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PILOT STUDY
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Pilot Study: Single-depth Superficial Ultrasound with Subdermal Injections of Diluted Calcium Hydroxylapatite for Improving Lower Face Skin Quality

Sylvia Ramirez, MD, MPH, MBA,
Dip Derm*
Gunther Scherz, MBA*
Rémi Leprince, MBA†

Background: The lower face can be challenging to treat. We assessed the effectiveness of combining single-depth superficial microfocused ultrasound with visualization (MFU-V, Ultherapy; Merz North America, Inc. Raleigh, N.C.) and subdermal injections of diluted calcium hydroxylapatite (CaHA, Radiesse; Merz North America, Inc. Raleigh, N.C.) in a single session for improving skin quality in the lower face.

Methods: This study enrolled women with moderate-to-severe fine lines and skin unevenness on the lower face who desired nonsurgical intervention. Single-depth MFU-V treatment (10 MHz/1.5 mm) was followed by subdermal injections of diluted (1:1) CaHA. Subjects were followed up for 24 weeks posttreatment. Objective skin quality assessments (Rv: wrinkle depth; R3z: skin unevenness) were performed using LifeViz Micro (QuantifiCare, Sophia Antipolis, France). Subjective assessments included the modified Fitzpatrick Wrinkle Scale visual analog scale, Global Aesthetic Improvement Scale, and global satisfaction scale.

Results: Twelve subjects completed the study. The mean Rv value, mean R3z value, and mean modified Fitzpatrick Wrinkle Scale visual analog scale score improved significantly from baseline to week 24 (mean differences: −0.0321 mm, −0.0684 mm, −1.1667; all $P < 0.001$). All subjects were rated by the investigators as having demonstrated improvement in their overall aesthetic appearance as early as week 4. All subjects were "very satisfied" or "satisfied" with their treatment from week 12 onwards. No unexpected adverse events were reported.

Conclusions: Combination treatment with single-depth superficial MFU-V and diluted CaHA in a single session significantly improved lower facial skin quality, as assessed by both objective and subjective outcome measures. *(Plast Reconstr Surg Glob Open 2024; 12:e6210; doi: 10.1097/GOX.0000000000006210; Published online 3 October 2024.)*

INTRODUCTION

Aging, genetic, and environmental factors contribute to multiple changes in the skin that may manifest as reduced firmness and volume, and uneven or excess pigmentation.[1,2] With the loss of elastin and collagen, facial lines or wrinkles and skin unevenness become more prominent, which can result in a perception of poorer overall skin quality.[1,2] Such perception may have strong psychosocial effects on individuals, negatively affecting their self-esteem and overall well-being.[3,4] There has been a growing global demand for noninvasive procedures, with a recent survey showing facial rejuvenation treatment among the top 10 nonsurgical procedures performed worldwide in 2022.[5]

Aesthetic treatment of the lower face can be challenging due to its intricate anatomy and susceptibility to wrinkles and skin thinning with aging.[6] Treatment modalities for lower facial rejuvenation include topical agents (eg,

*From *Cutis Medical Laser Clinics, Singapore; and †QuantifiCare Asia, Manila, Philippines.*

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Limitations regarding long-term follow-up inherently exist in this article type.

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retinoids and chemical peels), injectables (eg, neurotoxin and dermal fillers), minimally invasive therapies (eg, microneedling), and energy-based devices (eg, laser and ultrasound technology).[7] However, several of these options are limited by drawbacks of the procedure or increased complexity when treating the lower face. For instance, skin resurfacing with peeling agents may lead to side effects such as irritation or permanent scarring.[8] Administering botulinum toxin to the lower face can be challenging due to the complex muscle networks, which can increase the likelihood of undesirable complications like asymmetrical facial expressions and drooling if not properly administered.[6] Excess volumizing with dermal fillers can disrupt overall facial harmony.[6] Although microneedling is generally considered safe, multiple sessions are often needed for optimal outcomes.[9] Laser therapy such as CO_2 laser therapy is associated with high adverse event (AE) rates and long downtime.[10]

A treatment approach that improves firmness and skin quality of the lower face while retaining overall facial harmony, with minimal downtime or side effects, would be desirable.[6,7] Two approaches to correction of facial lines/wrinkles [microfocused ultrasound with visualization (MFU-V, Ultherapy; Merz North America, Inc. Raleigh, N.C.) and diluted calcium hydroxylapatite (CaHA, Radiesse; Merz North America, Inc. Raleigh, N.C.)] have gained popularity. Guided by real-time visualization, MFU-V delivers focused ultrasound energy to precise depths within the skin, creating thermal coagulation points and stimulating endogenous collagen and elastin production.[11,12] The subsequent tissue remodeling promotes skin lifting and increases skin elasticity, leading to improved skin quality.[11,12] MFU-V achieves precise treatment of the target tissue layers while delivering durable results with minimal downtime.[11,12] Diluted CaHA stimulates neocollagenesis and elastogenesis within the injection site through a regenerative biostimulatory response, resulting in skin tightening and increased elasticity.[13,14] Diluted CaHA allows for greater diffusion of CaHA particles within tissues; this reduces the volumizing effect while stimulating collagen and elastin formation.[13]

Both MFU-V and diluted CaHA have individually demonstrated effectiveness in lower facial rejuvenation.[15,16] It was recently reported that treatment with single-depth superficial MFU-V improved accordion lines.[15] This protocol used a single transducer with a focal depth of 1.5 mm administered at a frequency of 10 MHz to target the superficial dermis for skin rejuvenation. Another study reported an improvement in aging severity in the lower face after treatment with hyperdiluted CaHA.[16] because these treatment modalities stimulate *de novo* collagen and elastin formation via different mechanisms,[11–13] combining single-depth superficial MFU-V with diluted CaHA may synergistically enhance skin tightening and elasticity and improve overall skin quality.

Studies have documented the benefits of combined use of multiple-depth MFU-V and diluted CaHA to achieve significant lift and skin tightening in other treatment areas, including the upper arms, neck, and buttocks,[17–19] indicating the feasibility and effectiveness of combining these modalities. In a recent study, combining dual depth MFU-V treatment (7 MHz/3.0 mm and 4 MHz/4.5 mm) with diluted CaHA in a single session resulted in significant improvements in brachial skin laxity and high patient satisfaction 24 weeks posttreatment versus baseline.[17] However, no studies to date have evaluated the combined use of single-depth superficial MFU-V and subdermal injections of diluted CaHA in a single session for lower facial rejuvenation. Hence, we conducted a study to assess the effectiveness of this combined treatment for improving lower face skin firmness and skin quality in women.

Takeaways

Question: Is combining single-depth superficial microfocused ultrasound with subdermal injections of diluted calcium hydroxylapatite effective for lower facial rejuvenation?

Findings: A single session of this combined treatment improved wrinkles and overall aesthetic appearance of the lower face over 24 weeks, with high patient satisfaction and good tolerability.

Meaning: This study demonstrates the effectiveness of combining ultrasound and calcium hydroxylapatite injections for enhancing lower face skin quality in Asian and White women.

METHODS

Study Design

This single-center, prospective, open-label, nonrandomized, single-arm pilot study of healthy female subjects was conducted in Singapore between August 2022 and November 2023. The study was approved by the Parkway Pantai institutional ethics committee (approval reference: PIEC/2022/026) and was conducted in accordance with the Declaration of Helsinki. All subjects provided written informed consent before study initiation. In addition, subjects gave written informed consent to publish their pre- and posttreatment photographs.

Subjects

The complete eligibility criteria are listed in Supplemental Digital Content 1. (**See document, Supplemental Digital Content 1,** which describes the methodology details. **http://links.lww.com/PRSGO/D540**). Briefly, female subjects aged 35–60 years who had moderate-to-severe fine lines [based on the validated modified Fitzpatrick Wrinkle Scale (MFWS)][20] and suboptimal skin quality (ie, the presence of lines/wrinkles and skin unevenness) on the lower face, and seeking improvement in skin quality on the lower face through nonsurgical interventions were included in this study.

Treatment

The procedure consisted of two sequential steps. First, the MFU-V treatment was applied as per the published single-depth superficial MFU-V protocol for accordion lines but doubling the treated area to ensure coverage of the wrinkles on the lower face for a total of 120 lines per side (rather than the previously published 60 lines/side).[15] Subsequently, CaHA was diluted in a 1:1 ratio and administered as per the consensus recommendations for using diluted CaHA as a biostimulatory agent.[21] After injection, the treatment areas were vigorously massaged to ensure that CaHA was evenly distributed. The timing and sequence of administering the modalities for same-day treatment were consistent with published consensus recommendations for combined aesthetic interventions.[22] Oral and/or topical analgesics were provided before the procedure to reduce pain/discomfort (**Supplemental Digital Content 1, http://links.lww.com/PRSGO/D540**).

The treatment areas on the lower face were marked, as shown in Figure 1A. A thin layer of ultrasound gel was applied to the lower face before the transducer was placed on the skin to obtain an ultrasonographic image of the treatment area. The transducer was evenly coupled to the skin surface before treatment was applied. The lower face was treated in a standardized pattern at a single depth using the 10 MHz–1.5 mm depth transducer to target the superficial dermis, as previously described.[15] A total of 240 treatment lines (60 lines per 2.5 x 2.5 cm^2 area) at energy level 2 (0.18 J) were delivered to the treatment areas.

Depending on each subject's availability, diluted CaHA was applied to the lower face either immediately or within a week after MFU-V treatment, as per guidelines' recommendations.[21] A total of 3.0 mL of diluted CaHA was administered to the subdermal plane (1.5 mL per side) using a 25-gauge cannula with a retrograde fanning technique (Fig. 1B).

Study Assessments

Subjects were evaluated at baseline and weeks 4, 12, and 24 after treatment. The primary outcome was the change in skin quality (lines/wrinkles and skin unevenness) of the lower face. The three-dimensional (3D) LifeViz Micro stereophotographic system (QuantifiCare, Sophia Antipolis, France) was used in conjunction with the Dermapix software (QuantifiCare, Cedex, France)[23,24] for 3D visualization and quantitative measurements of skin quality of the lower face. This validated tool has been used for objective assessment of various skin parameters in aesthetic dermatology.[25–29] Two parameters [maximum profile valley depth (Rv) and base roughness depth (R3z)[30,31]] were measured at each visit. Rv and R3z are objective 3D measurements of skin quality provided by the 3D stereophotographic system. These parameters were selected to facilitate understanding of different aspects of skin quality: Rv was used as a measure of wrinkle depth (a lower Rv value denotes shallower lines or wrinkles) and R3z as a measure of skin unevenness (a lower R3z value indicates lesser skin unevenness) (**Supplemental Digital Content 1, http://links.lww.com/PRSGO/D540**).[30,31]

Secondary outcomes included subjective assessments: the MFWS visual analog scale (VAS),[20] Global Aesthetic Improvement Scale (GAIS), and global satisfaction scale (GSS). The MFWS is a clinically validated tool used to assess facial wrinkle severity.[20] Photographs of the lower face were taken at each visit using a standardized photograph-taking tool (VISIA; Canfield Scientific Inc., N.J.) used in clinical studies.[32–34] Blinded investigators evaluated the photographs and rated wrinkle severity using the MFWS (0 = no wrinkle to 3 = deep wrinkle) at each visit. Photographs were assessed for changes in the overall aesthetic appearance using the GAIS (1 = very much improved to 5 = worsened) at each follow-up visit versus baseline. Average ratings across investigators were calculated. Subjects rated their treatment satisfaction using the GSS (1 = very dissatisfied to 5 = very satisfied) at each follow-up visit. AEs were recorded immediately after treatment and at all follow-up visits.

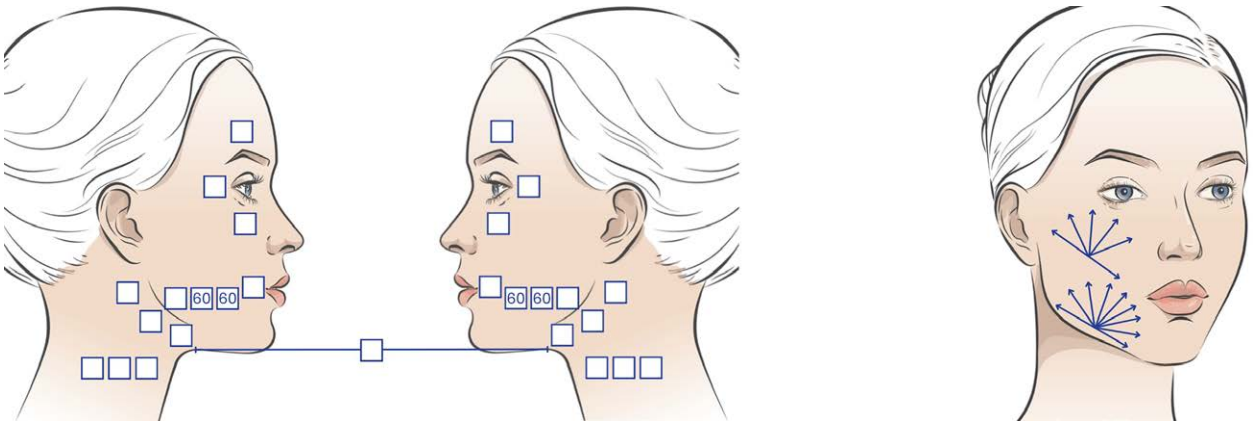


Fig. 1. Treatment administration. A, MFU-V treatment: The lower face was treated in a standardized pattern at a single focal depth using the 10.0 MHz–1.5 mm depth transducer, delivering a total of 240 treatment lines (60 lines per 2.5 × 2.5 cm^2 area). B, CaHA treatment: All subjects received subdermal injections of diluted CaHa 3.0 mL with a 25-gauge cannula using a retrograde fanning technique.

Statistical Analysis

Demographic data, skin surface roughness values (Rv and R3z), and MFWS VAS scores were presented as mean and SD. GAIS ratings, GSS ratings, and AEs were summarized using percentages. General linear models with one-way repeated measures analysis of variance were used to analyze Rv values, R3z values, and MFWS VAS scores. Multiple pairwise comparisons were performed between each visit and baseline to identify the visits with significantly different estimated marginal means relative to baseline. Bonferroni adjustments were applied to reduce the risk of type I error with these multiple comparisons. The Bonferroni adjusted cutoff for statistical significance was set at 0.0167 (0.05 ÷ 3). Statistical analyses were performed using SPSS, version 26.0 (IBM SPSS Statistics for Windows; IBM Corp., Armonk, N.Y.).

RESULTS

Subject Demographics and Baseline Characteristics

Of the 15 female subjects enrolled, three relocated to outside of Singapore during the study, whereas the remaining 12 completed the study. Three-quarters were White (75%, 9 of 12) and the remaining were Asian (25%, 3 of 12; Table 1). The mean age was 49.2 (SD 7.7) years. At baseline, the mean MFWS VAS score was 2.2 (SD 0.4), with all subjects (100.0%) having a VAS score of 2.0 or greater, indicating the presence of moderate-to-deep wrinkles.

Objective Assessment of Change in Skin Quality (Lines/Wrinkles and Skin Unevenness)

The Rv value showed continuous improvement from baseline through weeks 4, 12, and 24 (Fig. 2A). The mean Rv value reduced from 0.132 (SD 0.030) mm at baseline to 0.100 (SD 0.021) mm at week 24. Statistically significant improvements were observed at each follow-up visit, with mean differences of −0.0212 [95% confidence interval (CI) −0.0336, −0.0087 mm; $P = 0.0012$] at week 4, −0.0237 (95% CI −0.0381, −0.0093 mm; $P = 0.0016$) at week 12, and −0.0321 (95% CI −0.0483, −0.0158 mm; $P = 0.0003$) at week 24.

Table 1. Subject Demographics and Baseline Characteristics

Characteristic	All Subjects (n = 12)
Age, y	49.2 (7.7)
Ethnicity	
Asian, n (%)	3 (25)
White, n (%)	9 (75)
MFWS VAS score	2.2 (0.4)
MFWS VAS score, n (%)	
0	0 (0)
1	0 (0)
2	10 (83.3)
3	2 (16.7)

Data presented are mean (SD) unless otherwise stated.

Similarly, there was a progressive improvement in the R3z value from baseline at weeks 4, 12, and 24 (Fig. 2B). The mean R3z value decreased from 0.270 (SD 0.063) mm at baseline to 0.202 (SD 0.047) mm at week 24. The mean R3z value improved significantly from baseline to weeks 12 and 24, with mean differences of −0.0494 (95% CI −0.0792, −0.0196 mm; $P = 0.0015$) and −0.0684 (95% CI −0.0951, −0.0417 mm; $P = 0.0000$), respectively. There was an improvement in mean R3z value even at four weeks; however, this was of borderline statistical significance (mean difference −0.0370; 95% CI −0.0689, −0.0051 mm; $P = 0.0204$), considering the more stringent Bonferroni adjusted threshold ($P < 0.0167$) used to account for multiple comparisons.

Subjective Assessments of Aesthetic Appearance and Subject Satisfaction

Investigator-rated MFWS VAS score progressively improved from baseline at each visit (Fig. 3). The mean VAS score decreased from 2.2 (SD 0.4) at baseline to 1.0 (SD 0.0) at week 24, demonstrating a visible clinical improvement. Statistically significant improvements were observed from week 12 onward, with mean differences of −0.9167 (95% CI −1.1840, −0.6493; $P = 0.0000$) and −1.1667 (95% CI −1.5272, −0.8062; $P = 0.0000$) at weeks 12 and 24, respectively. Although there was an improvement in VAS scores from baseline to week 4, it did not achieve statistical significance (mean difference −0.5000; 95% CI −0.9836, −0.0164; $P = 0.0412$), given the more stringent cutoff due to Bonferroni adjustment.

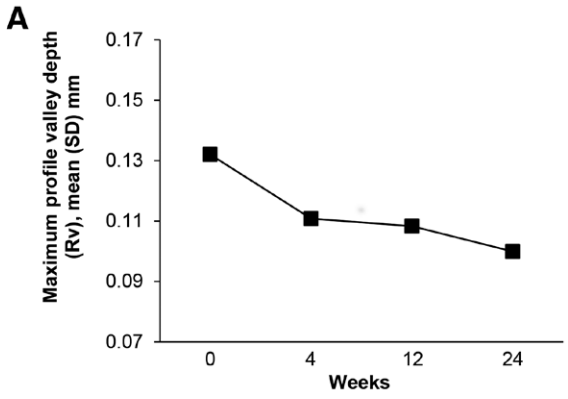
Figure 4 shows photographs of the left lower face of a representative subject at baseline and each follow-up visit after treatment, illustrating a substantial clinical improvement in wrinkles, texture, and overall skin quality of the lower face over time. This subject had a mean MFWS VAS score of 2.0 at baseline, which decreased to 1.0 at week 24

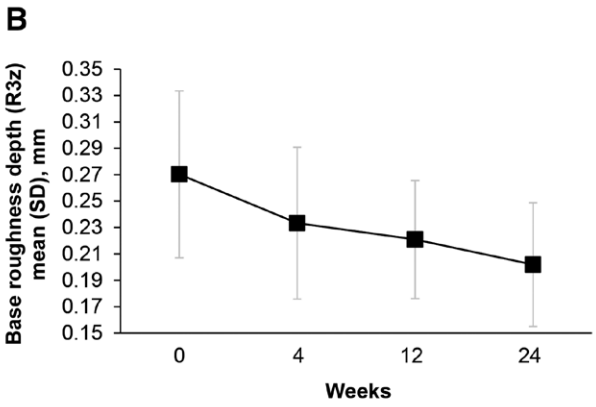
Based on the investigator's ratings, all subjects demonstrated improvement in their overall aesthetic appearance (Fig. 5). Notably, the proportion of subjects who were rated as "very much improved" increased from 8.3% (1 of 12) at week 4 to 41.7% (5 of 12) at week 12, and 91.7% (11 of 12) at week 24. No worsening in overall aesthetic appearance was noted.

Three-quarters of subjects (9 of 12) were "very satisfied" and 16.7% (2 of 12) were "satisfied" with their treatment as early as week 4 (Fig. 6). By week 12, all subjects were either "very satisfied" (75.0%, 9 of 12) or satisfied (25.0%, 3 of 12) with their treatment. No subjects reported any dissatisfaction with their treatment during the study period.

Adverse Events

No serious AEs were reported during the study. All AEs were mild and transient and included erythema (42%, 5 of 12), linear urticaria (33%, 4 of 12), edema (25%, 3 of 12), and bruising (17%, 2/12). Erythema resolved spontaneously within a few minutes, whereas edema and bruising resolved after 2–3 days. Areas with linear urticaria were massaged with 1% hydrocortisone and resolved within minutes after the procedure.





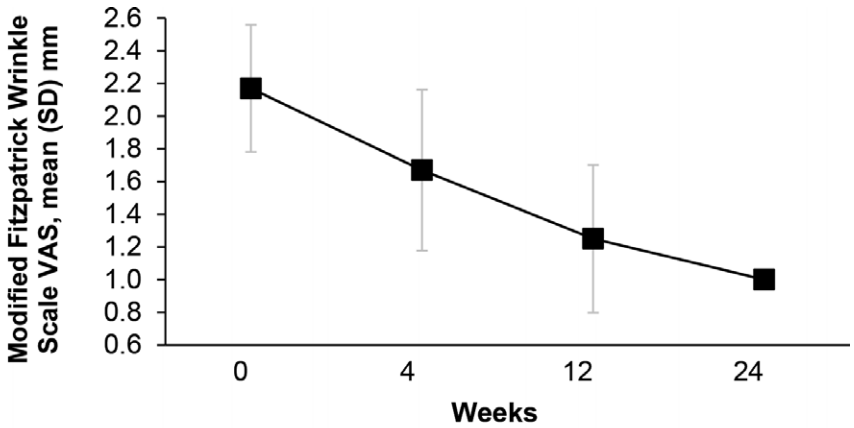
Rv assessment (n=12)	Baseline	Week 4	Week 12	Week 24
Mean (SD) mm	0.132 (0.030)	0.111 (0.022)	0.108 (0.022)	0.100 (0.021)
Mean difference from baseline (mm)	-	-0.0212	-0.0237	-0.0321
95% CI (mm)	-	-0.0336, -0.0087	-0.0381, -0.0093	-0.0483 -0.0158
P-value	-	0.0012	0.0016	0.0003

Bonferroni-adjusted cut-off = 0.0167

R3z assessment (n=12)	Baseline	Week 4	Week 12	Week 24
Mean (SD) mm	0.270 (0.063)	0.233 (0.058)	0.221 (0.045)	0.202 (0.047)
Mean difference from baseline (mm)	-	-0.0370	-0.0494	-0.0684
95% CI (mm)	-	-0.0689, -0.0051	-0.0792, -0.0196	-0.0951, -0.0417
P-value	-	0.0204	0.0015	0.0000

Bonferroni-adjusted cut-off = 0.0167

Fig. 2. Maximum profile valley depth (Rv) and base roughness depth (R3z) as measured by LiveViz micro. Objective measurement of surface roughness of the lower face over time. A, Mean (SD) Rv values before treatment and at weeks 4, 12, and 24 after treatment. Rv, maximum profile valley depth. B, Mean (SD) R3z values before treatment and at weeks 4, 12, and 24 after treatment. R3z, base roughness depth.



MFWS VAS assessment (n=12)	Baseline	Week 4	Week 12	Week 24
Mean (SD)	2.2 (0.4)	1.7 (0.5)	1.3 (0.5)	1.0 (0.0)
Mean difference from baseline	-	-0.5000	-0.9167	-1.1667
95% CI	-	-0.9836, -0.0164	-1.1840, -0.6493	-1.5272, -0.8062
P-value	-	0.0412	0.0000	0.0000

Bonferroni-adjusted cut-off = 0.0167

Fig. 3. Mean (SD) MFWS VAS scores before treatment and at weeks 4, 12, and 24 after treatment.

DISCUSSION

To our knowledge, this pilot study is the first to assess the effectiveness and safety of combined treatment with single-depth superficial MFU-V and subdermal injections of diluted CaHA in healthy Asian and White women to address wrinkles and improve skin quality

Fig. 4. Improvement in lower face appearance with standardized photography. Photographs of the left lower face of a representative subject at (A) baseline and (B–D) weeks 4, 12, and 24 after a combination treatment of MFU-V with diluted CaHA.

in the lower face. Our results showed that a single session of this combination treatment yielded progressive improvements in wrinkles and the overall aesthetic appearance of the lower face over 24 weeks. The treatment was well tolerated, and subjects reported high satisfaction levels.

Treatment modalities for lower facial rejuvenation include topical agents, injectables, minimally invasive therapies, and energy-based devices.[7] However, many of these options are limited by the procedure's drawbacks or increased complexity when treating the lower face, such as increased risks of side effects or undesirable complications, long downtime, and multiple treatment sessions.[6,8–10] A treatment approach that improves firmness and skin quality of the lower face while maintaining overall facial harmony, with minimal downtime or side effects would be desirable.[6,7]

As MFU-V and diluted CaHA stimulate neocollagenesis via different mechanisms of action, combining these modalities in the same treatment area could further enhance neocollagenesis. MFU-V delivers ultrasound energy to specific layers of the skin, causing

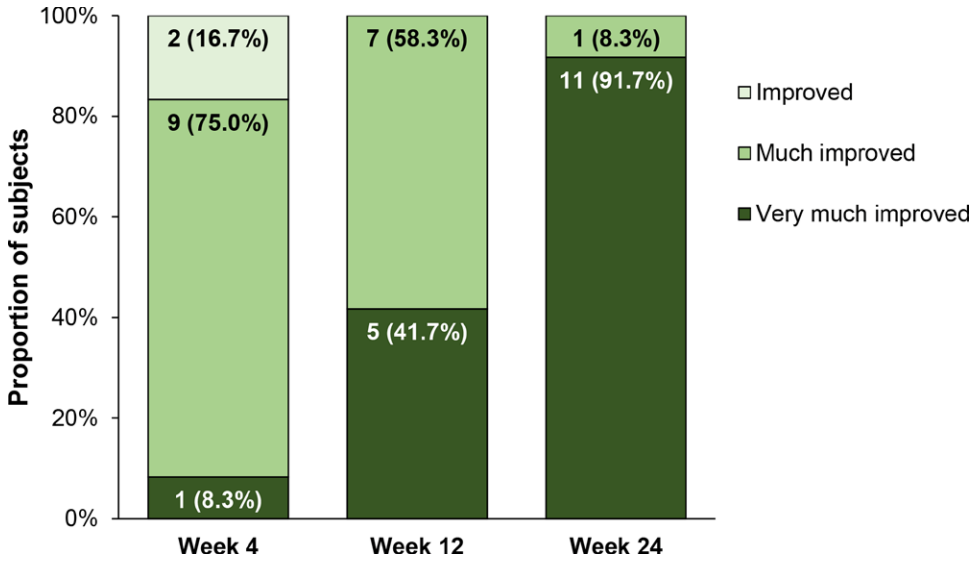


Fig. 5. Investigator-assessed GAIS ratings through the 24-week follow-up visit.

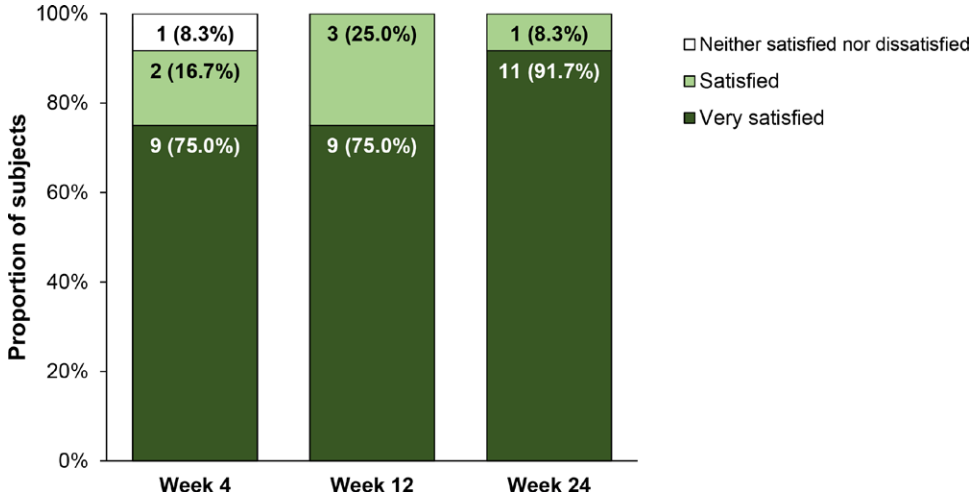


Fig. 6. Subject satisfaction with their treatment through the 24-week follow-up visit.

collagen denaturation and subsequent tissue remodeling.[11,12] Upon injection of diluted CaHA, direct contact between CaHA microspheres and fibroblasts results in fibroblast activation, consequently leading to collagen and elastin production.[13] Using a diluted CaHA formulation takes advantage of its collagen-stimulating effects while minimizing undesired volumization, thereby creating a desirable aesthetic improvement.[13] Our results are consistent with data from published studies using combined MFU-V and diluted CaHA in other treatment areas.[17–19] Indeed, a study showed that the combined approach led to thicker and denser collagen fibers than the single-modality treatment.[35] Although hyaluronic acid may be considered for combined treatment with MFU-V, offering the advantage of potential reversibility, a prior study comparing CaHA versus hyaluronic acid showed that CaHA treatment led to increased production of type 1 collagen and elastin and greater fibroblast proliferation.[36]

Recognizing the inherent limitations of subjective assessments, we used the 3D stereophotographic system and its associated software[23] for objective evaluation of skin quality (lines/wrinkles and skin unevenness) in the present study. This tool offers advantages such as precise quantification and analysis of different skin parameters, which enhances our understanding of skin quality beyond what subjective assessments can offer. This objective approach helps mitigate biases and inconsistencies associated with subjective assessments, thereby enhancing the robustness of our findings. Notably, the combined treatment was associated with improved skin quality in the lower face when assessed by both objective and subjective outcome measures. Objective evaluation of skin quality using the stereophotographic system

showed improvements in wrinkle depth and skin evenness in the lower face over the follow-up period. Similarly, investigator-rated MFWS VAS score improved progressively through all follow-up visits. Wrinkle severity in the lower face improved by more than one grade, from a rating of moderate-to-prominent wrinkle at baseline to fine wrinkle 24 weeks after treatment. Improvement in aesthetic appearance was noted in all subjects as early as 4 weeks after treatment.

When considering same-day combined treatments, it is important to carefully assess potential risks or treatment complications, including the possibility of severe AEs, prolonged recovery periods, or uneven lumps at the injection sites. Published studies on the combined use of MFU-V and diluted CaHA on the same day showed that the combined approach is well tolerated, with minimal side effects that are mild and transient. Subject satisfaction was high.[17–19] Similar observations were noted in the present study. No new safety concerns were noted. There were no reports of uneven lumps, and all subjects expressed satisfaction with the combined treatment at week 24.

This pilot study is limited by its small sample size and the open-label, single-arm design. Next, given that skin quality can vary across different ethnicities,[37] it would be of interest to evaluate whether there exist any ethnic differences in treatment response. Future studies should also consider a longer follow-up period to ascertain the durability and long-term safety of the combined treatment. Future studies are needed to evaluate the extent of enhanced effects achieved by the combined treatment versus either modality alone and the impact of time intervals between MFU-V and CaHA administration. Nonetheless, this pilot study provides valuable insights into the clinical experience of this combined approach for improving lower face skin quality.

CONCLUSIONS

Both MFU-V and diluted CaHA have individually demonstrated effectiveness in lower facial rejuvenation. This study showcases the effectiveness of combining single-depth superficial MFU-V and subdermal injections of diluted CaHA in a single session to address wrinkles and improve skin quality in the lower face. The combined approach is well tolerated and associated with high levels of patient satisfaction.

Sylvia Ramirez, MD, MPH, MBA, Dip Derm
Cutis Medical Laser Clinics
9 Scotts Road, #08-07
Scotts Medical Centre S228210
Singapore
E-mail: dr.sylvia@cutislaserclinics.com

DISCLOSURES

Dr. Sylvia Ramirez has received a speaker honorarium from Allergan Aesthetics and a research grant from Merz Aesthetics. Dr. Sylvia Ramirez has served on advisory boards for Allergan Aesthetics. All other authors have no financial interest to declare in relation to the content of this article. This study was supported by a research grant from Merz Aesthetics.

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