

Facial Skin Revitalization with Cohesive Polydensified Matrix-HA20G: Results from a Randomized Multicenter Clinical Study

Martina Kerscher, MD*
Welf Prager, MD†
Tanja C. Fischer, MD, PhD‡
Gerd G. Gauglitz, MD§
Tatjana Pavicic, MD¶
Ulrich Kühne, MD||
Maria Kravtsov, MSc**
Matthias Hofmann, PhD††
Hanna Dersch, MSc††
Sonja Sattler, MD††

Background: There is a growing interest in the application of hyaluronic acid (HA) derivatives in skin quality improvement. The aim of this study was to confirm safety and effectiveness of cohesive polydensified matrix-hyaluronic acid + glycerol (CPM-HA20G; Belotero Revive) in revitalization of early-onset photodamaged facial skin.

Methods: A total of 159 subjects with early signs of facial photodamaged skin were randomized in a 2:1 ratio to multiple- or single-dose treatment with CPMHA20G. Effectiveness assessments included biophysical measurements of skin hydration; elasticity, firmness, and roughness; investigator- and subject-assessed Global Aesthetic Improvement Scales; and FACE-Q Skin Changes and Treatment Satisfaction questionnaires.

Results: In both treatment groups, skin hydration improved from baseline to all follow-up visits in subjects with dry or very dry skin. This improvement was significant at week 16 after initial treatment in the multiple-dose group ($P = 0.0013$). Investigator- and subject-reported outcomes showed that the majority of subjects across all skin hydration types benefited from treatment, with higher satisfaction rates observed in the multiple-dose group. According to investigator-assessed Global Aesthetic Improvement Scale, 90.7% of subjects at week 12 in the multiple-dose and 74.6% of subjects at week 4 in the single-dose group were rated as at least “improved.” All related treatment-emergent adverse events were transient, expected injection-site reactions of mild to moderate intensity.

Conclusions: Effectiveness of CPM-HA20G for skin hydration in subjects with dry or very dry skin was demonstrated up to 9 months after last injection. Overall, CPM-HA20G demonstrated effective and safe use in facial skin revitalization among subjects with early-onset photodamaged skin. (*Plast Reconstr Surg Glob Open* 2021;9:e3973; doi: 10.1097/GOX.0000000000003973; Published online 3 December 2021.)

INTRODUCTION

Good skin quality is regarded as healthy and youthful in appearance and is associated with trustworthiness, competence, attractiveness, and self-esteem.^{1,2} As improvement

in skin quality has become a rising trend in aesthetic procedures,³ there is a growing interest in the application of hyaluronic acid (HA) derivatives.³ A global panel of aesthetic practitioners reached a consensus that HA microinjections, as part of a multi-layered treatment strategy, can improve emergent perceptual skin quality parameters.² The consensus features a novel HA product intentionally designed for revitalization of early-onset photodamaged facial skin characterized by dehydration, roughness, and lack of elasticity and firmness.^{2,4,5}

This novel product is a cohesive polydensified matrix-HA + glycerol (CPM-HA20G; Belotero Revive, Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany); it is a CE-marked, sterile, resorbable, viscoelastic, transparent, cross-linked sodium hyaluronate gel (20.0 mg/ml) of non-animal origin containing glycerol (17.5 mg/ml). The product is administered in one or three sessions into the mid to deep dermis using micropuncture, a technique which involves injecting micro aliquots of filler over the entire treatment area. Glycerol component further strengthens hydrophilic properties of injectable HA for deep and immediate hydration.^{6,7} The product is manufactured

From the *University of Hamburg, Hamburg, Germany; †Prager & Partner Dermatologische Praxis, Hamburg, Germany; ‡Skin and Laser Centre, Potsdam, Germany; §Department of Dermatology and Allergy, Ludwig Maximilian University, Munich, Germany; ¶Private Practice, Munich, Germany; ||Hautmedizin Bad Soden, Bad Soden, Germany; **Anteis S.A., Lonay, Switzerland; ††Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany; and ‡‡Rosenpark Klinik, Darmstadt, Germany.

Received for publication July 9, 2021; accepted October 1, 2021.

Copyright © 2021 The Authors. Published by Wolters Kluwer Health, Inc. on behalf of The American Society of Plastic Surgeons. This is an open-access article distributed under the terms of the [Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 \(CCBY-NC-ND\)](https://creativecommons.org/licenses/by-nc-nd/4.0/), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

DOI: 10.1097/GOX.0000000000003973

with CPM technology, renowned for seamless intradermal integration.^{8,9}

Although the safety and effectiveness of CPM-HA20G in improving facial skin quality and attractiveness was reported in a smaller cohort,¹⁰ the aim of the current study was to confirm its safety and effectiveness in a larger population in a multicenter “real-life” setting.

MATERIALS AND METHODS

This randomized multicenter study was performed in Germany in compliance with EN ISO 14155:2011 and the Declaration of Helsinki and was approved by the regional ethics committee (Ärztchamber Hamburg) and registered in the German Clinical Trial Register (DRKS00025699).

Subjects of both genders, between 25 and 45 years old, with early signs of facial photodamaged skin (ie, uneven skin tone, fine lines, dehydrated skin) desiring improvement in skin quality were included at seven sites. All subjects provided written informed consent and were checked for eligibility during screening.

Main exclusion criteria were severe solar elastosis; keloids or hypertrophic scarring; inflammation, infection, lesions or hyper- or hypopigmentation at the injection site; new oral or topical anti-wrinkle products in the target areas; history of permanent fillers; poly-l-lactic acid fillers,

Disclosure: *M. Kerscher has received research support from, conducted clinical trials for, and acted as a speaker and/or investigator for Merz Pharmaceuticals, Kythera, Q-Med/Galderma, and Pierre Fabre. T. C. Fischer has received grants from Merz Pharmaceuticals, Croma, Riemser, and PromoItalia. W. Prager has received research support from, conducted clinical trials for, and acted as a speaker and/or investigator for Merz Pharmaceuticals, Q-Med/Galderma, Allergan Aesthetics, Beiersdorf, SkinCeuticals, Cynosure, and Lumenis. U. Kühne has acted as a speaker for Merz Pharmaceuticals, Q-Med/Galderma, and Procutis and has conducted clinical trials for Merz Pharmaceuticals. S. Sattler has received research support from and conducted clinical trials for Merz Pharmaceuticals, Allergan Aesthetics, Q-Med/Galderma, LC Chem, Croma, and Crown Laboratories and acted as a speaker, advisor or investigator for Merz Pharmaceuticals, Venus Concept, Allergan Aesthetics, Crown Laboratories, Croma, and Pulse Biosciences Inc. T. Pavicic has received personal fees from and acted as a speaker and consultant for Merz Pharmaceuticals and AAT and received research support and acted as investigator for Merz Pharmaceuticals, AAT, LG, BTL, Lutronic, and Johnson & Johnson. G. G. Gauglitz has received research support from, conducted clinical trials for, and acted as a speaker and/or investigator for Merz Pharmaceuticals, Q-Med/Galderma, Sinclair Pharma, Beiersdorf, Cynosure, Candela, Asclepion, Lumenis, Urgo GmbH, Almira, and Johnson & Johnson. M. Kravtsov is an employee at Anteis S.A. (a wholly owned subsidiary of Merz Pharmaceuticals). M. Hofmann and H. Dersch are employees at Merz Pharmaceuticals. This clinical study was sponsored by Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany.*

Takeaways

Question: Can CPM-HA20G improve skin hydration in patients with early-onset photodamaged facial skin?

Findings: Effectiveness and safety of CPM-HA20G for skin hydration in subjects with dry or very dry skin was demonstrated up to 9 months after last injection. Overall, CPM-HA20G demonstrated effective and safe use in facial skin revitalization among subjects with early-onset photodamaged skin.

Meaning: CPM-HA20G is an effective and safe treatment for revitalization of early-onset photodamaged facial skin.

dermabrasion, or deep peels; skin-tightening procedures, HA, or calcium hydroxylapatite fillers; nonablative laser or light treatment; or botulinum toxin within certain time periods before enrollment or during the study.

A total of 159 subjects were randomized in a 2:1 ratio to multiple- or single-dose regimen using computer-generated block randomization, stratified by investigational site. CPM-HA20G was administered into the mid to deep dermis of the lower cheeks with serial micropuncture technique. The multiple-dose group was treated over three sessions at day 1, week 4, and week 8. A maximum of 2 mL (1 mL per side) were injected per subject per session, and the injections were evenly distributed over each lower cheek, with a maximum of 20 injection points 1 cm apart with 50 µL filler injected per point. The single-dose group received a maximum of 3 mL (1.5 mL per side) per subject at day 1, and the injections were evenly distributed over each lower cheek, with a maximum of 30 injection points with 50 µL filler per point.

Clinical assessments were performed at day 1 and weeks 4, 8, 12, 16, 24, 32, and 44 in the multiple-dose group and at day 1 and weeks 4, 8, 16, 24, and 36 in the single-dose group. Baseline data were recorded at day 1 before treatment. Hereafter, follow-up visits are counted from the first injection at day 1.

Skin hydration was assessed at baseline and all follow-up visits using Corneometer CM 825 (Courage & Khazaka, Cologne, Germany). Primary endpoint was defined as change from baseline in this value in the multiple-dose group at week 16. Secondary endpoints included change from baseline in this value at all follow-up visits in both treatment groups.

The seven-point Likert Global Aesthetic Improvement Scale (GAIS) was assessed by the treating investigator (iGAIS) and by subjects (sGAIS) from “very much improved” (grade +3) to “very much worse” (grade -3). The FACE-Q Satisfaction with Facial Appearance module included 10 questions rated on a four-point scale from “very satisfied” to “very dissatisfied.” The Skin Changes Questionnaire comprised four questions about skin hydration, tone, distressing/refreshing effect and softness/suppleness to touch rated on a four-point scale from “very important” to “light.” The Treatment Satisfaction Questionnaire recorded subject satisfaction and willingness to repeat and recommend the treatment.

Secondary endpoints in both treatment groups included iGAIS and sGAIS values, change in per question FACE-Q score from baseline, Skin Changes Questionnaire value, Treatment Satisfaction Questionnaire, and incidence of treatment-emergent adverse event (TEAEs).

At two of seven investigational sites, skin elasticity (R2) and firmness (R0) were assessed using Cutometer (Courage & Khazaka, Cologne, Germany), and skin roughness was evaluated (Rz) with PRIMOS (GFM, Berlin, Germany). Other endpoints in both treatment groups included change in skin elasticity, skin firmness, and skin roughness.

As subject on-site attendance from week 32 to 44 was affected by the COVID-19 pandemic, data from several self-assessments were collected via telephone.

Statistics

Electronic case report form (ClinCase) was used for data collection and SAS software version 9.4 for statistical analysis. Sample size was calculated to observe an adverse event, with an incidence of 1% at least once with a probability of 80% in this and the previous study.¹⁰ For the primary effectiveness endpoint, fewer subjects would have been required. All effectiveness analyses were based primarily on the full analysis set, including all treated subjects for whom skin hydration values at baseline and 8 weeks after last treatment were available.

For primary endpoint analysis, the hydration values were calculated as the mean value from three consecutive Corneometer measurements. The average over the means of both cheeks was applied. A one-sided paired *t*-test at type I error level 2.5% was used to test the mean difference in skin hydration from baseline and after repeated treatments in the multiple-dose group. Primary analysis was repeated for the subgroup of subjects with dry or very dry skin.

Secondary and other effectiveness endpoints were displayed using descriptive summary statistics for continuous variables and frequency tables.

Safety endpoints were tabulated as frequency tables based on the safety evaluation set, which included subjects treated with CPM-HA20G at least once during the study. Adverse events were coded using MedDRA, version 23.0.

RESULTS

Subjects were recruited from May to July 2019 and were followed until June 2020. Figure 1 shows 159 screened subjects randomized in a 2:1 ratio to the multiple-dose ($n = 106$) or single-dose ($n = 53$) group. As subjects without a skin hydration value at 8 weeks after the last treatment ($n = 11$) were excluded from the effectiveness analysis, the full analysis set comprised 148 subjects [multiple-dose group ($n = 97$); single-dose group ($n = 51$)]. No withdrawals due to adverse events occurred. Figure 2 shows subject demography. The majority of injections (~67% in both groups) were performed with the enclosed 30G needles, and the remaining ones mainly with 32G and 33G needles.

Skin Hydration

Primary endpoint results showed that in the multiple-dose group ($n = 97$), the mean (SD) skin hydration value

decreased slightly from 51.5 (13.54) a.u. at day 1 to 51.4 (12.68) a.u. at week 16. This mean (SD) change of -0.1 (10.83) a.u. was neither statistically significant ($P = 0.5534$; ie, above $\alpha = 0.025$ one-sided) nor considered relevant (difference is ≤ 4.0 a.u.). This indicates that the multiple-dose treatment did not lead to a difference in skin hydration at week 16 in the entire study population.

In contrast, when evaluating subjects in the “dry skin” (30–40 a.u.) and “very dry skin” (<30 a.u.) subgroup ($n = 19$), as defined by Heinrich et al,¹¹ the mean (SD) skin hydration value increased from 32.6 (7.70) a.u. at day 1 to 41.3 (14.42) a.u. at week 16. This mean (SD) change of 8.7 (10.82) a.u. was statistically significant ($P = 0.0013$; ie, below $\alpha = 0.025$ one-sided) and considered relevant. This indicates that the multiple-dose treatment led to a distinct improvement in skin hydration at week 16 in the subgroup with “dry skin” and “very dry skin.”

Figure 3 illustrates skin hydration values in the “dry skin” and “very dry skin” subgroup over the entire study in the multiple- and single-dose groups. In the multiple-dose group, the mean (SD) skin hydration value of 44.0 (14.02) a.u. peaked at week 8 [mean (SD) change 11.4 (13.04) a.u.]. It remained higher than baseline through week 44 with a value of 40.5 (17.39) a.u. (Fig. 3A). In the single-dose group, the mean (SD) skin hydration value of 44.7 (11.72) a.u. peaked at week 8 (mean [SD] change was 11.2 [9.41] a.u.). It remained higher than baseline through week 36 with a value of 43.9 (5.92) a.u. (Fig. 3B). In both groups the mean change from baseline to the last follow-up visit was over 4.0 a.u. and, hence, considered relevant. A decline was observed at week 32 and week 24 in the multiple- and single-dose groups, respectively, which could possibly be explained by the effect of outlier values on the small sample size or by the colder season, and naturally less hydrated skin,¹² at the time of measurements.

The Skin Changes Questionnaire results for the entire study population showed that in the multiple-dose group the majority of subjects noticed a difference in their lower cheeks in terms of skin hydration, tone, destressing and refreshing effect, and softness and suppleness to touch at the majority of follow-up visits. For the majority of these subjects, the effects were “very important” or “important.” In detail, over 60% of subjects reported a difference in skin hydration and softness from week 8 to week 24, observed a destressing and refreshing effect from week 8 to week 16, and saw a difference in skin tone at week 8 and week 12. In contrast, in the single-dose group, over 60% of subjects reported a difference in softness up to week 8, and in destressing and refreshing effect at week 4.

Other Biophysical Measurements

Data from 28 and 14 subjects in the multiple- and single-dose groups, respectively, was analyzed. In the multiple-dose group, mean skin elasticity (R2) increased with the first two treatments and returned to baseline at week 44. The best improvement was from a mean (SD) R2 value of 0.71 (0.094) at baseline to 0.73 (0.089) at week 8. Likewise, in the single-dose group, the mean (SD) R2 value increased from 0.65 (0.089) at baseline to 0.72 (0.077) at week 4 and remained improved to week 36.

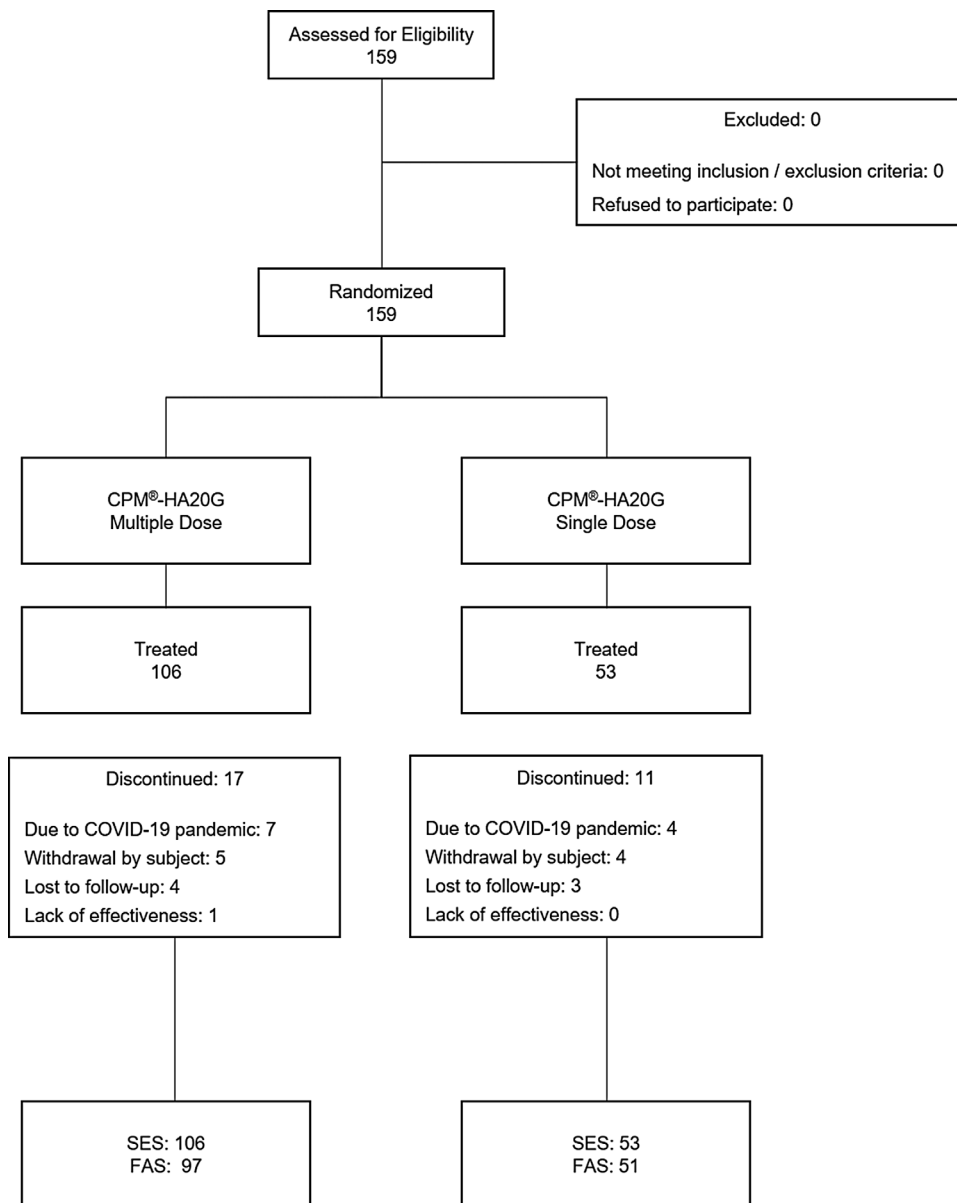


Fig. 1. Subject disposition. FAS: full analysis set.

Mean skin firmness (R0) values showed a slight variation with a mean improvement up to 20 µm at certain timepoints during the study in the multiple-dose group. However, in the single-dose group, skin firmness values in both cheeks remained stable during the study. Similarly, improvement in skin roughness (Rz) was reported only in the multiple-dose group at week 16 and 32.

Investigator- and Subject-reported Outcomes

Figure 4 illustrates iGAIS results. The highest improvement was reported upon treatment completion: 90.7% of subjects at week 12 in the multiple-dose group and 74.6% at week 4 in the single-dose group were rated as at least “improved.”

Similarly, the sGAIS results showed that a total of 82.3% of subjects at week 12 in the multiple-dose group

and 64.7% at week 4 in the single-dose group were rated as at least “improved.” Generally, iGAIS ratings were slightly higher than sGAIS ratings during the study, except for the last visit when the percentage of at least “improved” subjects was higher on the sGAIS than on the iGAIS.

Responses to FACE-Q questions were consistent in both groups throughout the study with the majority of subjects being “somewhat” and “very satisfied” for the majority of questions. Figure 5 shows subjects’ satisfaction with facial freshness appearance.

The Treatment Satisfaction Questionnaire results showed that the majority of subjects in both groups were satisfied with their aesthetic results, and they would repeat the treatment and would recommend it to family and friends. Nevertheless, multiple-dose treatment was associated with higher satisfaction rates throughout the study.

	Multiple dose (N=106)	Single dose (N=53)	Total (N=159)
Gender (n [%])			
Male	4 (3.8)	4 (7.5)	8 (5.0)
Female	102 (96.2)	49 (92.5)	151 (95.0)
Age (years)			
Mean (SD)	38.3 (5.10)	39.3 (4.91)	38.7 (5.04)
Min, max	26, 45	27, 45	26, 45
Race (n [%])			
White	104 (98.1)	50 (94.3)	154 (96.9)
Asian	1 (0.9)	3 (5.7)	4 (2.5)
Other	1 (0.9)	0 (0.0)	1 (0.6)
Baseline skin type (n [%])			
Very dry skin	7 (6.6)	2 (3.8)	9 (5.7)
Dry skin	14 (13.2)	6 (11.3)	20 (12.6)
Normal skin	85 (80.2)	45 (84.9)	130 (81.8)

Fig. 2. Demographics safety evaluation set. n, number of nonmissing observations; N, number of subjects in the treatment group and analysis set; SD, standard deviation.

For instance, 75.3% of subjects in the multiple-dose group and 66.0% of subjects in the single-dose group were satisfied with treatment results 8 weeks after last injection.

Figures 6 and 7 show photographs of representative subjects. Skin quality in the lower cheeks has visibly improved from pre- to posttreatment visits.

Safety Results

In total, 52.8% of subjects (57.7% in the multiple-dose and 43.4% in the single-dose group) experienced at least one treatment-related TEAE. These events were mild (88.1%) or moderate (11.9%) in intensity. The majority of treatment-related TEAEs resolved within 15 days. The most frequent injection-site reaction was hematoma (47.2% of subjects) and swelling (6.3%). No serious TEAEs or those leading to study discontinuation were reported.

DISCUSSION

In this study, the primary endpoint evaluated change in mean skin hydration 8 weeks after the last repeated injection (week 16) in the multiple-dose group, as assessed by the Corneometer. In the “dry and very dry skin” subgroup (n = 19), the mean hydration value improved by 8.7 a.u. from baseline to week 16. This improvement was statistically significant ($P < 0.025$) and considered relevant, thus

demonstrating effectiveness of CPM-HA20G in skin hydration in subjects with dry and very dry skin.

However, among the entire study population, which was the basis for the primary endpoint analysis, the change in mean skin hydration was neither statistically significant nor considered relevant. In fact, mean hydration values were within the normal range for the majority of subjects at baseline (78 of the 97 subjects in the multiple-dose group), making it difficult to achieve further improvement in hydration. Therefore, treatment effect could not be shown in subjects with normal skin.

Subgroup analysis of mean hydration values showed that in subjects with dry and very dry skin relevant improvement in hydration was maintained for 9 months after the last injection. Moreover, the Skin Changes Questionnaire results showed improvement in skin hydration in the entire study population, corroborating the clinical relevance of Corneometer measurements.

Numerical improvements in skin elasticity were observed in both treatment groups, suggesting effectiveness of CPM-HA20G. Elasticity values in the current study were similar to that of the previous CPM-HA20G study¹⁰ and the study by Kerscher et al on Restylane Vital.¹³ However, improvements in skin firmness and roughness were only observed in the multiple-dose group, corroborating results of the previous CPM-HA20G study.¹⁰

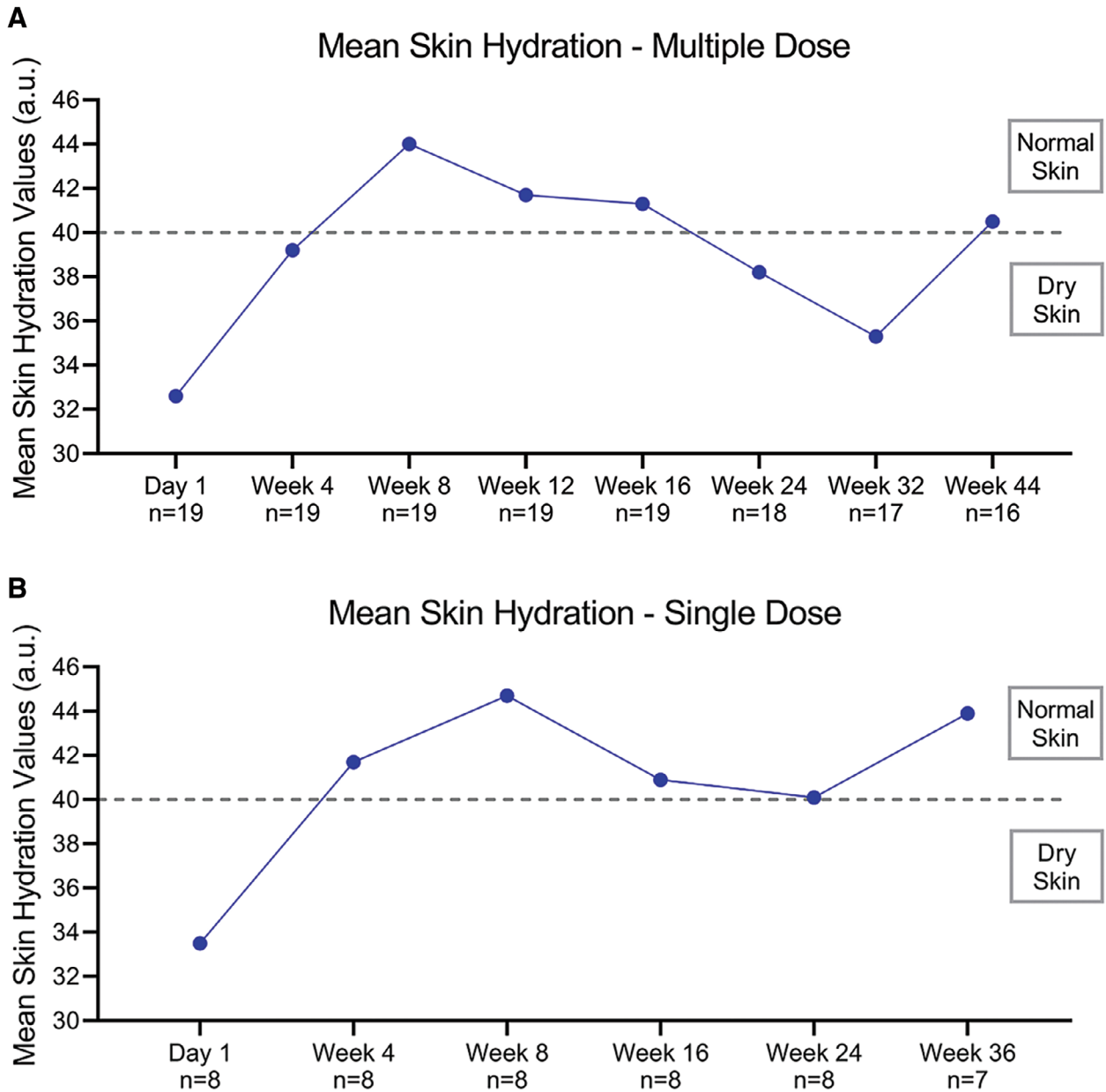


Fig. 3. Effectiveness results. A, Skin hydration in multiple-dose “dry and very dry skin” subgroup; B, Skin hydration single-dose “dry and very dry skin” subgroup; a.u.: arbitrary units.

To our knowledge this was the first multicenter clinical study evaluating changes in subject’s skin quality after revitalization treatment with HA based on measurements of biophysical skin parameters. Satisfactory improvements in skin quality were observed using investigator- and subject-reported GAIS measures. In both treatment groups, up to week 24, iGAIS showed higher percentages of subjects with at least “improved” score when compared with sGAIS. This trend is common in dermal-filler studies as subjects tend to be more critical of themselves and have higher expectations than experienced investigators.¹⁴⁻¹⁶ Interestingly, at the last follow-up visit, the trend reversed, suggesting that more subjects were still perceiving an aesthetic improvement

according to their ratings as opposed to the investigators’ ratings.

Subject-reported outcomes, including results from sGAIS, FACE-Q, and satisfaction questionnaires, demonstrated that the majority of subjects benefited from treatment. Their satisfaction was related to a multitude of factors, including improvements in skin hydration, softness, tone, refreshing effect, elasticity, and smoothness. It is challenging to quantify these benefits with biophysical measurements, as the current knowledge on clinical impact of numerical changes remains limited and reproducibility of measurements is influenced by environmental and patient-related factors.¹⁷ Nevertheless, Samson et al have shown that even

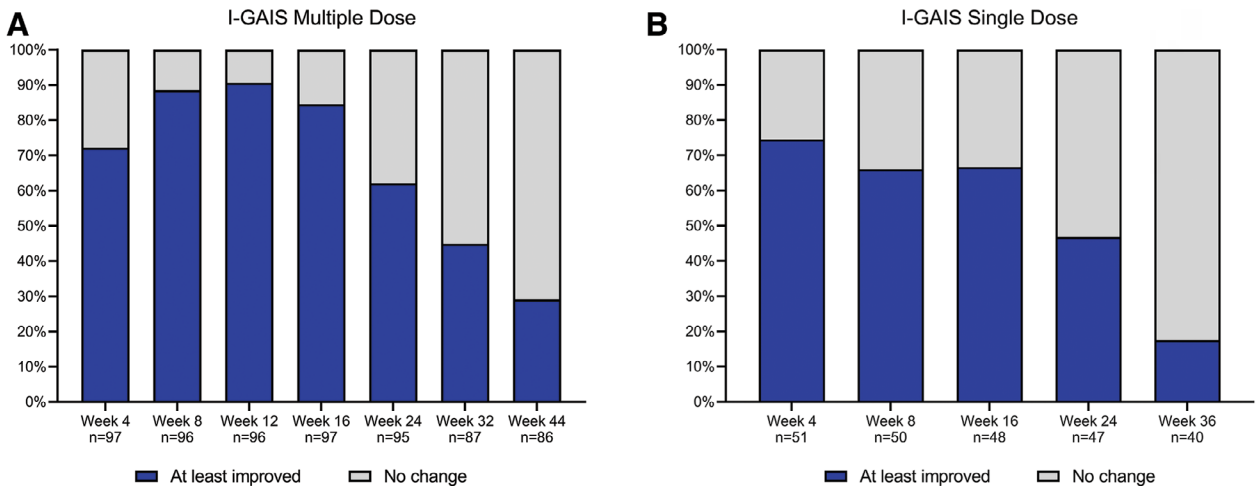


Fig. 4. Effectiveness results. A, iGAIS scores in multiple dose group; B, iGAIS scores in single-dose group. Blue color corresponds to the pooled percentages of subjects "improved," "much improved," and "very much improved."

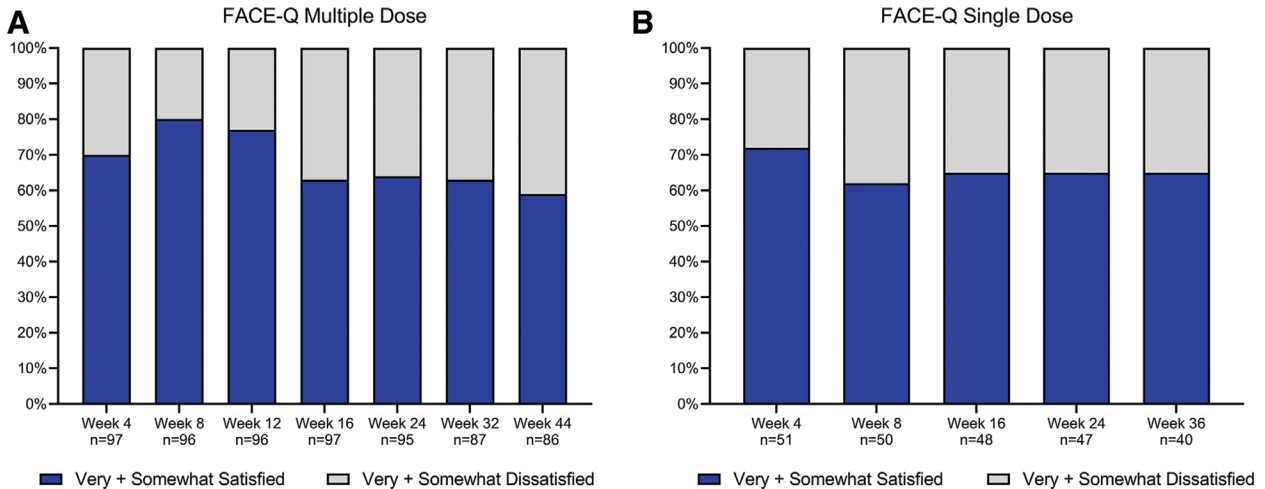


Fig. 5. Effectiveness results. Subject satisfaction with how fresh the face looks on FACE-Q: A, multiple dose group; B, single-dose group.

relatively small changes in skin surface topography can affect perception of facial age and attractiveness.¹⁸ Hence, it is important to consider positive subject satisfaction to corroborate clinical meaningfulness of study outcomes.

When compared with the single-dose group, better aesthetic improvement and higher satisfaction were observed in the multiple-dose group. Nevertheless, single-dose treatment could be proposed to patients desiring immediate skin revitalization with the option for repeated treatments as necessary.

This study was limited by the absence of a control group and a small sample size of the subgroup analysis.

Results of the present study confirm safe use of CPM-HA20G in both multiple- and single- dose administration regimens. Reported treatment-related TEAEs were expected reactions and were related to injection procedure rather than to product.

Remarkably, injection-site pain constituted only 2.4% of the treatment-related TEAEs, indicating that treatment was not painful for the majority of subjects. This observation suggests that fillers intended for revitalization and injected with the micropuncture technique may not necessarily need ancillary lidocaine in their formulation.

CONCLUSIONS

This first multicenter study with biophysical measurements showed that in subjects with dry and very dry skin, CPM-HA20G improved skin hydration in single- and multiple-dose groups up to 9 months after last injection. This improvement was statistically significant in the multiple-dose group at week 16. Global aesthetic improvement and treatment satisfaction were achieved in the entire study population across all skin hydration types. Both treatment



Fig. 6. Photographs of a 30-year-old man treated with multiple doses of CPM-HA20G. Top line: left side; bottom line: right side; A and D: Day 1 - Baseline; B and E: Week 16; C and F: Week 44.

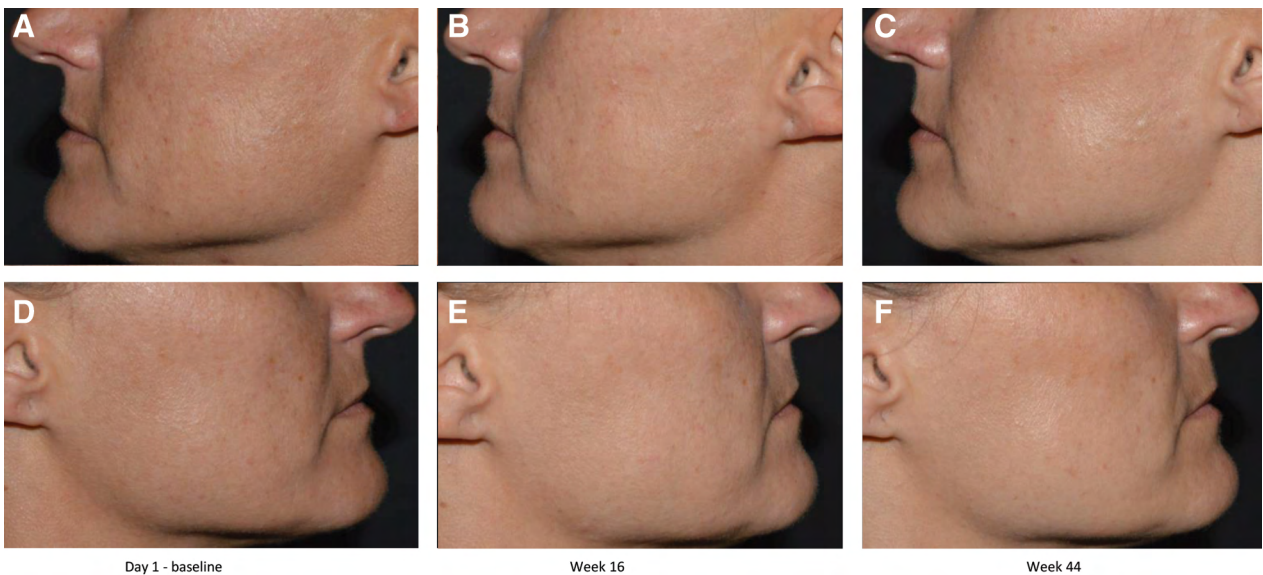


Fig. 7. Photographs of a 41-year-old woman treated with multiple doses of CPM-HA20G. Top line: left side; bottom line: right side; A and D: Day 1 - Baseline; B and E: Week 16; C and F: Week 44.

regimens were very well tolerated. Overall, CPM-HA20G demonstrated effective and safe use in facial skin revitalization among subjects with early-onset photodamaged skin.

Further research suggestions include treatment assessments by independent investigators and comparison with other revitalization modalities, such as nonablative laser.

Martina Kerscher, MD

Division of Biochemistry and Molecular Biology
Cosmetic Science
University of Hamburg
D-20146 Hamburg
Germany

E-mail: martina.kerscher@uni-hamburg.de

ACKNOWLEDGEMENTS

The authors thank the BELOVE study team, Dr. Christine Kliebe-Frisch, Dr. Nina Henke, Dr. Tanja Zwicker, Georg Comes, Irina Haller, and Dr. Petra Weissenberger for the support in realization of this study, as well as Michael Makara for support in realization of the figures in this article.

REFERENCES

1. Tsankova E, Kappas A. Facial skin smoothness as an indicator of perceived trustworthiness and related traits. *Perception*. 2016;45:400–408.
2. Goldie KK, Kerscher M, Fabi SG, et al. Skin quality – a holistic 360° view: consensus results. *Clin Cosmet Investig Dermatol*. 2021;14:643–654.

3. Landau M, Fagien S. Science of hyaluronic acid beyond filling: fibroblasts and their response to the extracellular matrix. *Plast Reconstr Surg*. 2015;136(5 suppl):188S–195S.
4. Choudhary S, Tang JC, Leiva A, et al. Photodamage, part 1: pathophysiology, clinical manifestations, and photoprotection. *Cosmet Dermatol*. 2010;23:460–466.
5. Ichihashi M, Ando H, Yoshida M, et al. Photoaging of the skin. *Anti-Aging Med*. 2009;6:46–59.
6. Korponyai C, Szél E, Behány Z, et al. Effects of locally applied glycerol and xylitol on the hydration, barrier function and morphological parameters of the skin. *Acta Derm Venerol*. 2017;97:182–187.
7. Succi IB, da Silva RT, Orofino-Costa R. Rejuvenation of periorbital area: treatment with an injectable nonanimal non-cross-linked glycerol added hyaluronic acid preparation. *Dermatol Surg*. 2012;38:192–198.
8. Flynn TC, Sarazin D, Bezzola A, et al. Comparative histology of intradermal implantation of mono and biphasic hyaluronic acid fillers. *Dermatol Surg*. 2011;37:637–643.
9. Tran C, Carraux P, Micheels P, et al. In vivo bio-integration of three hyaluronic acid fillers in human skin: a histological study. *Dermatology*. 2014;228:47–54.
10. Hertz-Kleptow D, Hanschmann A, Hofmann M, et al. Facial skin revitalization with CPM-HA20G: an effective and safe early intervention treatment. *Clin Cosmet Investig Dermatol*. 2019;12:563–572.
11. Heinrich U, Koop U, Leneveu-Duchemin MC, et al. Multicentre comparison of skin hydration in terms of physical-, physiological- and product-dependent parameters by the capacitive method (Corneometer CM 825). *Int J Cosmet Sci*. 2003;25:45–53.
12. Tagami H. Hydration of the skin surface. In: Farage M, Miller K, Maibach H, ed. *Textbook of Aging Skin*. Berlin, Heidelberg: Springer-Verlag; 2017:1117–1126.
13. Kerscher M, Bayrhammer J, Reuther T. Rejuvenating influence of a stabilized hyaluronic acid-based gel of nonanimal origin on facial skin aging. *Dermatol Surg*. 2008;34:720–726.
14. Prager W, Agsten K, Kerscher M. Patient-reported outcomes following split-face injection of 2 volumizing fillers in the upper cheeks. *Plast Reconstr Surg Glob Open*. 2017;5:e1412.
15. Micheels P, Vandeputte J, Kravtsov M. Treatment of age-related mid-face atrophy by injection of cohesive polydensified matrix hyaluronic acid volumizer. *J Clin Aesthet Dermatol*. 2015;8:28–34.
16. Callan P, Goodman GJ, Carlisle I, et al. Efficacy and safety of a hyaluronic acid filler in subjects treated for correction of mid-face volume deficiency: a 24 month study. *Clin Cosmet Investig Dermatol*. 2013;6:81–89.
17. Nikolis A, Enright KM. Evaluating the role of small particle hyaluronic acid fillers using micro-droplet technique in the face, neck and hands: a retrospective chart review. *Clin Cosmet Investig Dermatol*. 2018;11:467–475.
18. Samson N, Fink B, Matts P. Interaction of skin color distribution and skin surface topography cues in the perception of female facial age and health. *J Cosmet Dermatol*. 2011;10:78–84.