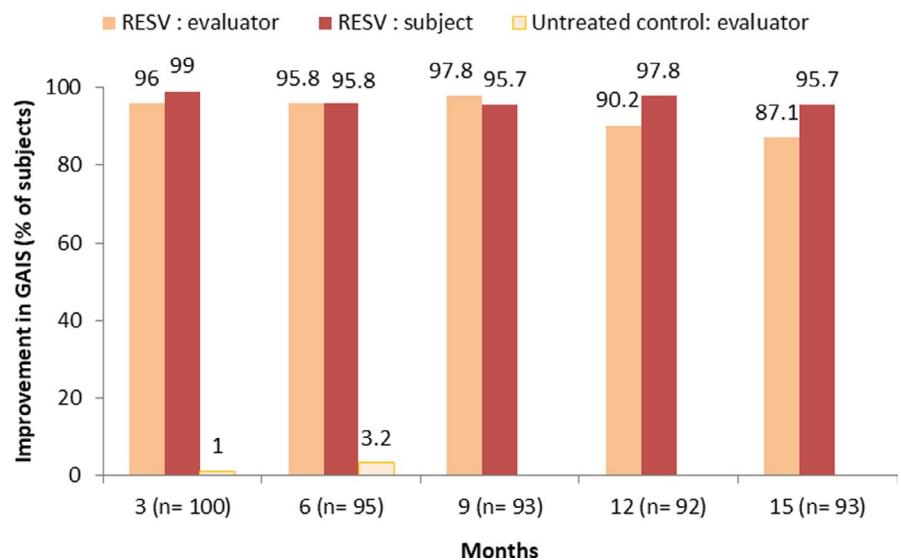
The in vitro assessment of skin surface roughness using silicon replicas was also significantly reduced in RES<sub>V</sub> hands in comparison with control hands, based on change from baseline in the parameter R<sub>z</sub> (mean depth of roughness) both at 3 and 6 months ( $P < .0001$ ). The analysis also showed a significant change from baseline in R<sub>z</sub> for the RES<sub>V</sub> hand throughout the study ( $P < .001$  at all visits except  $P < .05$  at 15 months). The average reduction in skin surface roughness (ie, improvement in skin structure) was maintained throughout the entire study period (Figure 7).

### 3.2.5 | Skin hydration

Skin hydration was improved in RES<sub>V</sub>-treated hands compared to control hands as assessed by change from baseline in tissue water content at 3 months (increased hydration in 12% for RES<sub>V</sub> vs 0.6% for control,  $P < .0001$ ). Similarly at 6 months, an improvement in skin hydration favoring RES<sub>V</sub> was observed (increased hydration in 18.5% for RES<sub>V</sub> vs 4.9% for control,  $P < .0001$ ). A statistically significant increase in tissue water content compared with baseline for RES<sub>V</sub> hands occurred at all study visits ( $P < .0001$ ), indicating sustained improvement in skin hydration. Mean skin hydration values are illustrated in Figure 8.

### 3.2.6 | Blinded evaluation of skin quality

Based on the blinded evaluator's live assessments of skin quality, RES<sub>V</sub> was statistically significantly superior to no treatment at both 3 months (at least 81% difference) and 6 months (at least 87% difference) ( $P < .0001$  for all quality parameters). This indicates that RES<sub>V</sub> compared to the untreated control showed the best treatment effect regarding skin structure, skin hydration, and skin elasticity (Figure 9).



**FIGURE 5** Improvement\* in the blinded evaluator's and subject's GAIS assessment (ITT). \*Improvement is defined as at least "somewhat improved" in GAIS

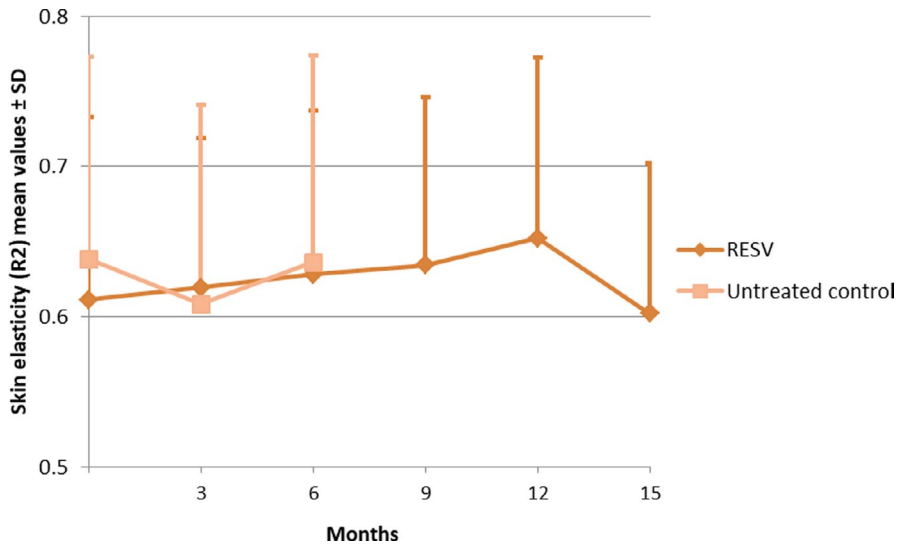


FIGURE 6 Skin elasticity (R2) throughout the study (ITT)

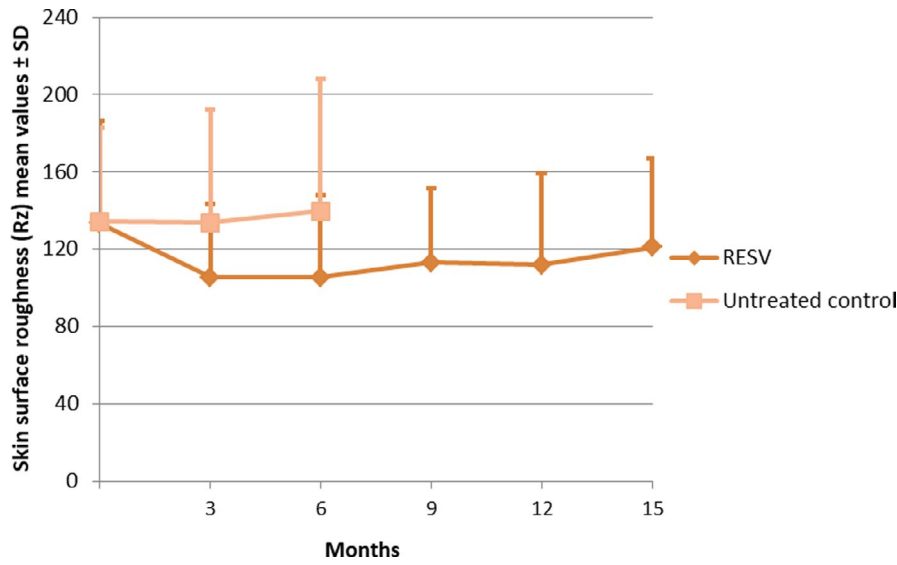


FIGURE 7 Skin surface roughness (Rz) throughout the study (ITT)

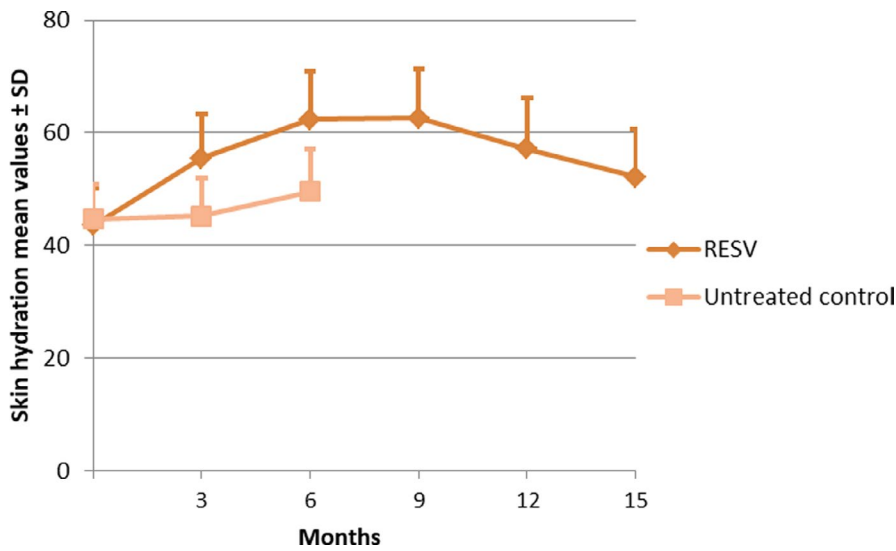


FIGURE 8 Skin hydration throughout the study (ITT)

### 3.2.7 | Subject satisfaction questionnaire

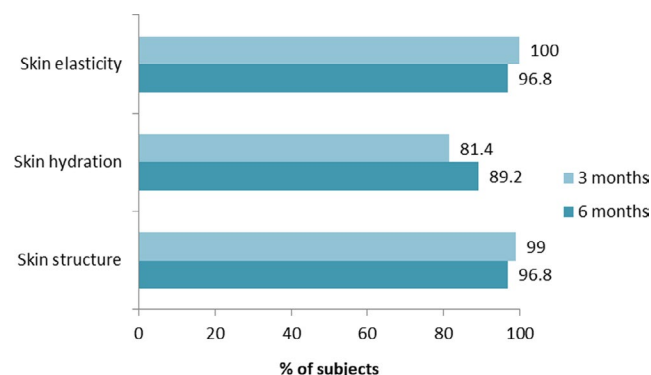
Subject satisfaction regarding treatment with RES<sub>V</sub> was generally high throughout the study, confirming results of the primary and secondary objectives. At both 3 and 6 months of follow-up, approximately 94% of subjects indicated that the RES<sub>V</sub>-treated hand showed the best skin quality with regard to softness, hydration, and elasticity. This is consistent with results of the blinded evaluator's assessment of skin quality.

Questionnaires administered at all visits revealed that most subjects agreed or strongly agreed with all statements (at least 87% at 3 months and 80% at 6 months) (Figure 10A). The natural look of treatment results was sustained throughout the study (88% at 3 months and 86% at 6 months) (Figure 10B). Subjects reported that RES<sub>V</sub> increasingly improved their self-esteem throughout the study (approximately 73% at 9 months to 82% at 15 months). Furthermore, the majority (89%) would recommend the treatment to a friend, and 86% were satisfied or very satisfied with the durability of the results.

### 3.3 | Safety

The majority of the subjects reported anticipated injection-related reactions through the subject diary after the treatments. The most commonly reported local tolerability reactions were redness, bruising, and swelling. The majority were mild in severity and resolved within 2-4 days. There was no increase in frequency, severity, or duration of local tolerability symptoms after repeated treatments in either hand. Anticipated injection site responses that were ongoing at the end of the diary entries were automatically considered to be adverse events (AEs).

In total, 27 treatment-related AEs were reported by 12 (12%) subjects, and the most common were injection site swelling (6%), injection site pain (4%), and injection site discoloration (4%). Most related AEs were mild or moderate. Five subjects reported related AEs with delayed onset (>21 days after last treatment) after the third treatment, such as injection/implant site pruritus, swelling, and discoloration. All AEs with delayed onset were resolved at study



**FIGURE 9** Blinded evaluation of skin quality: proportion of subjects with best treatment effect in RES<sub>V</sub> hand (ITT)

completion. No subjects withdrew from the study due to an AE, and there were no serious AEs reported that were treatment-related. Two pregnancies were reported in the study and were terminated by elective abortion.

## 4 | DISCUSSION

This study demonstrates an improvement in clinical appearance and skin physiology parameters of dorsal hands after treatment with RES<sub>V</sub>, and it is the first in a Chinese population. These results are particularly relevant to hand rejuvenation, since the hand is one of the most exposed parts of the body and one of the first areas to show signs of aging, and there is a trend toward increased awareness of the aesthetic appearance of hands. Indeed, many patients who undergo facial rejuvenation notice a discrepancy between their improved facial appearance and the aged appearance of their hands.<sup>5</sup> Premature skin aging is common and can occur not only due to sun exposure, but also smoking, alcohol consumption, and low body mass index (BMI) have been found to influence skin aging in Chinese subjects.<sup>11</sup> HA filler use across ethnic populations is also of interest to study for the hands, due to a different aging process in this area, with a 10-year delay in onset of age-related changes of skin from the dorsal hand in Chinese subjects compared to Caucasians.<sup>12</sup>

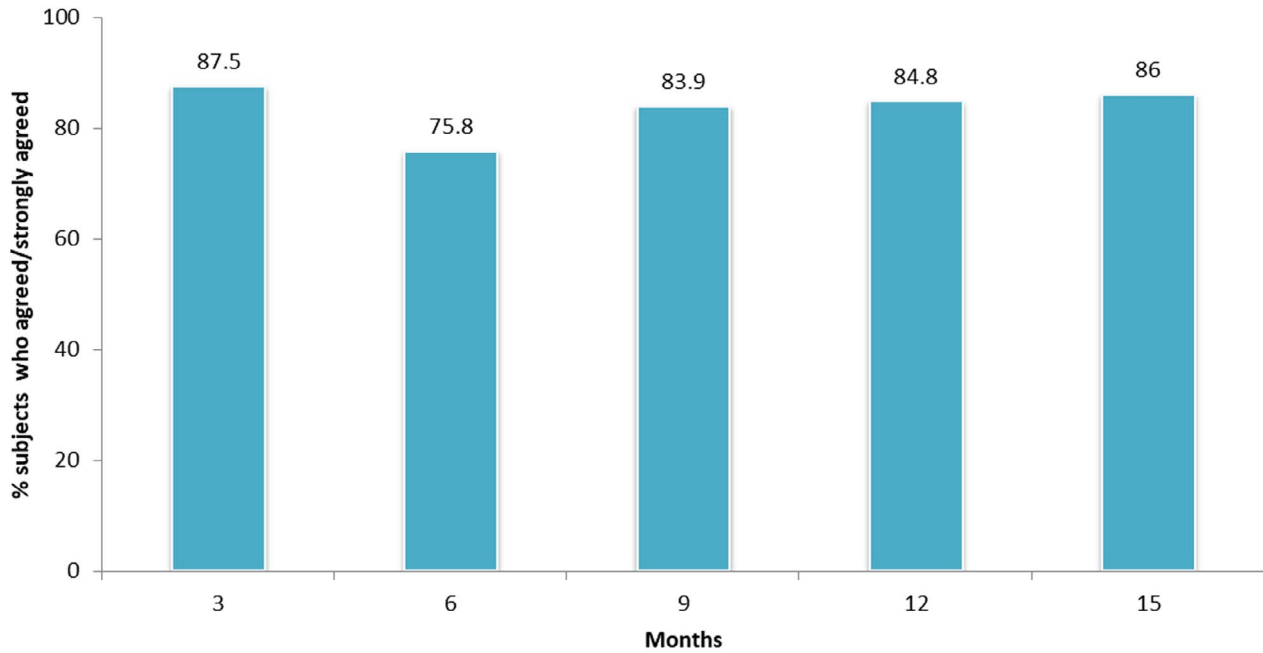
For the primary endpoint at 3 months, the difference in the mean HGS score between treated and untreated hands statistically significantly favored RES<sub>V</sub> treatment ( $P < .0001$ ), indicating reduction in the severity of hand aging. It was concluded that a statistically significant treatment effect was maintained throughout the whole study period ( $P < .0001$  at all visits), with a sustained 1-grade (0.99) improvement in HGS compared with baseline at the last visit. Furthermore, blinded evaluation of aesthetic improvement using GAIS resulted in high improvement rates at all follow-up visits, and after 15 months, the improvement rate was still 87% in the RES<sub>V</sub>-treated hand.

Similarly to the blinded evaluator, the great majority of subjects (at least 96%) reported improvement in their RES<sub>V</sub>-treated hand according to GAIS. Consequently, subjects reported high levels of satisfaction, and 94% indicated that the RES<sub>V</sub>-treated hand showed the best skin quality with regard to softness, hydration, and elasticity. They consistently considered RES<sub>V</sub> treatment to be natural and that it improved their self-esteem throughout the study, and the majority of subjects were satisfied or very satisfied with the durability of the results.

Additionally, the improved clinical appearance of RES<sub>V</sub>-treated hands (shown by HGS and both the evaluator's and subject's GAIS assessments) was further confirmed by ameliorated objective biophysical measurements. Statistically significant improvements for RES<sub>V</sub> hands compared to baseline were maintained until 12 months in terms of improved skin elasticity ( $P = .0016$ ), and through the end of the study at 15 months in terms of reduced skin surface roughness ( $P < .001$  at all visits except  $P < .05$  at 15 months) and improved skin hydration ( $P < .0001$  at all visits). This improvement in skin quality parameters was confirmed by the blinded evaluator's live

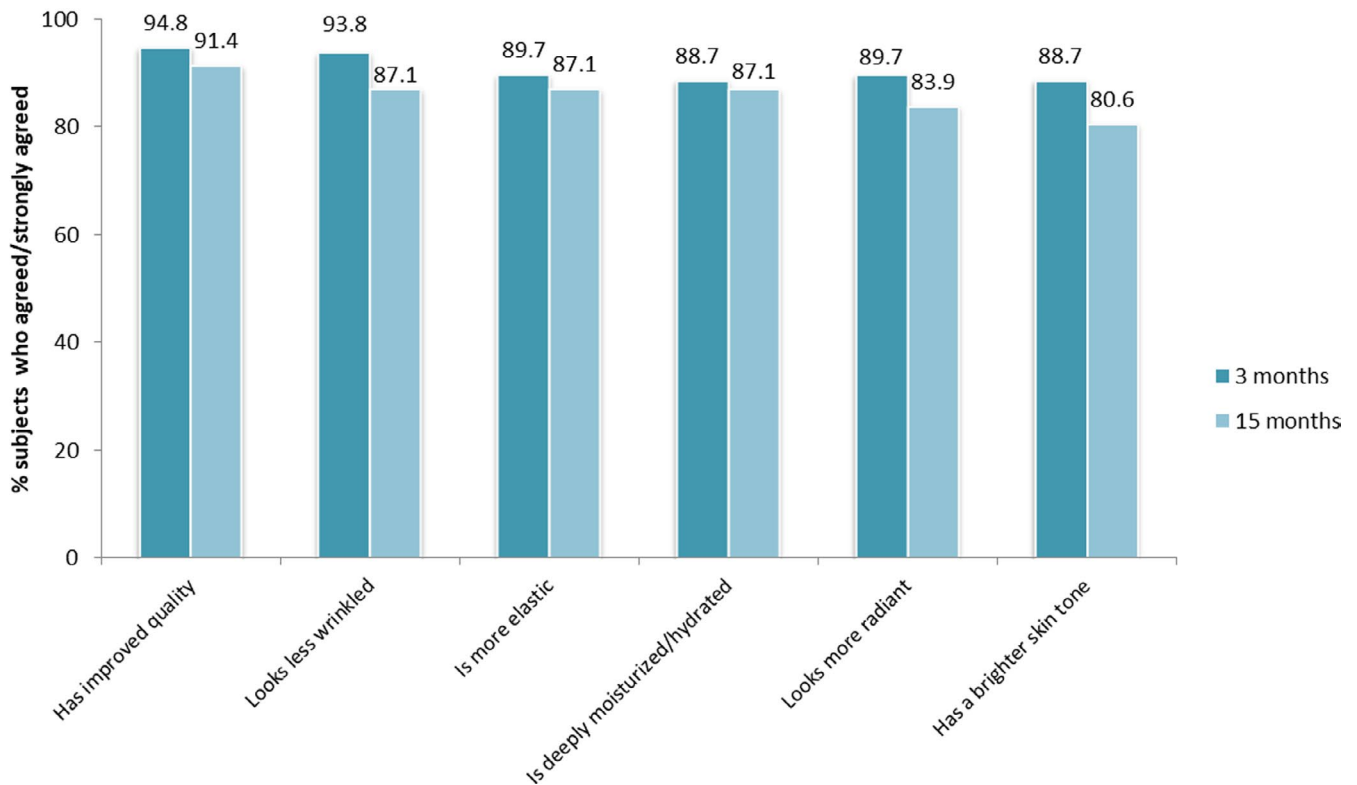
(A)

**"The effect of the treatment looks very natural."**



(B)

**"Compared to before having treatment with RESV, the skin on my hand..."**



**FIGURE 10** Subject satisfaction (A) the natural look of treatment with RES<sub>v</sub> and (B) compared to before treatment

assessment of skin quality. The objectively measured improvement in skin quality parameters may be related to the production of new collagen and slowing of the aging process, as HA gel injections have been found to stimulate de novo synthesis of collagen and partially

restore dermal matrix components that decrease in photodamaged or aging skin.<sup>13,14</sup>

RES<sub>v</sub> was well tolerated following injection. Five subjects had AEs with delayed onset occurring over 21 days after treatment. Four



of these subjects were found to have occupational risk factors for developing hand skin irritation, such as frequent hand washing.

A limitation of this study includes that a treatment control (eg, using normal saline) was not used; however, investigators confirmed that this was not preferred due to ethical concerns. Moreover, there are no other similar treatments in China with the same intended use.

Results from the present study are consistent with similar studies with smaller sample sizes performed with RES<sub>v</sub> in the rejuvenation of dorsal hands in non-Chinese populations.<sup>4,8,9</sup> Treatment with RES<sub>v</sub> has previously led to significant improvement in both biophysical properties (skin elasticity, skin hydration, and skin surface roughness) and the clinical hand aging score.<sup>4,8</sup> The unique methodology was similar to that of the 12-month study led by Gubanova et al, in that clinical (from a blinded evaluator), biomechanical (skin hydration, elasticity, and roughness) and subjective measurements (self-assessment questionnaires) were obtained.<sup>8</sup> Our study also achieved encouraging results without necessitating the use of a twice-daily whitening cream, since we focused more on other aspects of skin quality parameters that are perceived to be important by patients beyond pigmentation.

The blinded evaluator's assessment of skin quality favoring RES<sub>v</sub> in the current study (over 81% and 87% difference at 3 and 6 months, respectively;  $P < .0001$ ) is in line with the previous study by Gubanova, where evaluation of efficacy by a blinded independent expert was approximately 87% at 3 months.<sup>8</sup> Indeed, ameliorated skin quality using RES<sub>v</sub> was even observed in younger patients (eg, Figure 4 in a 27-year-old), where there was improvement with treatment in terms of less visible veins. This product targets not only symptoms of aging but also skin quality, which is essential for all age-groups. Additionally, our study demonstrates not only positive findings in a larger population, but also extends the follow-up beyond 1 year with sustained results.

## 5 | CONCLUSIONS

This study demonstrates that skin rejuvenation of the dorsal hands with RES<sub>v</sub> in a Chinese population is safe and improves the skin structure as shown by reduced severity of apparent hand aging, less skin surface roughness, and ameliorated skin hydration throughout the study. Indeed, objective evaluations of improved skin quality mirrored visible effects assessed by the blinded evaluator and subject. RES<sub>v</sub> treatment resulted in overall aesthetic improvement of the hand and led to high levels of subject satisfaction.

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## ORCID

Wenyu Wu  <https://orcid.org/0000-0003-1803-3006>

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