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RESEARCH LETTER

Evaluating the Properties of a Dual-Effect Facial Injectable: From Preclinical Data to Real-World Evidence

Patricia Ormiga[1], Claudia A Hernández[2], Rogério de Lima Romeiro[3], Aude Bernardin[4], Fabio Sambatti Crema[5], Lauren Nakab[6], Lital Shklanovsky[7], Graeme Kerson[8]

[1]Clínica Patricia Ormiga, Rio de Janeiro, Brazil; [2]CH Dermatologia, Medellin, Antioquia, Colombia; [3]Faculdade São Leopoldo Mandic, Instituto São Leopoldo Mandic, Área de Harmonização Orofacial, São Paulo, Brazil; [4]Allergan Aesthetics, an AbbVie company, Pringy, France; [5]Allergan Aesthetics, an AbbVie company, São Paulo, Brazil; [6]Allergan Aesthetics, an AbbVie company, Irvine, CA, USA; [7]Allergan Aesthetics, an AbbVie company, Lod, Israel; [8]Allergan Aesthetics, an AbbVie company, Marlow, UK

Correspondence: Patricia Ormiga, Clínica Patricia Ormiga, Av. Ataulfo de Paiva, 204 – Sala 908, Leblon, Rio de Janeiro, Brazil, Tel +21 98805-1848, Email paormiga@gmail.com

Facial aging requires a multi-targeted approach for optimal results; however, many combination approaches lack standardization, negatively impacting treatment results. Hyaluronic acid (HA) and calcium hydroxyapatite (CaHA) products are widely used for facial rejuvenation. HA is the gold standard for immediately restoring volume, but it is gradually degraded over time. CaHA acts indirectly by stimulating collagen production and restoring other key extracellular matrix proteins; however, there is a risk of early volume loss due to rapid degradation of the carboxymethylcellulose (CMC) carrier before neocollagenesis occurs.[1] To this end, combining the 2 products can overcome each product's shortcomings and provide immediate and long-term satisfactory outcomes. Such combination treatments have been delivered to patients by manually mixing two separate products into a single syringe. This can change the physicochemical properties of the fillers and can lead to highly variable and inconsistent results due to the lack of validated mixing protocols. HA-CaHA (HArmonyCa™; Allergan Aesthetics, an AbbVie Company) is a hybrid injectable developed by combining HA with CaHA in a controlled and consistent manner. Importantly, HA-CaHA is a manufactured product supplied as a ready-to-use pre-filled syringe.[2] The key characteristics of HA-CaHA are described here, along with considerations that distinguish this hybrid injectable from a mixture of individual HA and CaHA products.

HA-CaHA, developed by an Israel-based company (Panaxia R&D), received regulatory approval in Israel in 2016. The current developers and manufacturers acquired HA-CaHA in 2020 and expanded its approval to over 30 countries. HA-CaHA contains CaHA microspheres (55.7% w/w, approximately 30% by volume) embedded in a crosslinked HA matrix (20 mg/mL) and 0.3% w/v lidocaine. HA-CaHA is created by a stepwise combination of CaHA with HA during crosslinking, resulting in a composite material with dispersed CaHA particles with varying degrees of association with the HA matrix. This combination, manufactured with consistent physiochemical and morphological characteristics, provides a dual mechanism of action. The HA delivers immediate volume and sustained lift, unlike other CaHA products that use CMC carrier, which is degraded faster than HA.[3,4] The CaHA microspheres in HA-CaHA are intended to support fibroblast ingrowth and collagen biostimulation for sustained improvement in skin quality.

To confirm that the CaHA in the HA-CaHA combination effectively stimulates neocollagenesis, the study sponsor, Allergan Aesthetics, used a Sprague Dawley rat model to compare the biostimulatory effects of HA-CaHA to the effects of CaHA with CMC carrier, CMC-CaHA (Radiesse®, Merz Aesthetics), and another biostimulator polycaprolactone with CMC carrier, CMC-PCL (Ellansé™, Sinclair Pharma GmbH). Each product was injected subcutaneously at a volume of 125 µL; tissue was collected at 1- and 8-weeks post injection for chromogenic in situ hybridization (CISH) to measure collagen I gene expression and for immunohistochemistry (IHC) to measure collagen I protein expression. The CISH and

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IHC signals were quantified and are presented as a total positively stained area per time point. Our results showed that all products stimulated collagen production with no significant difference in the positively stained area at week 1 and 8 time points ($P > .05$, Figure 1A and B). These data suggest that the biostimulatory function of CaHA in HA-CaHA is equivalent to that of similar products on the market.

To ensure consistent clinical outcomes, it is important to characterize the size, quality, and uniformity of CaHA microspheres. Small (<15 µm), irregularly shaped, or damaged microspheres may have decreased efficacy due to accelerated phagocytosis, and larger microspheres (>50 µm) that are not effectively phagocytosed may increase the risk of granulomatous reactions.[1] Scanning electron microscopy (SEM) images show that HA-CaHA contains non-porous, uniform, and smooth CaHA microspheres 25 to 45 µm in diameter (Figure 2A). These properties are assessed against rigorous quality controls and confirmed for each batch of HA-CaHA in compliance with ISO standard 13779–6.

Additionally, the ready-to-use presentation of HA-CaHA removes several variables introduced by manual mixing, which can be a common practice in some clinics. First, mixing different HA products or ratios of HA to CaHA may cause unpredictable changes in filler rheology, potentially affecting performance and aesthetic outcomes. HA-CaHA is manufactured with consistent physicochemical properties, which promotes predictable and reliable results. Its high G′ (elastic properties) and cohesivity provide a unique lifting capacity, unlike the transient volumizing effect from the CaHA carrier (eg, CMC). Second, manual mixing of HA and CaHA dilutes the constituent components, which may reduce the effectiveness and duration of response. Anecdotally, one author has observed depressions and palpable irregularities in facial areas such as the forehead and mandible after injection of manually mixed HA and CMC-CaHA, potentially due to rapid resorption of CMC from CMC-CaHA and the mixture's visible inhomogeneity; they have not observed such depressions with HA-CaHA.[2] Third, using HA mixed with CaHA is an off-label use with unvalidated mixing protocols. When performed as described in previous studies, manual mixing introduced air bubbles and resulted in a non-uniform distribution of particles, as shown by X-ray visualization after 5 or 10 repeated passes through plastic syringes and filled into glass syringes for comparison (Figure 2B). The inhomogeneity may lead to inconsistent results at various treated facial areas during a single session. In contrast, HA-CaHA maintains uniform particle distribution throughout the syringe (Figure 2C). Finally, from a safety perspective, the mixing process and additional equipment can potentially increase the risk of environmental contamination and associated complications, if good clinical practices for maintaining sterility are not followed. HA-CaHA is supplied as a sterile product in a ready-to-use, pre-filled syringe, which offers convenience and reassurance to injectors.

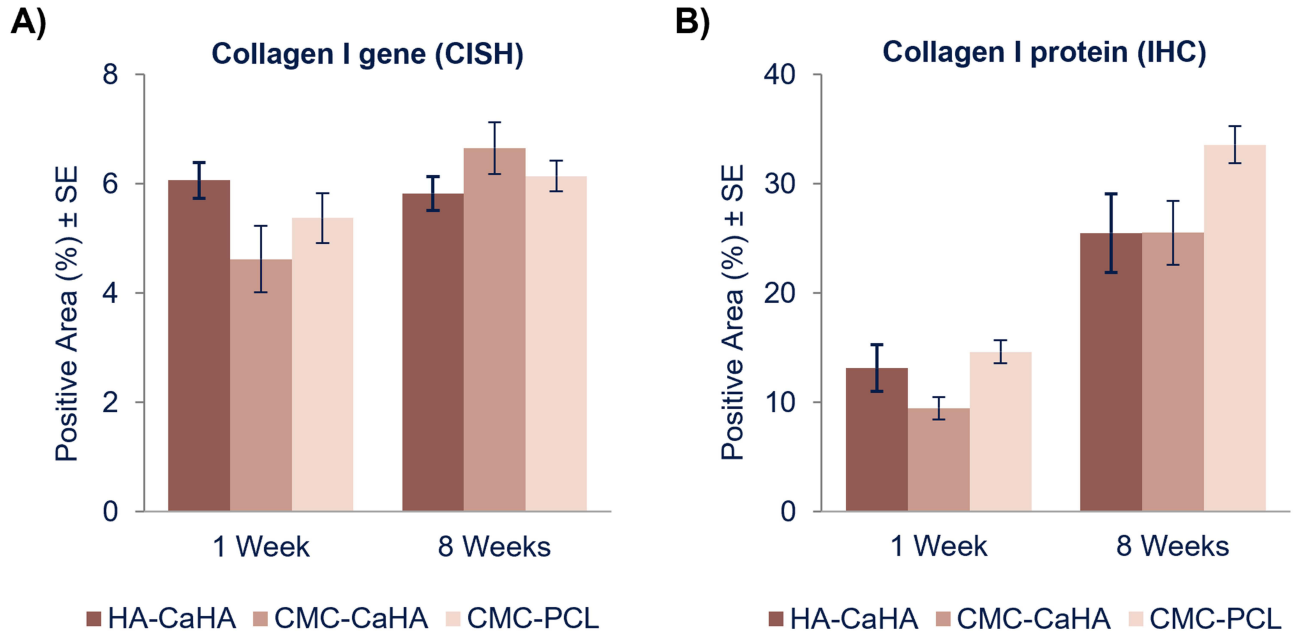

Figure 1 Collagen I levels in tissue explants of rats injected with biostimulator products. Quantified tissue staining from (**A**) chromogenic in situ hybridization (CISH) with probes against collagen I mRNA, and (**B**) immunohistochemistry (IHC) with antibodies against collagen I protein. Data represent mean ± standard error, n = 8. One-way ANOVA with Tukey post-hoc testing was performed at each time point ($P > .05$).

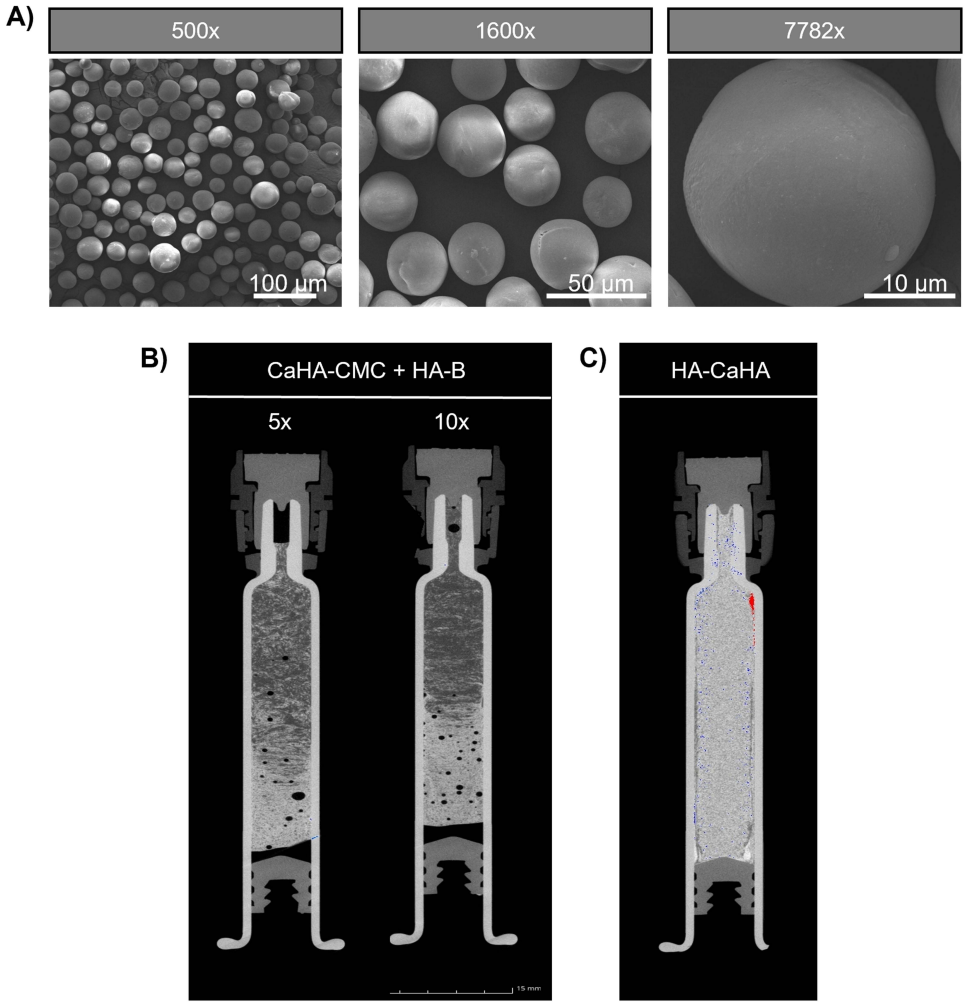

Figure 2 SEM and X-ray imaging of HA-CaHA. (**A**) Scanning electron microscope (SEM) images of CaHA isolated from HA-CaHA at the indicated magnifications. (**B**) X-ray images of CaHA-CMC and HA-B mixed at a 3:2 ratio by 5 or 10 repeated passes (5x or 10x) through plastic syringes and filled into glass syringes for comparison. (**C**) X-ray image of HA-CaHA as supplied.

Limitations of these analyses include the inability to directly extrapolate all the preclinical findings to the clinic, and further human biopsy studies are needed to support the product's biostimulatory properties in more detail, including genomic analysis. The results of 2 independent clinical studies support our preclinical results, where a single treatment with HA-CaHA resulted in high participant satisfaction and objective improvements in dermal thickness and viscoelastic properties.[3,5] Further interventional studies are necessary to validate the theoretical concerns raised and to assess the effects of mixing on filler performance and safety. Ongoing studies (NCT05119777 and NCT05452070) aim to address these limitations. Preliminary findings from the NCT05119777 study showed clinically meaningful and long-lasting improvements in midface volume deficits with low incidence of adverse events (AEs).[6]

Furthermore, post-marketing studies of HA-CaHA showed a low incidence of AEs that were predominantly mild in severity, no reports of serious AEs, and an overall safety profile that was comparable to those reported for HA or CaHA injectables.[7,8] The level of discomfort experienced during injection can be affected by high osmolarity. However, HA-CaHA has a nearly isotonic composition, making it a more favorable characteristic compared with hypertonic CMC-CaHA. Collectively, the preclinical and clinical data support HA-CaHA as an effective and well-tolerated hybrid injectable that provides aesthetic improvements.

In summary, HA-CaHA is a novel manufactured hybrid injectable that combines the volume restoration and lifting properties of HA with the biostimulatory properties of CaHA in a single consistent product. The currently available safety and efficacy data support the use of HA-CaHA to address multiple facets of facial aging.

Data Sharing Statement

Data reported in this manuscript may be requested by contacting AbbVie Inc.

Ethics Statement

All animal study procedures were approved by the Allergan Animal Care and Use Committee and were in compliance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health.

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Disclosure

P Ormiga is a speaker, consultant, investigator, and advisory board member for Allergan Aesthetics, an AbbVie company. CA Hernández is a consultant for Fillmed, Merz, Croma, and Allergan Aesthetics, an AbbVie company. R Romeiro is a consultant and speaker for Allergan Aesthetics, an AbbVie company. A Bernardin, F Crema, L Nakab, L Shklanovsky, and G Kerson are employees of Allergan Aesthetics, an AbbVie company, and may own company stock. The authors report no other conflicts of interest in this work.

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