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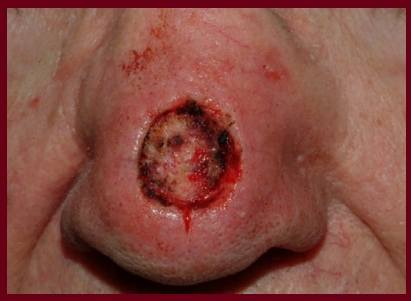

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Current Landscape of Hyaluronic Acid Filler Use in the United States

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ABSTRACT

Background: Hyaluronic acid (HA) fillers are among the most used fillers for soft-tissue augmentation. There are now many FDA approved HA products, and the successful use of injectable HA fillers requires an understanding of the available options.
Objective: The purpose of this manuscript is to provide a comprehensive list of HA fillers and their indications. An overview of their biochemical properties and formulations will aid dermatologists in appropriate use.
Methods: A comprehensive search of all the FDA approved dermal fillers was conducted via the FDA "pre-market approval" (PMA) site. Additional details regarding filler properties were obtained using the respective agent's package inserts.
Results: A total of 28 HA dermal fillers were identified and key pharmaceutical properties were discussed. These findings will help the physician match the appropriate HA filler with the area that is to be treated.
Conclusion: Understanding the available fillers and their properties can help physicians select the appropriate fillers for more predictable and sustainable results.

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INTRODUCTION

With the appreciation of facial aging mechanisms and increased patient demand for minimally invasive procedures, soft tissue dermal fillers have become a cornerstone for facial rejuvenation. Fillers are implants that are injected into the various layers of the skin and subcutaneous planes and lead to immediate volumization and aesthetic improvements with minimal recovery times.[1] Compared to many other forms of aesthetic intervention, dermal fillers (DFs) are temporary, less costly, ambulatory, and integrate well into the dermal matrix resulting in an improved appearance. DFs are either biodegradable or non-biodegradable. The former are gradually absorbed by the body and can last from 3-24 months while the latter are synthetic or artificial and can last nearly 5 years.[2,3] The primary indications of DFs are to restore lost volume and to correct rhytids.

All currently available HA products in the United States are biodegradable fillers. Other biodegradable fillers include poly-L-lactic acid (PLLA, Sculptra Dermik Laboratories 2004, Fort Worth TX), and calcium hydroxyapatite (Radiesse Merz Aesthetics 2006, Franksville WI).[4] HA was first utilized in dermal fillers in 1989 by Balazs and Denlinger and were derived from rooster crests.[5] Until the addition of crosslinking agents with the first generation of HA fillers they were rapidly metabolized when placed in the dermis. With the introduction of non-animal sources (NAS-HA), derived from the fermentation of staphylococcus aureus coupled with the increased demand for nonsurgical cosmetic procedures, clinicians currently often rely on HAs as a product of choice for dermal fillers.[6]

HA is the main polysaccharide in the human dermis and consists of long unbranched alternating units of D-glucuronic acid and N-acetyl –D-glucosamine (Figure 1). This enables HA to

FIGURE 1. Molecular structure of hyaluronic acid.

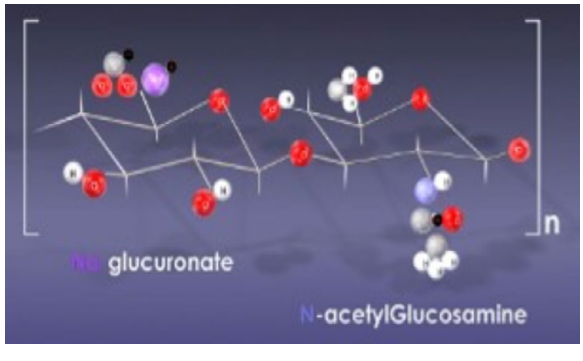

TABLE 1.

Common and Rare Hyaluronic Acid Filler Complications	
Common Dermal Filler Complications	Rare Dermal Filler Complications
Bruising	Hyaluronic Acid granulomas
Erythema	Anaphylaxis
Edema	Livedo Reticularis
Tenderness	Erythema Multiforme
Pruritus	--

bind 1,000 times its volume in water while acting as a lubricant and adsorbent for water. Therefore, HA is critical in maintaining skin moisture as evidenced by its abundance in various organs including the skin, vitreous humor, and synovial fluid.[7] When placed into the dermis, HA fillers promote neocollagenesis and affect fibroblast activity. The depth of injection depends on the extent of the defect: when addressing a superficial defect, a DF should be placed into the papillary dermis layer whereas deeper depressed areas require injection into the papillary dermis. Because of its identical chemical properties to HA in the extracellular matrix of the human dermis, HA in dermal fillers have less antigenic potential and are well tolerated without the need for initial hypersensitivity testing.[1,3]

There are many characteristics of the ideal filler agent including easy to administer, long lasting, nonallergenic, noncarcinogenic, inexpensive, and can be transported and stored at room temperature.[1-3] Hyaluronic acid fillers meet many of these characteristics. Furthermore, unlike many other filling agents, in the event of improper administration of HA, the injection of the enzyme hyaluronidase can metabolize extrinsic HA with possible loss of intrinsic HA and rapidly restore the patient to their baseline appearance. The safety profile for HAs is robust and the adverse events are often temporary and reversible (Table 1).

While there any many variations of HA fillers, the concentration of HA is the characteristic that is regularly referenced. Insoluble HA concentration is more of a predictor for clinical effectiveness and therefore the HA concentration that accompanies the product may not truly reflect the filler's utility.[2] Other variations when considering HA fillers include the degree of crosslinking, gel hardness and consistency, viscosity, extrusion force, and extent of hydration.[2] The various permutations and expansion of new formulations approved by the FDA for HA fillers have made it difficult for clinicians to select the appropriate filler for the corresponding cutaneous defect in question. The pharmacodynamics of HA dermal fillers are all similar, with use in restoring lost facial volume by strong anionic HA filler properties enhancing skin viscoelastic properties. All commercially available HA fillers are clear, colorless, odorless, and come in single use prefilled 0.5 ml or 1.0 ml, ready to use syringes, that should be stored at room temperature. They are all indicated for soft tissue augmentation in patients older than 21 years of age. This article will tabulate the important characteristics of HA fillers and review the current state of these products.

MATERIALS AND METHODS

A comprehensive search of all the FDA approved dermal fillers was conducted via the FDA "pre-market approval" (PMA) site. The FDA PMA listing was screened for dermal filler products that were approved in the US. The approved dermal fillers were ascertained using "LMH" for dermal fillers for the face and "PKY" for dermal fillers for the hand in the PMA database product code search criteria. The product code "LMH" yielded 500 search results, and "PKY" yielded 2 results. Records of duplicate products and non-HA dermal fillers were excluded and 29 products that met the search criteria were identified. After a list of initial cosmetic dermal fillers was obtained, detailed information regarding the brand name, particulate description, FDA approval date, and indication were obtained from each agent's respective package insert. Table 2 summarizes the different formulations and characteristics of HA dermal fillers based on their manufacturer.

RESULTS

Belotero Balance and Belotero Balance (+)

Belotero balance is made using HA from streptococcal cultures cross linked with 1,4-butanediol diglycidyl ether (BDDE) and reconstituted in pH7 buffer with an HA concentration of 22.5 mg/mL. The Belotero Balance + has a similar chemical composition with the addition of lidocaine 0.3% to reduce the pain upon injection.[8] Belotero is administered into the mid to deep dermis for the treatment of moderate to severe facial wrinkles and folds (such as the nasolabial folds). A study evaluating the magnitude of product spread across facial soft tissue layers showed that products that were more fluid and less viscous distributed into more superficial fascial layers compared to products that were less fluid and more viscous.[9]

RHA Redensity and RHA 2,3,4

RHA redensity and RHA 2,3,4 products are FDA approved HA dermal fillers that were initially introduced by Teoxane and manufactured by Revance Therapeutics. The RHA 2,3,4 products are created similarly with different levels of cross linking. They are all produced with sodium HA (NaHA) a concentration of 23 mg/g from streptococcal Equis crosslinked with 1,4-butanedioly diglycidyl ether (BDDE) reconstituted in a buffer (pH 7.3).[10-13] The products are all made of sterile, biodegradable viscoelastic HA. The different formulations 2,3,4 are in order of increasing level of crosslinking, with RHA 2 being the least crosslinked and RHA 4 being the most cross linked. The level of crosslinking ensures product stability and aims to minimize the degradation of the HA chains. RHA redensity is a similar product type that is produced

by crosslinking NaHA at a lower concentration of 15 mg/g from streptococcus equia with BDDS (reconstituted in physiological buffer).[13]

RHA 2,3,4 are FDA approved for injection in the dermis for the correction of facial wrinkles and folds, whereas RHA 4 is the only one indicated for deeper dermis/superficial subcutaneous injection for similar indications.[12] Studies have shown that RHA 2 is applicable for superficial placement, whereas RHA 3 has more balanced stretch and dynamic properties making it more versatile. RHA 4 has the highest strength and sufficient stretch that allows for its deeper facial placement.[14] RHA redensity is one of the only agents that is FDA approved for the correction of perioral rhytids.

Prevelle Silk Dermal Filler

Prevelle Silk is an injectable HA dermal filler product introduced by the Mentor Corporation. It is a colorless HA gel that is made from bacterial origin cross linked with divinyl sulphone (DVS) at 4.5-6.5 mg/ML with 0.3% lidocaine solution. It is approved for injection into the mid-deep dermis to treat moderate/severe facial wrinkles and creases.[15]

Juvéderm Dermal Fillers

Juvéderm products are FDA approved HA fillers by Allergan Aesthetics with the earliest products being available since 2006. All Juvéderm products are made of sterile, viscoelastic clear, colorless HA gel (made by streptococcus) crosslinked with BDDE with 0.3% lidocaine in a physiologic buffer.[16-20] The various Juvederm formulations vary with respect to concentrations and FDA approved indications. The products in order from least to strongest concentrations are: Volbella XC, Vollure XC, Voluma XC, Ultra XC/Ultra plus XC, Volux XC.[16-20] Juvéderm Vollure XC, Juvederm Ultra XC and Juvederm Ultra plus XC are available for injection in the mid-deep dermis for the treatment of facial wrinkles and folds.[18,20] Juvederm ultra XC is available for injection into the lip and perioral area for lip augmentation.[20] Juvederm Volbella is also available for lip augmentation and correction of perioral rhytids as well as infraorbital sulcus.[16] Juvederm Volux XC is approved for deep injection to improve jawline definition and Juvederm Voluma is available for cheek restoration and chin augmentation.[17,19] The key difference between Juvederm ultra and Juvederm ultra plus is that ultra plus has a thicker formulation with larger sized particles with a higher degree of cross linking. There has been a reported utility of Juvederm products in the treatment of depressed scars for natural contouring of the skin with a duration of 24 months without the need for repeat injections.[21,22]

Juvederm Skinvive is a recently approved HA product and the first intradermal microdroplet injection filler for the treatment of skin smoothness of the cheek.[23] It has been reported to improve skin rejuvenation for 6 months. This formulation has a long duration of effect, is minimally invasive, and does not need recurring treatments within 6 months. Emerging studies have shown that Skinvive has great potential in hydrating the cheek by increases in aquaporin levels.[24] The adverse effect profile was similar to other HA fillers with redness, swelling, and tenderness being among the most common reported. A rare adverse effect reported was needle abrasions and papules.

Revanesse Dermal Fillers

Revanesse products are all HA based FDA approved dermal fillers made by Prollenium Medical Technologies first introduced in 2017.[23] Revanesse Lips + and Revanesse Versa + are the more commercially available, Revanesse Ultra were utilized previously and are now under the brand named Revanesse Lips +. All Revanesse products are HA fillers that are chemically cross linked with BDDE at a concentration of 22-28 mg/mL. The formulations Revanesse Lips and Versa (without the +) are similar to the + formulations without lidocaine. Revanesse Kiss products are FDA approved for lip augmentation and Revanesse Versa products are approved for facial wrinkles and creases.

Restylane

Restylane products are HA based FDA approved dermal fillers developed by Galderma and first introduced into the market in 2003. Like most HA dermal fillers, the HA is made from streptococcus bacteria and chemically crosslinked with BDDE at a concentration of 20 mg/mL and suspended in a physiological pH buffer. The chemical composition of the Restylane fillers are similar with 0.3% lidocaine being added to most formulations after Restylane L was introduced in 2010.[25-32] Although the Restylane products have similar compositions, the different brand names correlate with a different FDA approved indication. Restylane silk and Lyft products have similar formulations to Restylane L.[26-28] Restylane Kysse is similar with moderate lifting capacity with lidocaine.[29] Restylane Refyne is used for the correction of facial wrinkles and folds, and Restylane Defyne is used for deep facial wrinkles and chin augmentation/retrusion. Restylane Contour is utilized for cheek augmentation and correction.[32] Both Restylane Refyne and Defyne have similar compositions to Restylane Kysse, whereas Restylane Contour has a similar formulation but is listed as having a "higher" lifting capacity.[30-33] Restylane Eyelight is the newest market addition and the first HA dermal filler FDA approved for the treatment of undereye hollows.[34] Some individual cases have reported that Restylane can persist in the dermis as long as 23 months after initial implantation.[35] Restylane is efficacious in patients with darker skin complexions with similar safety endpoints, further suggesting its broad clinical use.[35,36]

Hydrelle "CTA" and Hylaform

Two products that have been withdrawn from the market are Hydrelle and Hylaform which are included for historical reference. CTA HA dermal filler was first FDA approved in 2006

TABLE 2.

Summary of FDA approved Hyaluronic Acid Fillers

Brand Name Of Ha Dermal Filler (Approval Year)	Approved Indication	Particulate (Summarized, Description)	Properties: Ph, Concentration, Cross Linking Agent	G', Particle Size
Belotero Balance (R) Dermal Filler (2011)[8] Belotero Balance + Lidocaine Dermal filler (2011)[8]	Belotero Balance: Moderate to severe facial wrinkles and folds Belotero Balance + : Moderate-severe facial wrinkles and folds	Belotero balance: Sterile, bioresorbable, non-pyrogenic, viscoelastic, clear, colorless homogenous gel device. Bacterially fermented, injectable HA filler. HA from streptococcal cultures is crosslinked and reconstituted in a buffer. Belotero Balance (+): Same as above with lidocaine 0.3%	Belotero Balance and Belotero Balance +: pH 7, 22.5 mg/mL, BDDE[35]	410 um size
RHA Redensity (2021)[13] RHA2 (2017)[10] RHA3 (2017)[11] RHA4 (2017)[12]	Rha Redensity: Mid-Moderate to severe dynamic perioral rhytids in patients 22 years + Rha 2: Moderate to severe dynamic facial wrinkles and folds, in 22 year + RHA 3: Moderate to severe dynamic facial wrinkles and folds, in 22 year + RHA 4: Moderate to severe dynamic facial wrinkles and folds in 22 year +	RHA redensity: Viscoelastic, sterile, non-pyrogenic, clear, colorless homogenous and biodegradable gel implant with crosslinked and Non crosslinked HA. Processed from Sodium HA from streptococcus equi. Also has 0.3% lidocaine HCL. RHA 2,3,4: Same profile as RHA redensity, however they are made with a higher concentration. The degree of crosslinking is the main difference between RHA 2,3,4. RHA 2 is the least cross-linked and RHA 4 is the most cross linked.	RHA redensity: pH 7.3, 15 mg/g, BDDE[35] RHA 2,3,4: pH 7.3 and 23 mg/g, BDDE[35]	--
Prevelle Silk with 0.3% Lidocaine (2008)[15]	Moderate to severe facial wrinkles and creases	Colorless HA gel from non-animal (bacterial) origin with lidocaine crosslinked. It is formulated with 0.3% lidocaine	Prevelle: 4.5-6.5 mg/mL, DVS	G' 230-360
Juvederm Volbella XC (2016)[16] Juvederm Volux XC (2022)[19] Juvederm Voluma XC (2013)[17] Juvederm Vollure XC (2013)[18] Juvederm Ultra XC (2006)[20] Juvederm Ultra Plus XC (2006)[20] Juvederm Skinvive (2023)[23]	Volbella: Lip augmentation, correction of perioral rhytids and infraorbital hollowing in patients 21+ Volux XC: Moderate-deep loss of jawline definition in patients 21+ Voluma XC: Cheek augmentation in mid-face and for chin augmentation in patients 21+ Vollure XC: Moderate/severe facial wrinkles and folds in patients 21+ Ultra XC: Moderate/severe facial wrinkles and folds. Lip augmentation in patients 21+ Ultra Plus XC: Moderate/severe facial wrinkles/folds.	Volbella XC: sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless homogenous gel cross linked HA (made by streptococcus) crosslinked with BDDE formulated with 0.3% w/w lidocaine in physiologic buffer. Volux XC: Same as above with 0.3% lidocaine Voluma XC: Same as above with 0.3% lidocaine Vollure XC: Same as above with 0.3% lidocaine Ultra XC: Same as above with 0.3% lidocaine Ultra Plus XC: Same as with 0.3% lidocaine	Volbella: 15 mg/mL,[35] Volux: 25 mg/mL Voluma: 20 mg/mL, 35 Vollure: 17.5 mg/mL Ultra XC: 24 mg/mL Ultra Plus XC: 24 mg/mL Skinvive: 12 mg/mL All formulated in a physiologic buffer crosslinked with BDDE	Volbella: G' 274, 634 ± 255 Volux: G' 665 Voluma: G'353, 703 ± 389 Vollure: G' 317 Ultra Plus: 74-105 Ultra: 28 Skinvive: G' 166
Revanesse Lips + (2020)[23] Revanesse Lips (2020) Revanesse Versa (ultra) + (2017)[23] Revanesse Versa (2017)	Revanesse Lips: submucosal implantation for lip augmentation in patients 22+ Revanesse Versa (ultra): Moderate to severe facial wrinkles and folds in 22+	Revanesse Lips and Versa: Biocompatible, biodegradable, non-pyrogenic, sterile injectable viscoelastic clear colorless hydrogel cross-linked HA Revanesse (+) formulations all contain additional 0.3% lidocaine	Revanesse products: 22-28 mg/mL, BDDE	--

TABLE 2. (CONTINUED)

Summary of FDA Approved Hyaluronic Acid Fillers				
Brand Name Of Ha Dermal Filler (Approval Year)	**Approved Indication**	**Particulate (Summarized, Description)**	**Properties: Ph, Concentration, Cross Linking Agent**	**G', Particle Size**
Restylane (2003)[25] Restylane L (2010)[26] Restylane silk (2014)[27] Restylane Lyft (2007)[28] (formerly Perlane), Restylane Kysse (2020)[29] Restylane Refyne (2016)[30] Restylane Defyne (2016)[31] Restylane Contour (2021)[32] Restylane Eyelight (2023)[34]	Restylane: Moderate-severe facial folds. Lip augmentation in patients 21+. Restylane L: Same as above. Restylane silk: Lip augmentation and dermal implant for correction of perioral rhytids in patients 21+ Restylane Lyft: Moderate to severe facial folds and wrinkles. Subcutaneous to supraperiosteal implantation for cheek augmentation and age-related midface contour deficiencies in 21+. Injection into subcutaneous plane in dorsal hand to correct volume deficit in 21+. Restylane Kysse: lip augmentation and correction of upper perioral rhytids Restylane Refyne: Moderate to severe facial wrinkles and folds in patients 21+ Restylane Defyne: Moderate-severe deep facial wrinkles in patients 21+ , chin region to improve chin profile in patients 21+ with chin retrusion Restylane Contour: Cheek augmentation and correction of midface contour deficiencies Restylane Eyelight: Treatment of undereye hollows	Restylane: HA gel made by streptococcus bacteria chemically crosslinked, stabilized and suspended in phosphate buffered saline Restylane-L: Same as above but with 0.3% lidocaine. Restylane silk: Same formulation as Restylane L Restylane Lyft: Same formulation as Restylane L Restylane Kysse: Sterile, biodegradable, viscoelastic, non-pyrogenic, clear, colorless, flexible and homogenous gel composed of HA with moderate lifting capacity crosslinked with BDDE. Sodium hyaluronate concentration and 3 mg/mL lidocaine HCL. Restylane Refyne: Same as Restylane Kysse Restylane Defyne: Same as above Restylane Contour: Same as above but "high" lifting capacity.	Restylane: 20 mg/mL, pH 7, BDDE[35]	Restylane: G' 349 Pa, particle size 547 ± 280 G' 513Pa, 677, 250 microns 300 um, G' 660 Restylane: 513

and made commercially by Coapt Systems and was the first HA filler to include lidocaine in its formulation. Similar to other HA gels, it is composed of an HA produced by streptococcus species that is crosslinked and suspended in a buffer at a high concentration of 28 mg/L with 0.3% lidocaine HCL. Hylaform was an injectable FDA approved HA dermal filler that was created by the Inamed Corporation and Genzyme corporation that was approved in 2004. Unlike most other dermal fillers, the HA from this gel is from avian (bird) origin and chemically crosslinked with divinyl sulphone (4.5-6.5 mg/mL).

DISCUSSION

The increased use of HA dermal fillers has corresponded to the increased FDA approval in the past few decades. Correspondingly there has been an increase in formulations of HA products, degree of cross linking and their agents (BDDE, DVS), concentration, and the different FDA approved indications. The FDA has stated that approved uses of temporary dermal fillers include correction of moderate/severe facial wrinkles and skin folds, and augmentation of lips/cheeks/chin and back of the hand. Perhaps within the standard of care in each community, all other areas are considered off label. Unapproved uses are for any other body enhancement (should be performed with the patient's full written consent).[36] Dermal fillers should not be implanted into vessels, bones, tendons, ligaments, and muscles. It is recommended that patients who are allergic to bacterial proteins and lidocaine should not be treated with dermal fillers. Additionally, dermal fillers should be used with caution in patients with bleeding diathesis.

In general, the fillers with the higher HA concentration and a higher degree of cross linking tend to be used for deeper injection and deeper significant wrinkles/folds. Some companies have utilized similar formulations across different FDA indications; however, they changed the brand product name to fit the specific indication. We found that most dermal filler manufacturers have a filler approved for the correction of facial wrinkles, 1 agent approved for non-facial areas, 3 for use

in cheeks, 7 for lip augmentation, 1 for the jaw, 1 for undereye hollows, and 2 for chin use. One novel intradermal microdroplet HA filler (Skinvive) has recently been introduced to the market in 2023 with greater efficacy and less need for retreatments. Long term comparator studies should evaluate the efficacy of these novel dosage forms compared to traditional intradermal HA filler injections. Agents have been used off label for other indications, this is done at the physician's discretion. Most formulations include lidocaine to reduce pain upon injection. While not sanctioned by the FDA, to further reduce discomfort upon injection, some physicians will blend additional lidocaine into the HA filler. Although uncommon, infections from nonsterile sites of infection and filler migration can occur.[7] Poor aesthetic outcomes can occur with improper use/administration of dermal fillers and/or unrealistic expectations from patients.

Although HA dermal fillers have been predominantly used for cosmetic purposes including facial feature correction and augmentation of facial rhytids, there has been promising use for these products in other clinical areas including atrophic scars and those resulting from surgery.[37-40] DFs can also help correct post-surgical asymmetry, and atrophy from radiation therapy.[41] DFs have been shown to be effective in wound healing and have also been used in other post-surgical/oncology fields such as for post-breast surgery reconstruction and non-surgical rhinoplasty.[42,43]

Although some studies have shown promise, there is a lack of large scale randomized clinical trials evaluating dermal fillers for post-surgical cosmetic/clinical complications. Additionally, with the availability of many different HA dermal filler options, there is a need for more objective comparison trials to evaluate these agents in different clinical uses to better standardize agent selection for use. These studies will help physicians in selecting the optimal agent for the corresponding defect with the best efficacy and safety profile for the best patient outcomes.

CONCLUSION

As dermal fillers become more popular for cosmetic use, an updated list of all the commercially available and FDA approved HA fillers will be invaluable for physicians to determine what filler best suits their patient's requirements. Hyaluronic acid fillers have become popular because of their low immunogenicity and allergic response, ease of injection, rapid recovery, reproducibility, reversibility, and rapid results. Currently, there are many HA fillers available on the market with more on the horizon. The appropriate filler should be selected based on various scientific characteristics, sound knowledge of the many hyaluronic acids, and their FDA indication is fundamental to optimize the correction of age-related loss of volume. Future studies may aim to look at use in medical procedures as well for newer indications. More precise standardizations of HA fillers in future studies may allow more accurate comparisons and will impact evolving indications.

DISCLOSURES

The authors have no funding or conflicts of interest to declare

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ORIGINAL ARTICLE

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Promoting a Healthy Skin Barrier Using Skin Care in People With Mature Skin Xerosis

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ABSTRACT

Introduction: Most people are living into their sixties and beyond. Fundamental changes in chronologically aged skin have significant and widespread dermatological implications. This review discusses aging-associated alterations in epidermal function leading to xerosis and related pruritus and the benefits of maintaining or restoring a healthy skin barrier using skincare, specifically ceramide-containing skincare.

Methods: A panel of 7 dermatologists convened for a meeting to review aspects of xerosis in mature skin, skin barrier changes, and nuances in the treatment and maintenance of mature skin using gentle cleansers and moisturizers.

From the selected literature, 13 statements were drafted. During the meeting, the draft statements underwent the panel's evaluation at a workshop, followed by a plenary discussion adopting 5 statements using evidence from the literature coupled with the panel's opinions and experiences.

Results: The exact etiology of xerosis is not entirely understood and likely depends on several genetic and environmental mechanisms. Aging-associated changes in epidermal function include a marked reduction in total lipids in the stratum corneum relative to young skin due to reduced epidermal lipid synthesis. In aging skin, xerosis is significantly associated with pruritus. Studies have shown that lipid-containing skin care, such as a gentle ceramide-containing cleanser and moisturizer, promotes a healthy barrier reducing xerosis and pruritus in individuals with mature skin.

Conclusions: The development of xerosis in mature skin involves several genetic and environmental mechanisms. Skincare, including gentle cleansers and moisturizers, has reduced xerosis and pruritus in mature skin individuals.

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INTRODUCTION

With advances in medical biology and healthcare technology over recent decades, human lifespans are increasing worldwide, resulting in a proportionate increase in the aged population.[1,2] Today, most people can expect to live into their sixties and beyond.[1]

Fundamental dermal and epidermal changes in chronologically aged skin have significant and widespread dermatological implications.[3,4] As early as 50, the frequency of aging-associated skin conditions increases, in parallel with epidermal dysfunction such as compromised permeability homeostasis, reduced stratum corneum (SC) hydration, and elevated skin surface pH.[5-8] Studies have shown that epidermal dysfunction predisposes to xerosis, pruritus, atopic dermatitis, and contact dermatitis.[9,10] Skin conditions affect up to 70% of matured individuals, with xerosis and pruritus as the most common skin disorders.[5] The etiology of xerosis in mature skin is not fully understood but likely involves genetic and environmental factors leading to changes in the keratinization process and lipid content in the SC.

TABLE 1.

Intrinsic Factors for Xerosis	
Category	**Examples**
Dermatological diseases	Atopic dermatitis, allergic contact eczema, irritant contact dermatitis, ichthyoses. Fungal and bacterial infections, pediculosis, scabies. Cutaneous lymphoma (eg, mycosis fungoides).
Internal diseases	Chronic kidney disease, diabetes mellitus, hepatopathies (eg, primary biliary cholangitis, primary sclerotic cholangitis, drug-induced cholestasis, extrahepatic cholestasis), hyperparathyroidism, hypothyroidism, and malabsorption.) Chronic inflammatory bowel disease (gluten-sensitive enteropathy), rheumatic disease. Diarrheal diseases, helminths, hepatitis B and C virus, HIV. Menopause, andropause, pregnancy. Myeloproliferative disorders (eg, polycythemia vera, essential thrombocytosis), Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma.
Psychiatric disorders	Obsessive skin cleansing/washing, anorexia, alcohol, and drug abuse.
Dietary disorders	Insufficient fluid intake, excessive perspiration, Hypovitaminosis (vitamin D, vitamin A, niacin deficiency), zinc or iron deficiency.
Medication-related	Retinoids, topical corticosteroids (prolonged use), diuretics, lipid-lowering agents, calcium antagonists, beta-blockers, antirheumatic drugs, contraceptives/antiandrogens, cytostatic agents, radiation dermatitis (following radiation therapy), and possibly immunomodulators.

This review discusses aging-associated alterations in epidermal function leading to xerosis and related pruritus and maintaining or restoring a healthy skin barrier using skincare, specifically ceramides-containing (CER-containing) skincare.

MATERIALS AND METHODS

The project used a modified Delphi process comprising face-to-face discussions followed up online.[11,12]

Literature Review

The structured literature searches (01-August 2022) on PubMed and Google Scholar, as a secondary source, of the English-language literature (2010 – July 30, 2022) were performed by a dermatologist and a physician/scientist (searchers). Additionally, the searchers manually reviewed the selected literature for additional resources. The searches prioritized studies on mature skin xerosis, SC barrier function, and skincare benefits using cleansers and moisturizers. The searches for mature* skin included senile xerosis, xerosis in aging skin, and xerosis in the elderly, and explored present clinical guidelines, treatment options, and therapeutic approaches addressing mature skin xerosis using the following terms:

Mature skin xerosis AND skin barrier physiology OR function OR dysfunction OR depletion of stratum corneum lipids OR atopic dermatitis.*

Mature skin xerosis AND skincare OR cleansers OR moisturizers OR emollients OR ceramides OR ceramides containing skincare OR efficacy OR safety OR tolerability.*

The searches yielded 42 papers deemed clinically relevant to mature skin xerosis and skin care to promote a healthy skin barrier and potential mitigation of xerosis using over-the-counter (OTC) skincare and CER-containing cleansers and moisturizers.

Role of the Panel

The panel of 7 dermatologists (panel) convened for a meeting (September 3, 2022) to review unique aspects of xerosis in mature skin and the skin barrier changes and to discuss nuances in the treatment and maintenance of mature skin using gentle cleansers and moisturizers.

From the selected literature, the searches (AA and TE) and MG drafted 13 statements. During the meeting, the draft statements underwent the panel's evaluation at a workshop, followed by a plenary discussion adopting 5 statements using evidence from the literature coupled with the panel's opinions and experiences. The second step consisted of a post-meeting review by individual advisors of the manuscript.

Statement 1: *The exact etiology of xerosis is not entirely understood and likely depends on several genetic and environmental mechanisms.*

A healthy skin barrier function depends on the complex interplay among SC pH, desquamation rate, and the appropriate ratio of intrinsic lipids.[13,14] The lipids comprise approximately 20% of the volume of the healthy SC and are composed of CERs (40-50%), cholesterols (20-33%), and free fatty acids (7-13%).[13,14] Further lipids include cholesterol-3-sulfate (0-7%) and cholesteryl esters (0-20%).[13,14] The slightly acidic surface of healthy skin is required to maintain the SC barrier, inhibiting the growth of pathogenic microorganisms.[13] Skin acidification plays a vital role in SC barrier health and activates enzymes in the extracellular processing of SC lipids.[13] The SC pH influences barrier homeostasis, integrity, cohesion, and antimicrobial defense mechanisms.[13,15,16]

Occupational screening studies (n = 48,380) showed that approximately every third employee (29.4 %) between the ages of 16 and 70 years is affected by xerosis.[14] The prevalence of xerosis increases in mature skin at 55.6 % at a mean age of 75.1 years.[14] Xerosis is characterized by decreased quantity and quality of lipids and/or moisturizing factors and is generally diagnosed on clinical presentation.[9,10,13,14-16] It is essential to distinguish between constitutional xerosis and xerosis due to dermatoses such as atopic dermatitis (AD), psoriasis, or ichthyosis and xerosis triggered by exogenous factors.[9,10,13,14] Xerosis may be due to systemic diseases such as diabetes, renal and biliary diseases, infections, and hormonal changes, or triggered by medication (Table 1).[13,14]

Statement 2: *Xerosis in older adults is multifactorial and may include: intrinsic age-related changes, use of diuretics and similar medications, systemic conditions, hypothyroidism, and overuse of heaters or air conditioners.*

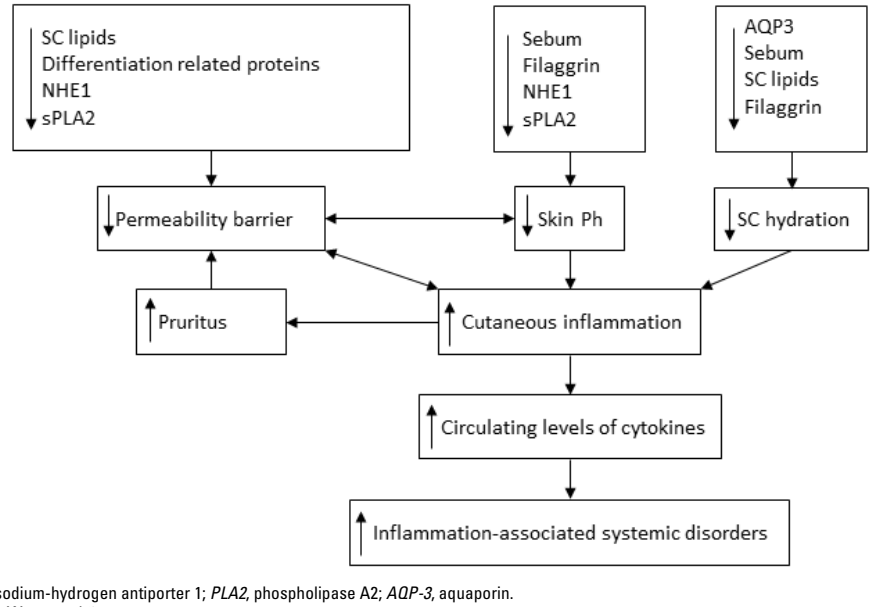
Xerosis is a common skin condition in matured skin characterized by xerosis, and pruritic, excoriated, and exfoliated skin.[17-24] The exact etiology of mature skin xerosis is not understood and likely depends on several genetic and environmental mechanisms.[17-19]

Intrinsic aging is a fundamentally unsustainable process that affects the entire body, including sun-protected sites.[16] Intrinsic skin aging is primarily characterized by atrophy, as the number of cells that make up the skin and the amount and quality of the extracellular matrix decrease.[16] Further, the amount and the conduction of blood vessels and nerves that supply the skin deteriorate or decrease.[16] Xerosis in older adults is multifactorial: intrinsic changes in keratinization and lipid content, use of diuretics and similar medications, systemic conditions, hypothyroidism, medications, and overuse of heaters or air conditioners can all contribute to the disease.[19-24] Skin is a target of reactive oxygen species (ROS) and oxidative stress from both extrinsic (solar radiation) and intrinsic sources (oxidative metabolism).[17] Chronic exposure to extrinsic factors, such as ultraviolet radiation, air pollution, smoking, alcohol consumption, or malnutrition, induces an age-associated skin microenvironment, including inflammation and reduced collagen production.[17,18]

Changes in the keratinization process and lipid content in the SC probably represent the main factors in mature skin xerosis.[19-24] From about 50 years of age, epidermal dysfunction may occur, such as compromised permeability homeostasis, SC hydration reduction, and skin surface pH elevation.[19-23] The reduction of epidermal growth factors, keratinocyte proliferation, and increased keratinocyte apoptosis has been shown to lead to a thinner epidermis and SC.[7] Further aging-related skin changes included a decline in the levels of structural proteins for the epidermal permeability barrier, including filaggrin, loricrin, and other late cornified envelope proteins.[8] In mature skin, the barrier function weakens, leading to increased transepidermal water loss (TEWL) and decreased protective functions (Figure 1).[20-23]

The speed of the aging process depends mainly on individual genetic factors.[16] Women develop these signs earlier due to a decrease in the protective effects of estrogen hormones during menopause.[14-16]

FIGURE 1. Mature-skin-associated stratum corneum function changes.



SC, stratum corneum; NHE1, sodium-hydrogen antiporter 1; *PLA2*, phospholipase A2; *AQP-3*, aquaporin.
Adapted with permission from Wang et al.[16]

Statement 3: *Aging-associated changes in epidermal function include a 30% reduction in total lipids in the stratum corneum relative to young skin due to reduced epidermal lipid synthesis.*

Ceramides, cholesterol, and free fatty acids are essential constituents of the SC.[14,16] They form a highly ordered matrix called the lipid lamellae and fill the space between the corneocytes.[14,16] The composition and structure of the lipid lamellae are critically important to the permeability barrier function of the skin and form an effective waterproof barrier.[14,16] The composition of SC lipids is influenced by age, genetic disposition, time of year, diet, hormone-mediated sebum production, and medication such as cholesterol-lowering agents.[14,16] Reductions in SC lipid content may be due to the delayed barrier recovery in mature skin.[6,16] In aged skin, the number and function of sebaceous glands reduce, leading to xerosis.[20-23] In mature skin, along with the gradual degeneration of the innervation of the skin and the decrease in the number of sweat glands, the heat balance and cold tolerance of aging individuals deteriorates.[20-23]

Studies have shown that baseline TEWL rates on several body sites are lower in matured vs young skin.[6] The demonstrated TEWL rates on the décolleté region correlated positively with age, but TEWL rates on the neck, forearm, and hand were comparable between young and aged women.[6]

Studies from the mid-nineties have shown that the aged SC displays a >30% reduction in total lipid content compared with young SC due to reduced epidermal lipid synthesis, particularly in cholesterol synthesis, both under basal conditions and after barrier disruption.[25,26] Studies have further shown that epidermal dysfunction predisposes to various cutaneous abnormalities, including atopic dermatitis, contact dermatitis, pruritus, and xerosis.[9,10,20-23,27]

In support of evidence that reduced lipid levels contribute to aging-associated dysfunction in the skin barrier, topical applications of SC physiologic lipid mixtures such as ceramides may improve epidermal permeability barrier function.[14]

Statement 4: *In older people, xerosis is significantly associated with pruritus.*

Pruritus is common in matured skin and has been attributed partially to a decline in normal physiology due to advanced aging.[24,27-31] Pruritus significantly impacts the quality of life and is reported by patients to be as bothering as skin pain or even worse.[31] Changes in mature skin structure and its ability to regenerate, along with cumulative effects of the environment, diminish the SC barrier function and hydration.[21,24] These changes make the elderly more susceptible to the entry of irritants and allergens through the skin, leading to inflammation and pruritus.[24]

A cross-sectional study including 756 patients aged 65 and older reported a prevalence of xerosis of 56%.[19] Of these patients, 9% had moderate to severe xerosis associated with a significant disease burden, including pruritus and feelings of very dry or unbearably dry skin.[19] Another cross-sectional study of a population of 11,730 showed that the prevalence of chronic pruritus was 20.3% in people between 60 and 70 years.[30] The large study demonstrated significant xerosis-associated risk factors for pruritus, including older age, female sex, atopic dermatitis, or concomitant treatment that may be associated with xerosis.[30] Additional causes of pruritus may include various comorbidities, such as renal failure, cholestasis, systemic infections, diabetes mellitus, liver failure, malignancies, or certain hematological disorders.[28-30]

Xerosis is often associated with pruritus, mainly involving the extremities, and is more prominent at low temperature and humidity conditions.[19,30] Scratching can lead to secondary infections, ulcerations, and chronic wounds.[24,27-29]

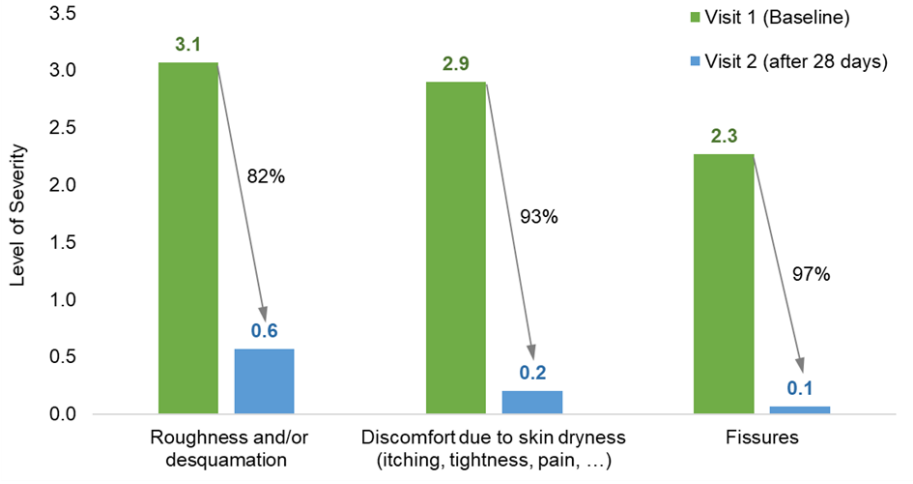
SC lipids containing moisturizers such as ceramides combat xerosis and may reduce pruritus.[13] Components of topical products such as polidocanol, menthoxypropanediol (derivate of menthol and an agonist of the TRPM8 receptor), or N-palmitoylethanolamide, a fatty acid, may have antipruritic effects.[32-35] A double-blind, vehicle-controlled study including patients with xerosis and pruritus (N=70) showed that those topically treated for 6 weeks with menthoxypropanediol combined with cyclohexane carboxamide reported a significantly more robust and longer-lasting antipruritic effect than those receiving the placebo.[34] A study on topically applied N-palmitoylethanolamide demonstrated antipruritic effects in patients with xerosis.[35]

Treating pruritus with systemic medication is outside the scope of this review and is not discussed here.

Statement 5: *Moisturizers containing urea, ceramides, and lactate have shown benefits in promoting a healthy skin barrier structure and function in older people with xerosis.*

Skincare using gentle cleansers and moisturizers can promote a healthy skin barrier and is crucial for mature skin to reduce TEWL and minimize exposure to irritants and allergens.[14,36-42] Acidification of the SC may improve epidermal structure and function in chronologically aged humans. In aged subjects, using a moisturizer at pH 4.0 for 29 days improved SC hydration and lamellar bilayer structure, along with increased resistance to challenges from topical sodium dodecyl sulfate.[36] Following acute SC barrier disruption in aged subjects, a topical pH 4.0 moisturizer improved SC barrier recovery faster while significantly improving SC integrity after 28-day treatments compared with a pH 5.8 moisturizer.[37]

FIGURE 2. Physician evaluation of roughness/desquamation, discomfort, and fissures.

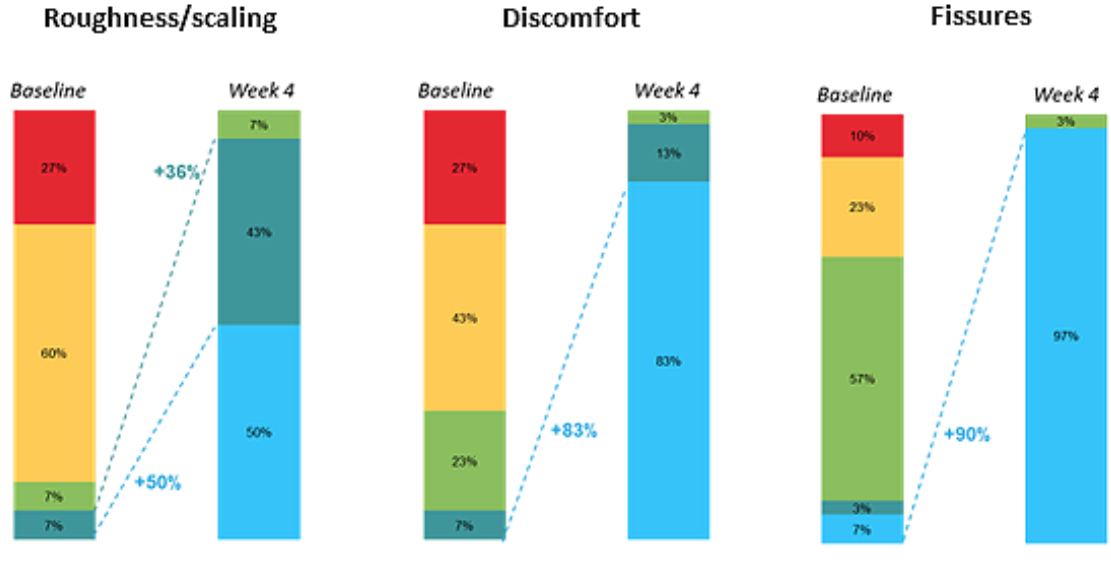


N = 30 men (63%) and women (37%) age ≥ 70 years with xerosis and/or scaly skin.
Treatment: ceramides-containing cleanser and moisturizer at least once per day.

Danby and colleagues included 2 cohorts (N=21) of patients with senile xerosis 60 years and older and one test group.[38] The comparative 28 days study treated group 1 with the test emollient (Urea 5%, ceramide NP) on the forearm vs no treatment on the other arm. Group 2 received the test emollient on the forearm vs the control emollient (soft white paraffin, liquid paraffin) on the other arm. Effects on the skin barrier were evaluated by measuring skin barrier function, hydration, and skin surface pH, and by analyzing Fourier transform infrared spectra before and after treatment. Group 3 (6 young adults) applied the test emollient once and, with a tape-stripping technique, the effect on the skin barrier's molecular structure was measured. The test emollient showed significantly better and longer-lasting results and addressed the pathological features of xerotic mature skin, supporting its use as first-line therapy for xerotic skin conditions in this population.[38]

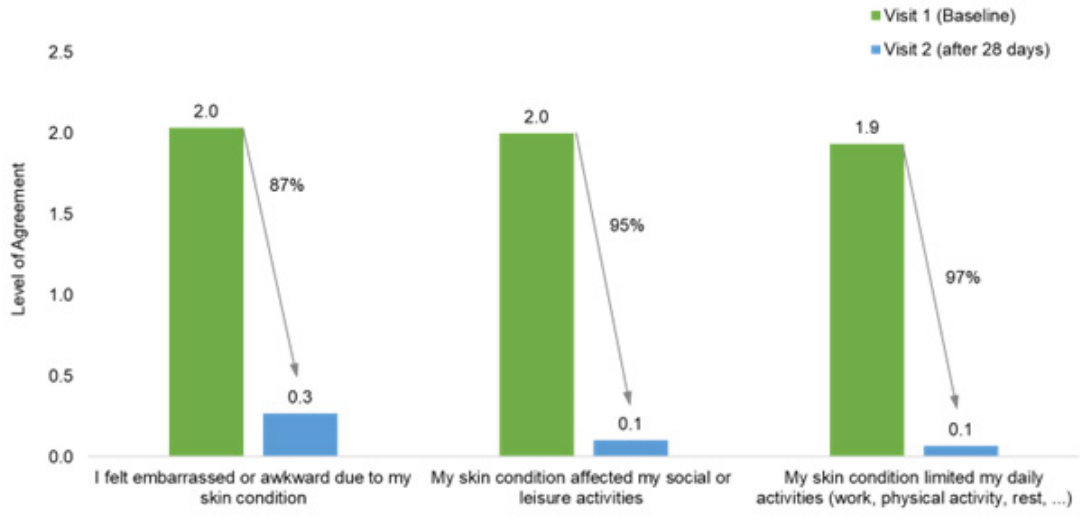
Another study included 20 patients with senile xerosis aged 62 to 82 years who received 10% urea cream for 14 days. Pruritus (Visual Analog Scale) scores and dermoscopy were used for evaluation. At the end of the study, all scores showed a significant improvement (P<0.05). The Pearson's test showed a correlation

FIGURE 3. Patient evaluation of roughness/desquamation, discomfort, and fissures.



5-point scale: 4 (intense), 3, 2, 1, 0 (none)
N = 30 men (63%) and women (37%) age ≥ 70 years with xerosis and/or scaly skin.
Treatment: ceramides-containing cleanser and moisturizer at least once per day.

FIGURE 4. Improvement in patient quality of life after four weeks of treatment.



Average calculated on the scale of level of severity: Strongly disagree (0) - Strongly agree (3)

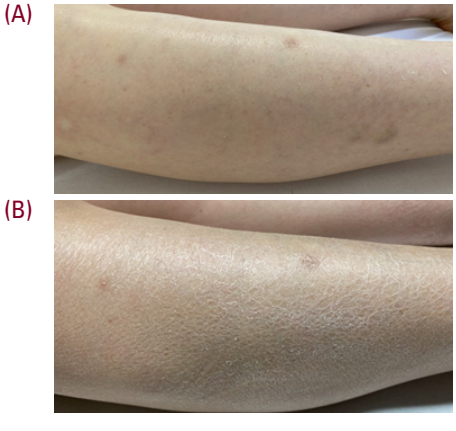
between clinical and dermoscopy evaluation both at baseline, day 7, and day 14 ($r = 0.73$, $r = 0.76$, $r = 0.71$, respectively).[39]

A randomized, investigator-blinded, split-leg study treated xerosis in 53 women using a ceramides-containing cleanser and moisturizer for 4 weeks. Skin hydration, visible signs of xerosis, subject sensory discomfort, ceramides, cholesterol, and free fatty acid levels in the SC were evaluated. The skincare regime improved skin water content through corneometry, a reduction in the subject's perceived sensory discomfort, and the dermatologist investigator-assessed resolution of the signs of dry skin. Improvement continued for 48 hours after moisturizer withdrawal.[40]

Another study in matured skin subjects showed that topical applications of a moisturizer containing SC lipids improved SC hydration and reduced skin surface pH and circulating levels of proinflammatory cytokines.[41] A further investigator-blinded randomized clinical trial of 52 patients with moderate-to-severe xerosis treated group 1 ($n = 39$) with a mild cleanser and moisturizer twice daily for 2 weeks and group 2 ($n = 13$) with a gentle cleanser without moisturizer. Total Clinical Score (TCS; erythema, scale, and fissures), Visual Dryness Score (VDS), and subjective itch-related quality of life (ItchyQoL) were assessed at week 2. Group 1 showed more improvement in TCS and VDS compared with group 2. ItchyQoL (symptoms, functioning, and emotions) showed significantly greater improvements for group 1 compared with group 2.[42]

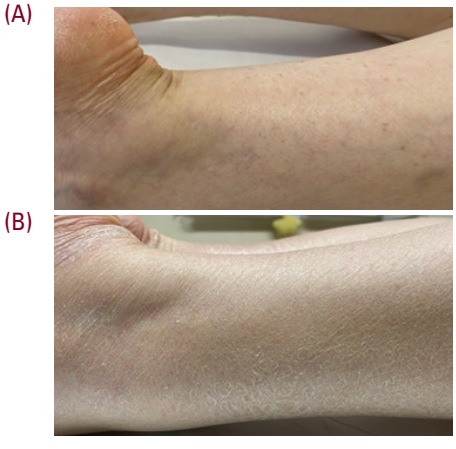
In an unpublished study by Filippi and colleagues, 30 men and women over 70 years of age with xerosis, applied a ceramides-containing cleanser and a ceramides-containing moisturizing

FIGURE 5. Case 1 (A) before (B) after 28 days of skincare.



Case courtesy of Filippi et al.

FIGURE 6. Case 2 (A) before (B) after 28 days of skincare.



Case courtesy of Filippi et al.

cream at least once daily for 4 weeks. Physician and patient evaluation (5-point scale) were at baseline and after 28 days, scoring dryness, roughness and/or desquamation, discomfort, fissures, and cracks. Patients scored the quality of life (4-point scale) aspects at baseline and 4 weeks. The mean physician scores at week 4 decreased for roughness and desquamation from 3.1 to 0.6 (-82%), discomfort due to xerosis from 2.9 to 0.2 (-93%), and fissures from 2.3 to 0.1 (-97%) (Figure 2).

The patients reported that xerosis improved for all parameters (Figure 3). In addition, patient quality of life (QoL) improved, with 77% no longer feeling embarrassed due to their condition, and ≥ 90% not feeling that their condition affected their social/leisure activities or daily activities (Figure 4). Two typical patients are shown to illustrate these results (Figures 5 and 6).

Limitations

The exact etiology of mature skin xerosis is not understood and requires more research. The small number of studies specifically addressing skincare in mature skin did not allow for rating the evidence and recommendations on skincare preferences.

CONCLUSION

Aging-associated alterations in epidermal function lead to xerosis and related pruritus. The development of xerosis in mature skin involves several genetic and environmental mechanisms. Daily use of skincare offers the benefits of maintaining or restoring a healthy skin barrier. Skincare, including gentle cleansers and moisturizers, specifically CER-containing products, have reduced xerosis and pruritus in mature skin individuals.

DISCLOSURES

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All authors participated in the project's steps, reviewed the manuscript, and agreed with the content. All authors read and approved the final version of the manuscript.

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Comparing the Efficacy and Tolerability of Moderate to Severe Hyperpigmentation and Skin Unevenness

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ABSTRACT

Dyschromia is the result of irregular facial pigmentation. These cutaneous manifestations can have a significant impact on the quality of life of those affected, especially among females and skin of color. In this randomized, double-blinded, two-cell, single-center, 16-week clinical study, all subjects had moderate to severe (scores 4–9 on the Modified Griffiths Scale) hyperpigmentation and skin unevenness of the face such that approximately 20% of subjects had post-inflammatory hyperpigmentation (PIH), 40% had overall mottled hyperpigmentation, and 40% had superficial melasma (Superficial Melasma was determined by Wood's Lamp Assessment). Study participants received either Product A (proprietary new formulation – Cysteamine HSA) or Product B (current marketed product - Cyspera®) and used the test product either in the morning or at night, beginning with every other day application, and then advanced to every day, or as tolerated. The results revealed that both Product A (Cysteamine HSA) and Product B (Cyspera®) had statistically significant improvement in facial hyperpigmentation and skin unevenness, however, Product A (Cysteamine HSA) had better tolerability results for scaling, peeling, burning, stinging, erythema, and dryness, indicating that Product A (Cysteamine HSA) outperformed Product B (Cyspera®).

J Drugs Dermatol. 2024;23(1):1260-1265. doi:10.36849/JDD.7584

INTRODUCTION

Dyschromia conditions such as melasma, hypopigmentation, and post-inflammatory hyperpigmentation can prove to be distressing to patients, particularly those with Fitzpatrick skin types II-VI. Dyschromia is known to be the fifth most common diagnosis in African Americans, and the tenth most common diagnosis in Hispanic patients.[1]

Melasma is a condition commonly seen in women of Fitzpatrick skin types III-VI and negatively impacts patients physically, emotionally, socially, and financially. It presents as tan and brown irregular patches on the face and neck. Risk factors include UV radiation exposure, pregnancy, oral contraceptives, and hormonal therapy, amongst others. Melasma is a clinical diagnosis, with the help of a Wood's lamp[2] to examine disease extent, or a dermatoscope to differentiate between epidermal melasma and dermal melasma.[3]

Treatment options include topical hypopigmenting agents (hydroquinone, tretinoin, kojic acid, and azelaic acid) such as Cyspera® and Kligman's formula, chemical peels, laser therapy, and dermabrasion.[3] It is imperative, however, to be intentional about the treatment options for darker skin types, including, but not limited to, the family history of dyschromia, as medium to deep peels and some laser treatments may lead to post-inflammatory hyperpigmentation and scarring.[3] Therefore, there is a greater push towards safe, curative treatment options for Fitzpatrick skin types IV-VI,[4] which contains larger and more numerous melanosomes that are more dispersed amongst the epidermis. These melanin containing melanosomes are produced by melanocytes, which respond easily to irritation and inflammation, resulting in increased susceptibility to hyperpigmentation.[5]

Therefore, we conducted a study of a novel treatment, known as Cysteamine HSA (Product A) containing the active ingredients

Cysteamine HCl and heparan sulfate which can counteract this process. Heparan sulfate is a naturally occurring, linear polysaccharide that is derived from glycosaminoglycans.[6] It is normally attached to core proteins but is also located within the extracellular matrix of cells and other molecules.[7,8] It has properties associated with wound healing, bone tissue regeneration, collagen fiber formation, and basement membrane renewal.[8,9] Importantly, it is a known moisturizing agent that binds and retains water.[6] Cysteamine HCl is a biological antioxidant that reduces tyrosinase activity without producing cytotoxic effects and improves dyschromia.[10] Therefore, their effectiveness together is prone to have promising effects. This study was conducted to evaluate the efficacy and tolerance of this proprietary new formulation (Product A/Cysteamine HSA) vs the currently marketed product (Product B/Cyspera®), in subjects with moderate to severe hyperpigmentation and skin unevenness.

MATERIALS AND METHODS

This randomized, double-blinded, two-cell, single-center, 16-week clinical study was approved by the Institutional Review Board and conducted at the KGL Skin Study Center, from September 2021 to March 2022. All participants were provided written informed consent and photo release forms prior to participation.

Study Participants

Eligible participants were female adults from age 25 to 65 years, inclusive with a Fitzpatrick Skin Type II-VI and a clinical diagnosis of either moderate to severe 'post-inflammatory hyperpigmentation', moderate to severe 'overall mottled hyperpigmentation', or 'superficial melasma'. The severity of the diagnosis was determined by a Modified Griffith's scale[11] score of 4–9. Participants were willing to withhold all facial treatments during the study and had not undergone facial treatments – including peels, laser treatments, microneedling, or filler treatment – within the last six months. Key exclusion criteria included nursing, being pregnant or planning to become pregnant; having a health condition and/or pre-existing or dormant dermatologic disease on the face; having been placed on hormone replacement therapy or hormones for birth control less than three months prior to the study; was currently taking or had taken oral isotretinoin within the last 12 months, prescription strength skin lightening products within 1 month, or products meant to reverse skin aging or dyschromia within 2 weeks.

A sample size of thirty-five patients met the inclusion criteria and were assigned interventions by the clinical investigator. Each participant was assigned to one of two groups, Cell 1/Product A-proprietary new formulation (Cysteamine HSA), n=17, or Cell 2/Product B – current marketed product (Cyspera®), n=18. Clinical assessments for efficacy were evaluated using the 0-9 point Modified Griffiths scale[11] and clinical assessments for tolerance were evaluated using Clinical Tolerance Endpoints collected to capture any product-related changes in erythema, edema, scaling/peeling, burning/stinging, itching, or tightness/dryness. Both assessments were completed at baseline and in weeks 2, 4, 8, and 16. Three sets of facial photographs were also captured at each visit using the high-resolution Canfield VISIA System at each visit; this system takes a series of high-resolution images captured sequentially in rapid succession to minimize panelist movement and maximize registration of images. The rate of water evaporation from the skin was determined using the cyberDERM RG-1 Evaporimeter with DermaLab Trans Epidermal Water Loss (TEWL) probes which collect readings to determine the rate of water evaporation from the skin to assess stratum corneum barrier function; in this way, investigators could assess a decrease in TEWL and ultimately, an improvement in skin barrier function. The moisture content of the skin was determined using Corneometer (Courage + Khazaka, model #CM825) measures; with an increase in measurements correlating with an increase in skin surface hydration. The DSM II ColorMeter, which uses a special lens arrangement to focus on the target area and highly reduces the influence of ambient light, was also used to assess increasing levels of redness and pigmentation in the skin.

Study Design

The study was conducted over 16 weeks and consisted of 5 visits. At the initial visit, all participants were provided the test product, written and verbal instructions, and a diary to track daily compliance. The instructions were verbally explained at each visit. A protocol was given to each participant, depending on their usage of Test Product (either Product A/Cysteamine HSA or Product B/Cyspera®) in the morning or evening. If used in the morning, participants were instructed to apply 1 pump of Test Product to the dry facial skin for 15 minutes before either washing face or showering. After 15 minutes, the participant must wash off the test product with Cetaphil Gentle Skin Cleanser; then apply the Cetaphil Moisturizing Lotion; lastly, apply the Neutrogena Ultra Sheer Dry-Touch SPF 45 Sunscreen and reapply it as needed. Then at night, the participant was instructed to wash their face with Cetaphil Gentle Skin Cleanser and Apply the Cetaphil Moisturizing Lotion. If using the Test Product in the evening, the participants were instructed to wash their face with Cetaphil Gentle Skin Cleanser followed by the Cetaphil Moisturizing Lotion; they were then to apply the Neutrogena Ultra Sheer Dry-Touch SPF 45 Sunscreen and re-apply it throughout the day as needed. Then at night, participants were instructed to wash their face with the Cetaphil Gentle Skin Cleanser, and wait 20 minutes before their skin was completely dry before applying 1 pump of the Test Product for 15 minutes. After 15 minutes, the Test Product was to be washed off with Cetaphil Gentle Skin Cleanser, and the Cetaphil Moisturizing Lotion was applied afterward. At each visit, patient adherence to study instructions was reviewed, facial images were taken,

instrumental measurements previously described were taken, diary instructions were also reviewed, and a questionnaire was answered.

Study Endpoints

The primary outcome was to determine the efficacy and tolerance of Product A (Cysteamine HSA) vs Product B (Cyspera®) in reducing facial hyperpigmentation and skin unevenness. This was measured by a statistical difference in the self-reported assessment, such as erythema, tolerability, and dryness, described by each patient, from baseline to weeks 2, 4, 8, and 16 after starting the test product. Secondary outcome measures included TEWL assessment for improvement of skin barrier function, DSM II ColorMeter assessment for levels of erythema and pigmentation, corneometer measurements to assess the moisture content of the skin, full face photographs, and subject self-assessment questionnaire.

Statistical Analysis

A paired t-test was used to compare the mean and percentage change from baseline to each of the post-baseline visits, weeks 2, 4, 8, and 16. A *P*-value of ≤ 0.05 was considered a statistically significant outcome.

RESULTS

Demographics and Baseline Characteristics

Ultimately, 35 subjects met the enrollment criteria and completed the investigation with n=17 receiving Product A (Cysteamine HSA), and n=18 receiving Product B (Cyspera®). Participants were randomized to receive one of the two interventions: Product A (Cysteamine HSA) containing the low weight heparan sulfate analog (HSA) or Product B (Cyspera®). All participants were provided Cetaphil Gentle Skin Cleanser, Cetaphil Moisturizing Lotion, and Neutrogena Ultra Sheer SPF 30+.

DSM II ColorMeter and Questionnaire Analysis

Compared to Product B (Cyspera®), Product A (Cysteamine HSA) achieved better tolerability results for scaling, peeling, burning, stinging, erythema, and dryness (Figure 1). DSM II ColorMeter bioinstrumentation measurements of erythema (redness) and melanin (pigmentation) provided inconsistent readings and were therefore not used for comparative purposes. The full-face images revealed an apparent reduction in redness and pigmentation for both products. As shown in Figure 2, Subject 012 had a 70.37% improvement at 16 weeks. Analysis of the questionnaires completed by subjects regarding product effects showed that a greater percentage of subjects agreed that Product A (Cysteamine HSA) compared to Product B (Cyspera®) made their skin: overall appearance look better, stubborn dark patches appear less noticeable, feel smoother, look brighter, and discoloration (dark spots) look lighter (Figure 3). Overall results indicated a statistically significant improvement from baseline in hyperpigmentation, skin unevenness, global photodamage, and MASI (Melasma Area Severity Index)[12] at week 16 for both Product A (Cysteamine HSA) and Product B (Cyspera®).

Limitations

One limitation of the study was the small sample size (n=35). Although limited, there was inclusion of skin of color (SOC) participants, as 21.74% were Black/African American and 2.17% were Asian, compared to 76.09% who identified as White. Increased inclusivity of Hispanic or Latino ethnicities is also warranted as only 4.35% of participants were Hispanic Latino as compared to 95.65% who did not identify as such. As previously stated, dyschromia and hyperpigmentation are commonly seen in women with Fitzpatrick skin types II-VI it is important to increase the representation of these skin types when conducting treatment clinical trials. In this regard, we can produce more effective and tolerable treatments that would

FIGURE 1. Comparison of tolerability between Product A (Cysteamine HSA) vs Product B (Cyspera®). Compared to Product B, Product A achieved better tolerability results for scaling, peeling, burning, stinging, erythema, and dryness.

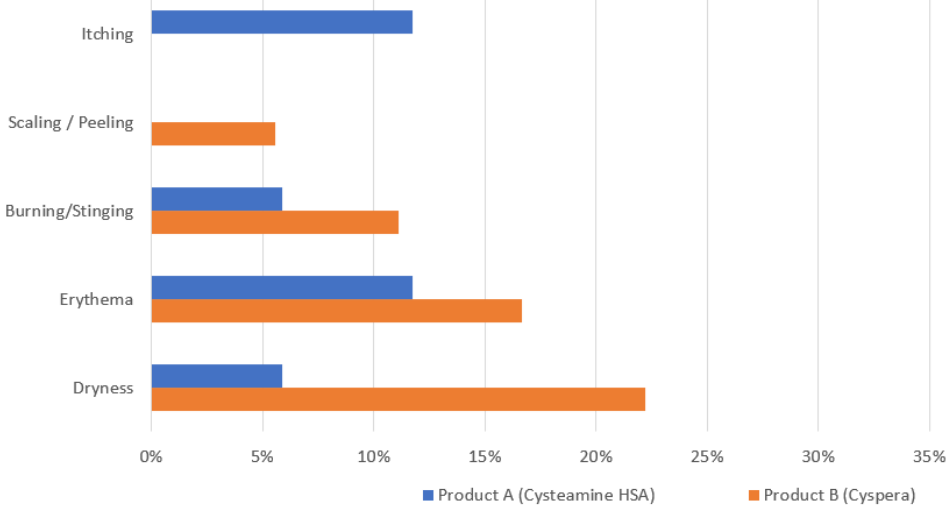


FIGURE 2. Before and after images at baseline and 16 weeks. 60-year-old African American female. Fitzpatrick skin type V with melasma. Masi-score: baseline (16.2); week 16 (4.8), indicating a 70.37% improvement over baseline.

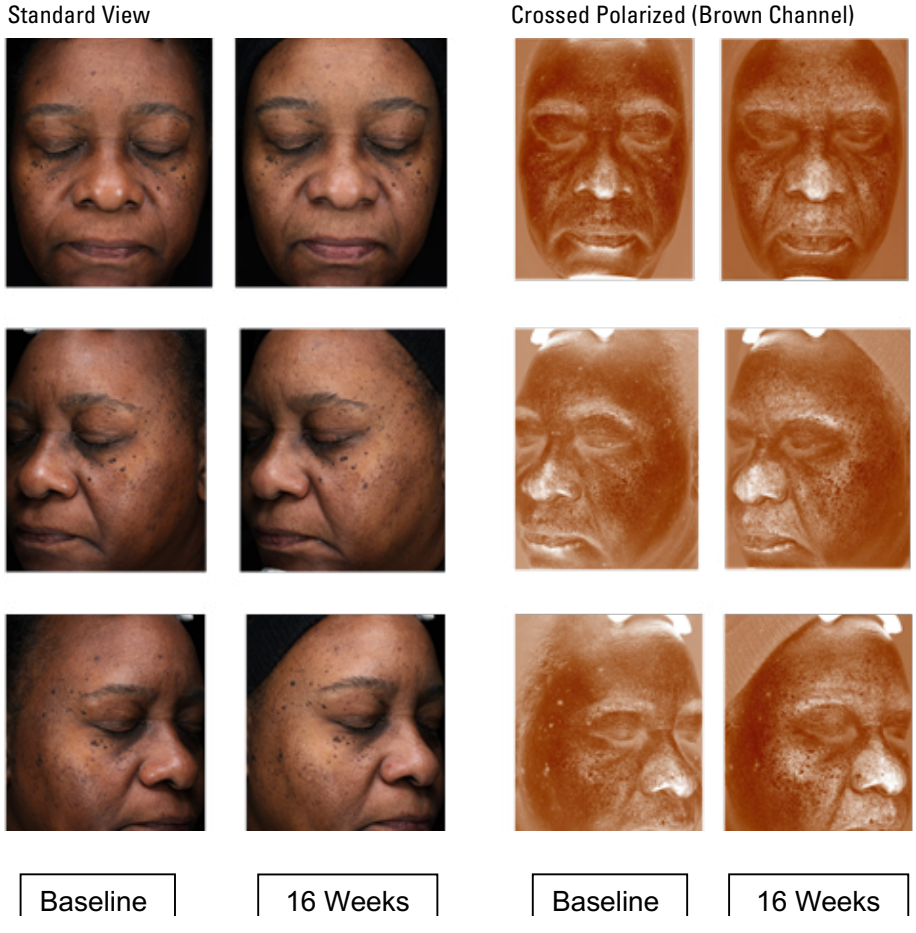
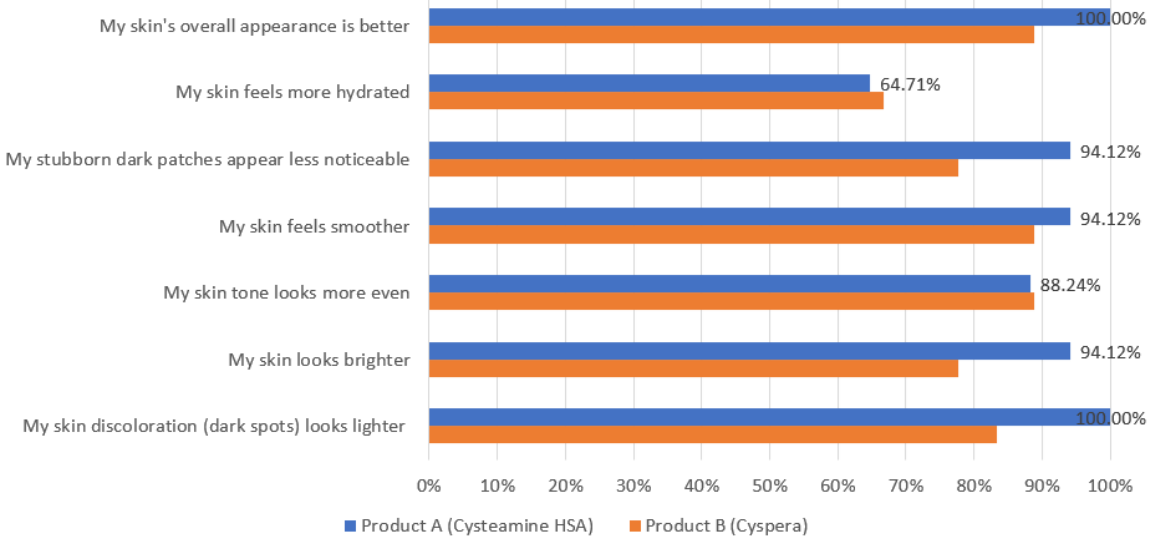


FIGURE 3. Self-Assessment of Product A (Cysteamine HSA) vs Product B (Cyspera®). Analysis of the questionnaires completed by subjects regarding product effects showed that a greater percentage of subjects agreed that Product A compared to Product B made their skin: overall appearance look better, stubborn dark patches appear less noticeable, feel smoother, look brighter, and discoloration (dark spots) look lighter.



be more appropriate for a more racially and ethnically diverse market.

DISCUSSION

The typical treatments for dyschromia include the gold standard for melasma treatment, Kligman's formula - 4% hydroquinone, 0.01% fluocinolone acetonide, and 0.05% tretinoin. However, long-term use may result in corticoid-induced skin atrophy along with exogenous ochronosis which is characterized by blue-black pigmentation. Hydroquinone has also been linked to a higher incidence of melanoma as well as mutagenic and carcinogenic risks due to its cytotoxic effects. Patients prescribed hydroquinone-containing creams have complained of perilesional pigmentation and erythema upon usage, along with skin redness and burning sensations upon treatment discontinuation.[1,13,14]

Therefore, biological antioxidants such as Cysteamine HCl have been used for the treatment of dyschromia. The product reduces tyrosinase activity and produces a greater amount of pheomelanin leading to improved hyperpigmentation, perilesional hypopigmented lesions, and telangiectasias.[15] Patients have also reported minimal side effects and no recurrence of the lesions. The efficacy of topical Cysteamine HCl supports its use as an anti-mutagenic, anti-melanoma, and anti-carcinogenic alternative. Product A (Cysteamine HSA), which contains heparan sulfate analog (HSA), allows for easier skin penetration due to its lower molecular weight, reduced negative charge, and modified linear shape. This study confirms the widespread efficacy of Cysteamine HCl and heparan sulfate in treating dyschromia and melasma, with less burning, scaling, and dryness than the traditionally marketed product (Product B/ Cyspera®).

In recent years, there has been an increase in the medical methods used to treat common facial cosmetic conditions, ranging from topical agents to chemical peels and laser treatment. As clinical trials are conducted with these new treatment options, consumers, manufacturers, and dermatologists need to consider patients with skin of color's specific dermatologic needs. The multifaceted presentation of dyschromia, erythema, and scarring in this patient population delays diagnosis and ultimately treatment, which results in physical and mental distress, reducing their quality of life. Because dyschromia is prevalent in patients with skin of color, racial and ethnic subgroup inclusion in clinical trials is particularly important. Performing inclusive clinical trials with a wider variety of skin types will produce treatments that are effective in alleviating the major cosmetic symptoms seen in all patients.

CONCLUSION

This study demonstrates the efficacy and increased tolerability of Cysteamine HSA (Product A) in producing a better overall appearance, less noticeable dark patches, and reduced discoloration in study participants in the 16-week period. The reduction in hyperpigmentation and improvement in overall skin health is due to the unique topical formulation which implements dual technology of Cysteamine HCl, and the propriety HSA ingredient designed to reduce inflammation, redness, and hyperpigmentation.

Dyschromia, particularly melasma, treatment is complex because of the complex nature and pathogenesis of the disease. Melasma can develop as a result of genetics, solar radiation, hormonal factors such as estradiol, and skin inflammation resulting from contact dermatitis and esthetic procedures amongst other factors.[16] Recent studies have discussed how certain populations, from African Americans to Latin Americans, are more affected by melasma than their Northern European counterparts, with Brazilian women with mixed or African ancestry being more affected by facial melasma.[17] This may be due to an upregulation of genes related to melanogenesis or the transfer of melanosomes, or promote inflammation which may activate or inhibit melanogenesis-related signaling pathways.[16,18]

It is known that sun exposure is a significant environmental factor in the pathogenesis of melasma as chronic exposure results in photoaging, oxidative stress, and inflammation, continuously promoting and sustaining the melanogenesis seen in melasma.[19] UVB in particular, is known to increase the activity of melanocytes, while UVA is more known to induce darker pigmentation and delayed tanning in those with a darker complexion.[20] Hormonal factors such as estradiol promote the production of keratinocyte growth factor, activates ER2 in melanocytes, and increases MC1R expression; through each of these roles, estrogen is able to stimulate and support melanogenesis. This may account for the prevalence of melasma in women experiencing hormonal imbalance due to pregnancy or contraceptive usage.[16]

Skin exposure to oxidative stressors or failure of the skin's antioxidant systems may result in reactive oxygen species and oxidative damage. Further studies must be done to assess the pathogenesis of melasma due to oxidative imbalance, however, prior research has suggested a link between high-oxidative stress environments and melasma severity.[16]

Given the multifactorial nature of melasma, it is important to consider one's ethnic background and environment when developing a treatment plan. This study demonstrates the importance of promoting patient of color participation when assessing the utility, effectiveness, and satisfaction of clinical treatments. The Glycosaminoglycan (GAG) heparan sulfate has many functions, such as interacting with growth factors, and facilitating the structural integrity of extracellular matrix

components;[7,8] however, it has limited penetrating ability due to its large molecular weight.[21-24] Therefore, it must be included in cosmetics as a Low Molecular Weight Heparan Sulfate (LMW-HS) form, known as Heparan Sulfate Analog (HSA)[22,23] to achieve successful skin penetration. By combining the currently marketed Cysteamine HCl ingredient with low molecular weight HSA to create Cysteamine HSA (Product A), dermatologists and other healthcare providers can alleviate the hyperpigmentation, which is distressing to patients of color, while simultaneously ameliorating the irritation commonly seen in other recommended products.

Increasing the tolerability in populations of color can support adherence to the treatment of an already distressing condition. Further racially and ethnically inclusive studies are the focus of future studies to fully understand the benefits and possible incorporation of the HSA molecule in other recommended topical treatments.[21-24]

DISCLOSURES

VDC, DO, and ES-O have participated in Advisory Boards for Senté. ASB is a consultant for Senté. All other authors declare no conflict of interest.

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Extension Phase of a Multi-Center, Randomized, Blinded Clinical Study Evaluating the Efficacy and Safety of a Novel Topical Product for Facial Dyschromia

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ABSTRACT

Background: Dyschromia can be associated with increased production and/or reduced clearance of pigmentation in the skin. Multiple pathways are involved in causality. A novel topical product was recently developed, which contains actives that have been validated through in-vitro and clinical studies to counteract pigmentation related to photodamage, PIH, and melasma. This study further evaluates the safety and efficacy of this product for facial dyschromia during an additional 3-month extension period following the completion of the previous 12-week multi-center trial.

Study Design: Subjects from the previous multi-center trial with mild to severe facial dyschromia at baseline were eligible to participate in this 3-month extension study upon completion of that trial. This extension study evaluated the continued use of the novel topical product with PATH-3 Technology (Alastin Skincare, Carlsbad, CA) over a 3-month period. Subjects who were previously randomized to the novel topical product continued using it and for those previously randomized to hydroquinone 4% discontinued its use. Both cohorts continued daily sunscreen use. Blinded investigators assessed subjects at follow-up visits at 16, 20, and 24 weeks.

Results: Twenty-six (26) subjects completed the extension phase of the pivotal trial, with 13 subjects in each of the AL and HQ-BREAK cohorts. Significant improvements were seen within the AL cohort from weeks 12 to 24 for facial dyschromia (P=0.0158) and skin tone/clarity/evenness (P=0.0067), while there were no significant improvements seen in the HQ-BREAK cohort. The HQ-BREAK cohort had more subjects who worsened with facial dyschromia and skin tone/clarity/evenness. For the mMASI, the HQ-BREAK cohort demonstrated regression at week 24 compared to week 12, while the AL cohort instead experienced continued improvement. This difference was found to be significant (P=0.02). No study related adverse events were reported for either cohort.

Conclusion: A novel topical product designed to counteract various steps in pigmentation pathways using PATH-3 Technology has been demonstrated to be safe and effective in treating facial dyschromia on a long-term basis. In contrast to the significant rebound experienced by subjects with HQ, the AL cohort continued to demonstrate ongoing improvement.

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INTRODUCTION

Dyschromia continues to be a challenging cutaneous condition to treat, which has been complicated by the complex pathways involved and the nuances of individual cases. The sheer number and variety of potential triggers are vast, which mimic the nature of the signaling pathways and cellular interactions involved, especially those between melanocytes, keratinocytes, and endothelial cells. Recent gene expression and cellular studies using melanocytes, keratinocytes, and endothelial cells, as well as melanocyte production models, have identified novel topical agents that are active in the pigmentary pathways, including those pertaining to photodamage, post-inflammatory hyperpigmentation (PIH), and melasma.[1] Many of these ingredients were more recently formulated into a novel topical product aimed at improving dyschromia without any limitations in long-term use.

A previous multi-center pivotal trial was completed evaluating the clinical outcomes of this novel topical product (AL) (A-LUMINATE Brightening Serum, Alastin® Skincare, Inc., Carlsbad, CA) compared to hydroquinone 4% (HQ4%).[2] Subjects applied either AL or HQ4% twice daily, and every subject was dispensed a cleanser (Gentle Cleanser, Alastin® Skincare, Inc., Carlsbad, CA), sunscreen (SilkSHIELD SPF 30, Alastin® Skincare, Inc., Carlsbad, CA or Cetaphil® SPF 30+, Galderma Laboratories, L.P, USA), and moisturizer (Cetaphil® Daily Lotion, Galderma Laboratories, L.P, USA) to use throughout the study. A total of 43 subjects were enrolled and randomized to either the AL (n=22) or HQ4% (n=21) cohort. At 12 weeks, the AL cohort had significant improvements in mMASI scores for the right cheek (P=0.0097), left cheek (P=0.0123), combined cheeks (P=0.0019), and total facial area (P=0.0046), while the HQ4% cohort had none of these significant improvements. Although both cohorts demonstrated improvements in dyschromia and skin tone using investigator grading, the AL cohort also had significant improvements in skin radiance (P=0.0015) and skin texture (P=0.0058), which the HQ4% cohort did not demonstrate. The HQ4% cohort experienced 5 adverse events in contrast to none in the AL cohort. Subjects in the HQ4% cohort also more frequently experienced burning, stinging, tingling, itching, erythema, and dryness.

While the pivotal trial originally evaluated subjects for up to 12 weeks with topical use, an extension phase was more recently completed to continue evaluation from week 12 to week 24. During this extension period, the AL cohort continued their topical regimen with the novel topical product, while the HQ4% cohort discontinued their use of hydroquinone to mimic real-world conditions of a drug holiday (HQ-BREAK).

MATERIALS AND METHODS

This multi-center extension study was approved by the US Investigational Review Board (Miami, FL). Subjects who previously enrolled into and completed the initial 3-month pivotal trial were eligible to participate in this 3-month extension study. For the original trial, eligible subjects were men and women, who were 18-71 years old presenting with mild to severe facial dyschromia at baseline, as graded by the investigator using the modified Griffiths 10-point scale. Subjects agreed not to use any new topical products or have any procedures on the facial area during the duration of the study and to avoid extended periods of sun exposure and the use of tanning beds. Subjects were excluded if they had known allergies or reactions to any of the ingredients within the study products, a dermatologic disease or uncontrolled systemic disease, had used prescription strength retinol or lightening products within 1 month, used any skin lightening or anti-wrinkle products known to affect dyschromia or aging skin within 2 weeks, or used isotretinoin within 12 months. Additionally, subjects were excluded if they underwent laser/light treatments, microneedling, or chemical peels within 2 months, initiated hormone replacement therapies (HRT) or hormones for birth control within 3 months, or planned on modifying doses of HRT or hormones for birth control. Additionally, individuals nursing, pregnant, or planning to become pregnant were excluded.

The extension study evaluated the continued use of the novel topical product with PATH-3 Technology (Alastin® Skincare, Carlsbad, CA) over a 3-month period. All subjects previously randomized to HQ4% discontinued its use and only used the study provided cleanser (Gentle Cleanser, Alastin® Skincare, Inc., Carlsbad, CA), sunscreen (SilkSHIELD SPF 30, Alastin® Skincare, Inc., Carlsbad, CA or Cetaphil® SPF 30+, Galderma Laboratories, L.P, USA) and moisturizer (Cetaphil® Daily Lotion, Galderma Laboratories, L.P, USA) to use throughout the study. Both cohorts were followed for an additional 3 months, with visits occurring at 16, 20, and 24 weeks to evaluate safety and efficacy. Evaluation included modified MASI (mMASI), modified Griffiths 10-point scale for the overall appearance of dyschromia, skin tone/clarity/evenness, skin radiance, and skin texture, and tolerability assessments using a 5-point scale (0: none, 1: minimal, 2: mild, 3: moderate, and 4: severe).

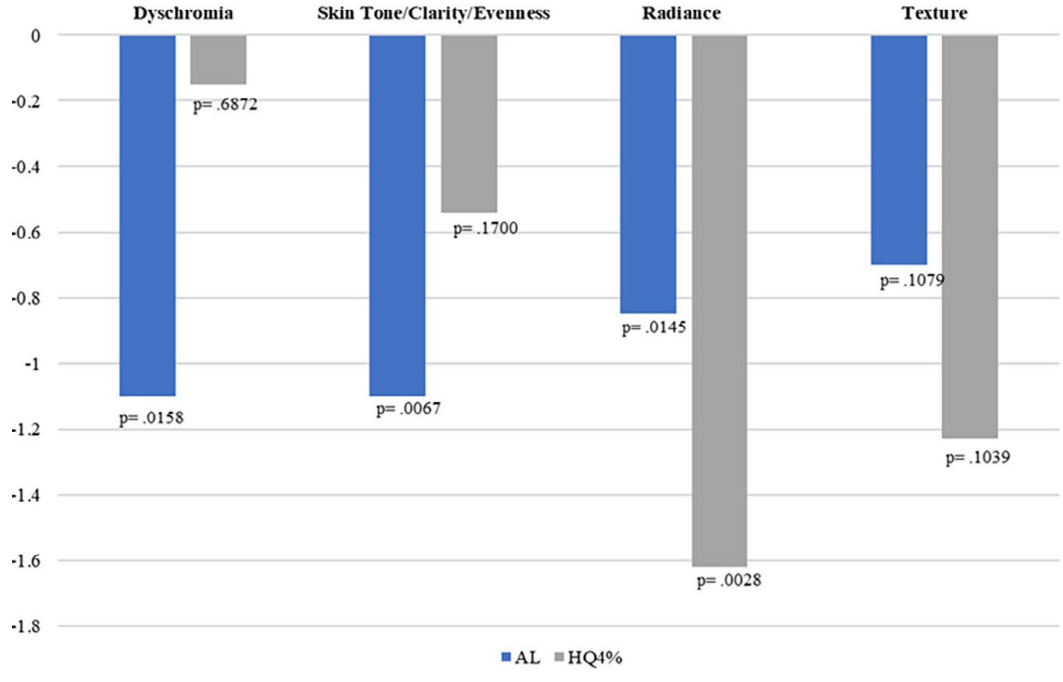
An independent statistician completed the analyses using the following methods. Mean, standard deviation, and two-sample t-tests were used to summarize and compare changes in the blinded investigator assessments and mMASI scores from week 12 to week 24 between the AL and HQ4-BREAK cohorts. In addition, paired t-tests were used to test for significant changes from week 12 to week 24 within each cohort. Chi-square tests were used to compare the percentages of favorable ratings between AL and HQ-BREAK cohorts for subject questionnaires.

RESULTS

Overall, 26 subjects completed the extension phase of the pivotal trial. Mean age was 48.9 years (R: 26-70 years), and 88.5% (n=23) were women. For Fitzpatrick skin type, 3.8% (n=1) were Type I, 19.2% (n=5) were Type II, 34.6% (n=9) were Type III, 34.6% (n=9) were Type IV, and 7.7% (n=2) were Type V. There were 13 subjects each in the AL and HQ-BREAK cohorts. There were no significant differences in the collected demographic data between them.

Investigator assessments demonstrated significant improvements within the AL cohort from week 12 to week 24 for facial dyschromia (P=0.0158) and skin tone/clarity/evenness (P=0.0067), while there were no significant improvements seen in the HQ-BREAK cohort (Figure 1). The HQ-BREAK cohort had more subjects who worsened with facial dyschromia (4 vs 1) and skin tone/clarity/evenness (5 vs 1) compared to the AL cohort. Interestingly in the first 12-week segment of the original trial, patients on HQ4% had poor radiance and texture scores, which were generally related to the skin reactions to the topical. However, upon stopping the HQ4%, skin recovery is represented by an improvement in these scores as sun protection and moisturization took effect. In contrast, subjects using AL had

FIGURE 1. Blinded Investigator Assessments - Mean Change from Week 12 to week 24



improved scores across the board at 12 weeks (ie, dyschromia, skin tone/clarity/evenness, radiance, and texture), which even continued to improve at 24 weeks.

Analyses were again conducted using AI-enabled skin imaging software that can precisely score skin based on an image, which was developed to conform to existing validated scales (Skintelligent, Atlanta, GA). For the automated skin measurements of mMASI, the HQ- BREAK cohort demonstrated regression at week 24 compared to week 12 (0.39 +/- 0.53), while the AL cohort instead experienced continued improvement (-0.12 +/- 0.50; Figure 2). This difference was found to be statistically significant (*P*=0.02). These changes were reflected in clinical photography with long-term improvements noted in the AL cohort (Figure 3) and dramatic rebound pigmentation noted in the HQ-BREAK cohort (Figure 4).

FIGURE 2. Mean changes in mMASI from baseline in HQ-BREAK cohort (left) and AL cohort (right).

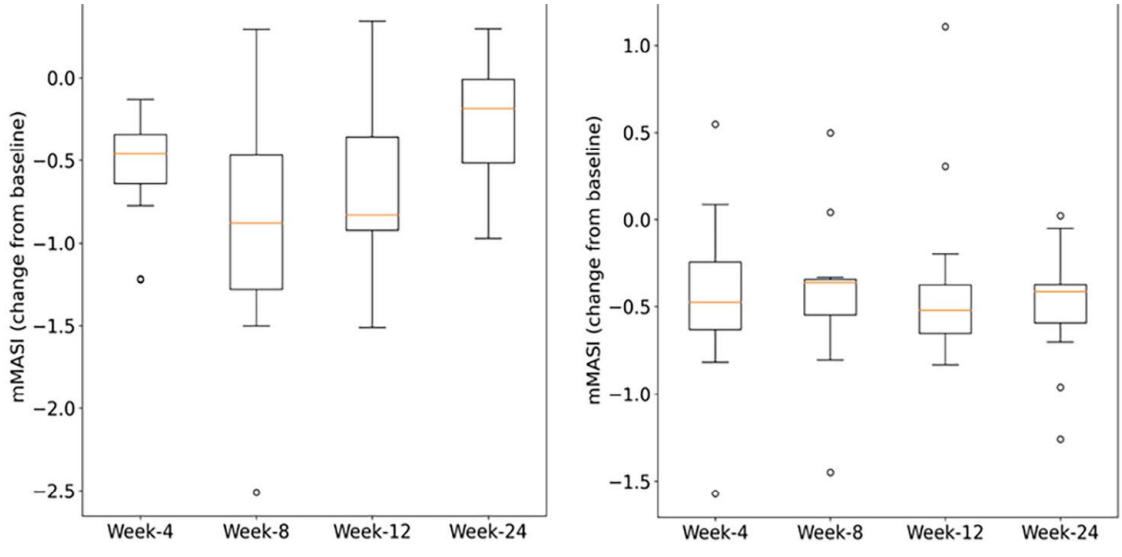


FIGURE 3. AL subject showing mMASI improvement between weeks 12 (left) and 24 (right).

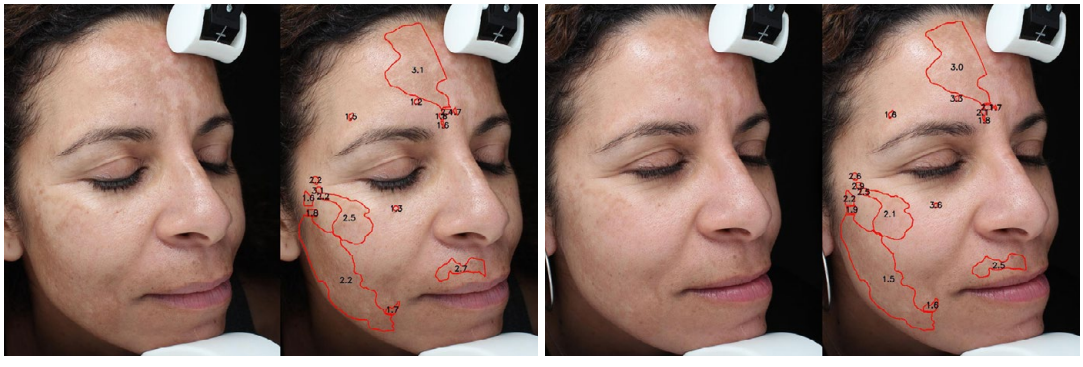
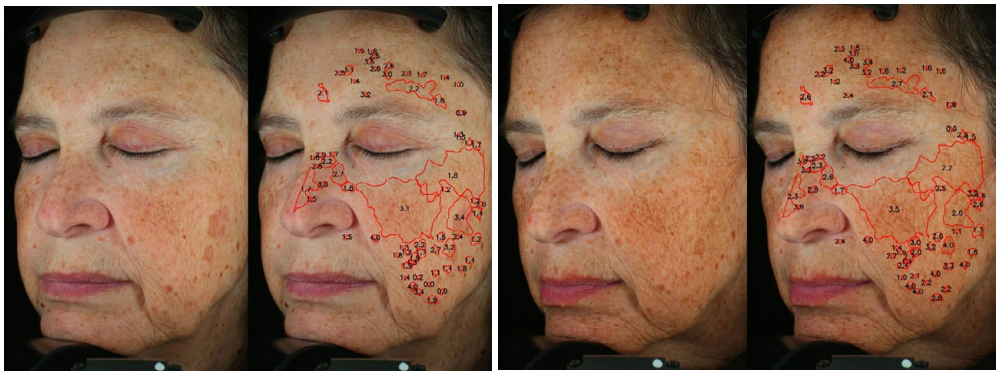


FIGURE 4. HQ-BREAK subject showing rebound between weeks 12 (left) and 24 (right). The larger distinct lesion on the lateral cheek largely disappears at week 24, but the overall pigmentation is much darker, which is reflected in the mMASI scores.



The tolerability assessments performed by both subjects and investigators demonstrated no significant differences between the AL and HQ-BREAK cohorts. This included no additional tolerability issues from long-term use of the AL product in terms of burning, stinging, tingling, itching, erythema, dryness, and peeling, compared to using no product at all. At the 24-week follow-up visit, 92.3% of subjects in the AL cohort believed the AL product faded their brown spots, 84.6% believed it improved evenness in their skin tone, and 92.3% believed it made their skin appear brighter and more radiant.

DISCUSSION

Over the years, hydroquinone has become the gold standard for topical lightening agents. Although it can be effective in improving various forms of dyschromia, it also has several limitations. Firstly, it has been associated with low tolerability and various side effects, which can limit its use in many patients. These include irritation, stinging, burning, tightness, peeling, scaling, and contact dermatitis. Secondly, its use is typically limited to 1-3 months in practice, due to the increased risk of patients developing exogenous ochronosis. Patients are usually instructed to take drug holidays at this point to prevent the development of this irreversible pigmentary condition. During this time, their dyschromia may flare, which is especially common in melasma. Thirdly, more recent concerns have increased about its cytotoxic and carcinogenic potential. These undesirable effects have caused the product to be banned in Europe for use in cosmetic products and to be pulled off the shelves more recently in the United States.

There is a great need for a topical product that can successfully and safely lighten various forms of dyschromia over the long term. The novel topical product used in this trial incorporates PATH-3 Technology, which targets prominent pigmentary pathways, including those associated with photodamage, PIH, and melasma. The novel ingredients within this formulation have all been validated in cellular models to simultaneously impact multiple levels of these pathways, which can influence melanocyte activation, melanin synthesis, melanin transfer, and melanin breakdown and clearance. Its effects not only work on melanocytes but also on both keratinocytes and endothelial cells, which play significant roles in influencing melanocytic pathways. The novel topical product can decrease inflammation and increase autophagy of melanosomes and exfoliation of keratinocytes containing melanosomes.

Using gene expression studies and cellular models, the various ingredients involved with PATH-3 Technology have been validated to counteract these pigmentary pathways. While hexapeptide-12 can significantly downregulate several

melanogenic genes, hexapeptide-11 can downregulate the delivery of melanin to keratinocytes and impact autophagy. Lactoferrin not only decreases melanin production and the transfer of melanosomes to keratinocytes, but it also prevents reactive oxygen species (ROS) formation and local inflammation. Phosphatidylserine can additionally prevent inflammation and vascular dilation through downregulating various factors associated with endothelial cells. Tranexamic acid can also downregulate melanin synthesis and positively impact autophagy. In combination, these ingredients have been clinically shown to offer improvements in facial dyschromia over an extended period of time.

Although the original pivotal trial demonstrated AL to be superior to HQ4% up to 12 weeks, this extension phase demonstrated its long-term effects and tolerability profile. Investigator assessments demonstrated continued improvements in dyschromia, skin tone, clarity, and evenness associated with the AL product, while computerized measurements revealed continued improvements in mMASI. In contrast, the HQ-BREAK group demonstrated regression in their mMASI, which mimics frequently experienced real-world cases, where patients tend to flare soon after beginning their drug holiday. With the AL product, no drug holiday is required due to its hydroquinone-free formula. Its high degree of tolerability was shown to continue up to 24 weeks, which is due to a lack of irritating chemicals and ingredients, such as retinol or salicylic acid. This novel product offers patients a long-term solution for their dyschromia.

CONCLUSION

In the extension phase of this multi-center, randomized, blinded clinical trial, a novel topical product with PATH-3 Technology, designed to counteract various steps in pigmentation pathways, has been demonstrated to be effective and tolerable long-term in treating facial dyschromia.

DISCLOSURES

JVW, SGF, and DMR are consultants for Alastin Skincare, Inc., a Galderma company; ADW is the Chief Scientific Officer of Galderma. MB and TR are Clinical Research Director & Manager, Alastin Skincare, Inc., a Galderma company.

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Revisiting the Anchor Flap for Nasal Defects: How It Fits in the Current Reconstruction Paradigm

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ABSTRACT

The anchor or Peng flap, first described in 1987, has not been comprehensively discussed in the literature since 2008. The anchor flap is worth revisiting as a useful advancement-rotation flap for medium-sized defects of the distal nose. More recent variations to the flap design incorporate medial cheek advancement and allow for versatility in its use for wide defects of the nasal tip, supratip, and dorsum. The anchor flap is a suitable reconstructive option for defects for which the bilobed/trilobed flap, dorsal nasal rotation flap, or interpolated flap would be considered. We review various designs of the anchor flap and discuss how it can be considered in the modern reconstructive paradigm.

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INTRODUCTION

Medium sized partial to full thickness defects of the nasal dorsum, supratip and tip remain aesthetically demanding reconstructive challenges. Midline or paramedian nasal defects are prominently central on the face and the slightest of nasal deformity or distortion after repair is perceptible. The anchor flap (aka "Peng" flap) is a bilateral advancement-rotation flap utilizing a tissue reservoir from the nasal sidewall and medial cheek. Initially described in 1987, this flap has only been updated in a few publications since that time.[1-4] We aim to revisit this useful flap, discuss its variations, and highlight how it integrates into the modern reconstructive ladder.

Anatomy and Indication

The anchor flap is a single-staged random pattern flap that consists of superiorly-based bilateral arms on the lateral aspects of a surgical defect. Its movement is a combination of rotation and advancement. A standing cone is removed superior to the defect in the midline. Its vascular supply is likely from small branches of the angular artery, lateral nasal artery, and dorsal nasal artery, with a rich myocutaneous pedicle. Flap necrosis is exceedingly uncommon.

The anchor flap is most suitable for nasal defects deep to the fibromuscular, perichondrium, or cartilage layer and located on the midline or paramedian distal nose (nasal tip, supratip, and dorsum). Undermining is performed in the supra-perichondrial layer on the nose and the mid-subcutaneous fat on the medial cheek. The literature indicates that the flap can be utilized in defect sizes ranging from 1.0 cm up to 1.6 cm in the horizontal axis and possibly up to 3.0 cm in the vertical axis.[1,3,4]

The anchor flap is ideal for patients with wide-set or flatter nasal shapes, a less acute angle of the nasofacial sulcus, and ample tissue reservoir in the medial cheek. The primary movement of the flap causes narrowing of the middle third of the nose, which can accentuate preexisting dorsal humps and aquiline nose shapes. This can lead to a sub-optimal cosmetic result. Patients who have a natural sharp slope of the nasofacial sulcus may complain of blunting of the sulcus due to the medial advancement of the cheek.

Flap Design

For nasal defects, the flap is superiorly based with rotation medially and slight advancement inferiorly. It may also be conceptualized as an inverted T-plasty with a rotational component. Over the years, there have been notable variations in the flap design (Figure 1). The initial description of the repair

FIGURE 1. Design modifications of the anchor or "Peng" flap, 1980s to 2000s.

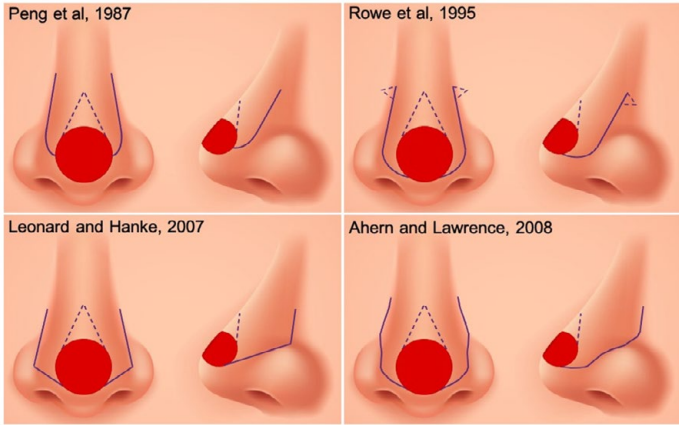
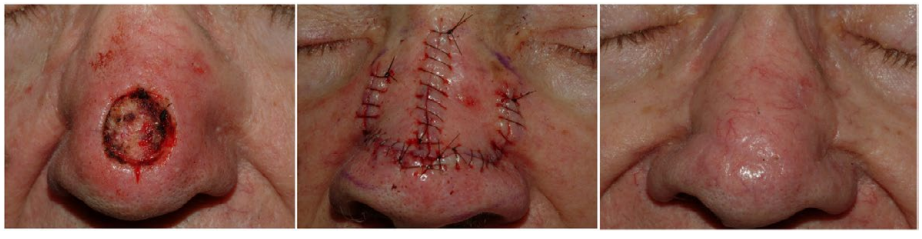


FIGURE 2. Example of the modern anchor flap. Note the preservation of the overall nasal shape and perfect textural match of the flap upon healing. Scar lines, even when atrophic, are masked in natural contours.



by Peng et al relied primarily on advancement, with the takeoff of the bilateral arms designed proximal from the distal edge of the defect and a large length to width ratio of the advancing arms.[1] The design by Rowe et al prioritized rotational movement of the bilateral arms, designing the takeoff as far distally on the defect as possible, thereby minimizing tension across the flap.[2] The Leonard/Hanke and Ahern/Lawrence variations extended the incision of the bilateral arms into the alar crease and the nasofacial sulcus to maximize the medial cheek tissue reservoir.[3,4] The arms can be further extended superiorly to the level of the nasal sidewall as necessary for further rotational movement. Incorporation of this cheek advancement allows further movement of the flap arms and minimizes the length to width ratio. A crescentic standing cone can be removed inferiorly along the nasofacial sulcus to ensure preservation of the alar crease and isthmus. Execution of the flap has been previously discussed in detail.[3,4]

Figure 2 demonstrates an anchor flap repair of a large midline defect. Paramedian defects are similarly repaired with a diagonally oriented standing cone, which can be excised according to tissue redundancy after insetting of rotating arms.

The Reconstruction Algorithm

Medium sized defects (1.0 to 1.5 cm) nasal supratip, tip, and dorsum have a plethora of reconstructive options. Linear repairs are precluded due to the excessive width of the defect. Second intention healing, full thickness skin grafts, and burow's grafts are appropriate for shallow defects. If these options are not preferred due to concern of cosmetic disfigurement, a local flap repair can be considered, which may require deepening of the defect. Deep defects of these anatomic regions of the nose can be repaired with the anchor flap, bilobed or trilobed flap, the dorsal nasal rotation flap, and the interpolated melolabial or paramedian forehead flap. The overall advantages of the anchor flap are its intuitive linear and curvilinear aesthetic lines that are placed in the natural contours of the nasal midline, alar crease, and nasofacial sulcus. Alternative flaps can create scar lines in more noticeable anatomic areas. The flap's natural symmetry ensures that any minimal distortion of the alar rim or nasal tip elevation is performed symmetrically so that it remains unnoticeable to the casual eye. Trapdooring complications are unlikely given the extent of undermining that the flap requires. Compared to alternative flap repairs, the anchor flap is by far the most intuitive in design. See Table 1 provides a comparison of alternatives to the anchor flaps.

TABLE 1.

A Comparison of Reconstructive Options for Medium-Sized Defects of the Nasal Supratip, Tip, and Dorsum

Repair	Ideal defect depth	Aesthetic considerations	Patient considerations
Second intention	Shallow	Depressed and atrophic scar likely on convexity of nasal tip and supratip	Longer wound care necessary Patients without concern for cosmetics may prefer this
Full-thickness skin graft	Shallow to medium	Textural mismatch likely	Additional donor site to care for
Burow's graft	Shallow to medium	Textural mismatch possible Best for midline defects for optimal scar placement of donor site	--
Anchor flap	Medium to deep	Accentuation of dorsal hump possible Narrowing of nose possible Scar hidden in natural aesthetic contours	--
Bilobed/Trilobed flap	Medium to deep	Less undermining required Scar in geometric configuration Nasal tip distortion possible Trapdooring possible	--
Dorsal nasal rotation flap	Medium to deep	Nasal tip distortion possible Significant undermining necessary	--
Interpolation flap (melolabial or paramedian forehead)	Deep	Creation of extra forehead or nasolabial fold scar "Blob" trapdooring possible	Flap inset to division period is difficult to tolerate

SUMMARY

The anchor or "Peng" flap is an excellent single-stage rotation-advancement flap option for medium to large defects of the nasal dorsum, supratip, and tip with distinct advantages over alternative options such as the bilobed flap. The modern design of the flap is intuitive and results in aesthetic repairs that camouflage well in cosmetic subunit boundaries and preserve symmetry.

DISCLOSURES

The authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Evaluation of a Moisturizing Cream With 20% Urea for Keratosis Pilaris

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ABSTRACT

Background: Keratosis pilaris (KP) is a benign dermatosis consisting of folliculocentric keratotic papules or pustules with surrounding erythema, often on proximal extensor surfaces of extremities. Management strategies for KP largely center on moisturization and exfoliation. Urea, a well-established ingredient in topical skincare, is a component of the natural moisturizing factors with concentration-dependent humectant, emollient, and exfoliative properties. Given the overlap of urea's properties and management goals of KP, a 4-week, open-label, noncomparative clinical study was conducted to evaluate a moisturizing cream formulated with 20% urea for use in KP. Thirty participants aged 18 to 65 years with KP completed this study. After a 5-day washout period, study participants applied a 20% urea cream once daily to areas of KP for 4 weeks. At baseline, 1-week, and 4-week visits, clinical grading of skin texture, adverse event monitoring, and participant satisfaction questionnaires were conducted. After 1 week and 4 weeks of product use, the percent change in skin smoothness/texture from baseline was significant ($P \leq 0.001$). Furthermore, after 4 weeks of use, the majority of participants indicated satisfaction with the feel of their skin, as well as improved confidence and decreased embarrassment related to their skin. No significant adverse events were reported. Overall, the results of this study support that 20% urea cream is generally well tolerated and suitable for use in treating KP.

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INTRODUCTION

Keratosis pilaris (KP) is a common benign dermatosis affecting an estimated 50-80% of adolescents and 40% of adults worldwide.[1] KP is diagnosed clinically based on the presence of folliculocentric keratotic papules or pustules with surrounding erythema, usually located on the proximal extensor surfaces of extremities.[2] The etiology of KP is unknown but theorized to result from an inherited or acquired defect in the keratinization process, which results in follicular plugging, local inflammation, and retention hyperkeratosis.[2,3] Despite its largely asymptomatic nature, KP can be associated with significant erythema or skin texture changes that are bothersome or cosmetically distressing to patients.[4] Therapies for KP can improve the affected skin's appearance and relieve associated psychosocial stress; KP patients have reported embarrassment, decreased self-confidence, and social dysfunction related to their skin.[5] KP may improve over time, but treatment options include topical emollients and keratolytics (typically containing lactic acid, salicylic acid, or urea), topical retinoids (particularly tazarotene), and other exfoliants, anti-inflammatory medications, or laser therapies.[2,6,7]

Urea-containing preparations have been studied in a variety of dermatologic conditions including KP, KP-related conditions such as atopic dermatitis and ichthyosis vulgaris, psoriasis, xerosis, and hyperkeratotic-type tinea pedis.[4,8–11] Urea is a component of the natural moisturizing factors with humectant, emollient, and keratolytic properties. At low concentrations (≤10%), urea-based preparations increase skin hydration and moisturization, while high-concentration preparations (>10%) are exfoliating and can improve hyperkeratosis.[9] Urea is generally well tolerated; mild and transient side effects reported at high doses include a stinging or burning sensation.[8,11] With these properties in mind, a clinical study evaluated the therapeutic effects and tolerability of a moisturizing cream formulated with 20% urea (20% urea cream) for KP.

MATERIALS AND METHODS

An open-label, prospective, non-comparative, single center study was conducted to evaluate 20% urea cream in KP. Thirty participants aged 18 to 65 years old with KP on their arms or legs completed the study (Table 1). After a 5-day washout period, all participants applied 20% urea cream once daily to affected areas of KP. There were 3 visits during the study: initial/baseline, week 1, and week 4. At the baseline visit as well as the follow-up visits, digital photographs were taken in a standardized fashion. Photographs were then evaluated by multiple expert clinical graders (PhD, BS, MHI) for appearance of smoothness/texture

of the skin, and these were scored according to the following scale: 0= Lack of Texture (Very Smooth), 1-3= Mild Texture, 4-6= Moderate Texture, 7-9= Severe Texture (No Smoothness). Half increments were used when applicable. Scores were compared to baseline at weeks 1 and 4, and statistical analysis was conducted using paired t-tests.

At each visit, adverse events assessments were conducted for all participants. Additionally, a questionnaire (Table 2) was administered to participants that included a series of statements to which respondents indicated a choice on the 5-point Likert scale (1= Strongly Agree, 2= Agree, 3= Neutral, 4= Disagree, 5= Strongly Disagree). Responses to questions were divided into 2 groups: *Agree*, which consisted of responses Strongly Agree (1) and Agree (2), and *Disagree*, which consisted of responses Disagree (4) and Strongly Disagree (5). For respondents that answered Neutral (3) to the question, half were added to the *Agree* group and half to the *Disagree* group. Statistical analysis was conducted using z-tests to assess the likelihood of participants agreeing with a statement compared to those who disagreed. The statistical significance of all evaluations was defined by a *P*-value ≤ 0.05.

DEMOGRAPHICS AND RESULTS

There were 30 total study participants (Table 1). Participant age ranged from 18 to 65 years, with a mean age of 39.7 (± 14.7). Of the participants, 83% self-identified as female, and 17% self-identified as male. Participants self-identified their race or ethnicity as follows: 53% Caucasian, 7% Asian, 23% Hispanic, 3% Native American, and 13% Multiracial.

Mean difference in skin scores from baseline was calculated at 1 week (M= -0.43, SD 0.50) and 4 weeks (M= -0.53, SD 0.64). A decrease in scores indicated decreased texture and increased skin smoothness. The percent change in skin smoothness/texture from baseline was significant after both 1 week (-9.25%; $P \leq 0.001$) and 4 weeks (-11.39%; $P \leq 0.001$) of 20% urea cream application. Representative photographs from the treatment period are shown in Figure 1. No adverse events were reported during the 4-week treatment period.

Responses to questionnaires administered at the initial visit, week 1, and week 4 are reported in Table 2. At the initial visit (15 minutes after the first application), a majority of participants agreed that their skin felt softer after the application of 20% urea cream (83.3% agreed; $P \leq 0.05$). All participants (100%) agreed that 20% urea cream was easy to apply. At the 1-week follow-up, a significant majority agreed that product application decreased skin roughness (83.3%; $P \leq 0.05$) and improved the appearance of skin health (83.3%; $P \leq 0.05$), softness (91.7%; $P \leq 0.05$), and overall appearance (78.3; $P \leq 0.05$). At the 4-week follow-up, participants reported improved confidence (86.7%; $P \leq 0.05$) and decreased embarrassment related to skin (81.7%; $P \leq 0.05$). Most respondents also indicated agreement when asked about improvements in skin softness (93.3%; $P \leq 0.05$), smoothness (91.7%; $P \leq 0.05$), and texture (91.7%; $P \leq 0.05$) at this timepoint. Ninety-three percent agreed that the product was suitable for their skin type ($P \leq 0.05$). A majority of participants agreed that they would recommend (83.3%; $P \leq 0.05$) or purchase (76.7%; $P \leq 0.05$) the product.

TABLE 1.

Self-Identified Participant Demographics	
Total Participants (n=30)	
Gender	n
Female	25
Male	5
Age	years
Mean	39.7 (± 14.7)
Median	41.5
Minimum	18
Maximum	65
Race or ethnicity	n
Caucasian	16
Asian	2
Hispanic	7
Native American	1
Multiracial	4

FIGURE 1. Representative clinical images from posterior arms of 2 female study participants during treatment with 20% urea cream.

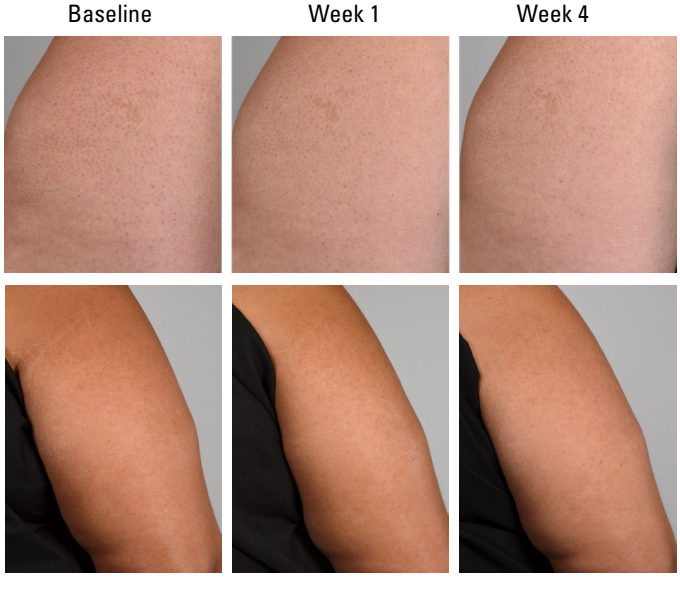

TABLE 2.

Subjective Evaluation of Moisturizing Cream With 20% Urea at Initial Visit, Week 1, and Week 4. Participants (N=30) Indicated Responses to Each Statement With the 5-Point Likert Scale		
Initial Visit (15 minutes after first application)		
Statement	% that agreed♦	Significance
My skin feels softer immediately after applying the product.	83.3	*
My skin feels smoother immediately after applying the product.	73.3	ns
The product was easy to apply.	100	*
I like the way my skin feels immediately after applying the product.	88.3	*
The product does not leave any greasy residue.	88.3	*
Week 1 Follow-up Visit		
Statement	% that agreed♦	Significance
My skin looks healthier since using this product.	83.3	*
My skin feels noticeably softer after one week of applying the product.	91.7	*
I've noticed an overall improvement in my skin's appearance.	78.3	*
My skin feels silky smooth.	73.3	ns
My skin feels less rough after 1 week.	83.3	*
Week 4 Follow-up Visit		
Statement	% that agreed♦	Significance
I like the way my skin feels.	95	*
I'm less embarrassed by the appearance of my skin bumps.	81.7	*
I feel more confident showing my skin.	86.7	*
My skin is softer.	93.3	*
My skin is smoother.	91.7	*
My skin has a smoother texture.	91.7	*
My skin feels significantly less rough after 4 weeks.	93.3	*
This product is suitable for my skin type.	93.3	*
I would recommend this product.	83.3	*
I would purchase this product.	76.7	*

♦Agreement was defined as those who indicated 1 (Strongly Agree), 2 (Agree) and half of the respondents that indicated 3 (Neutral) to that question. Statistical analysis was conducted using z-tests to assess likelihood of participants agreeing with the statement compared to disagreeing.
*indicated statistical significance, defined here as a *P*-value ≤ 0.05; ns= not significant.

DISCUSSION

This study provides initial evidence that the studied 20% urea cream clinically improves skin texture in KP and is generally well tolerated during a 4-week application period. Subjective evaluation by participants was favorable; after 4 weeks of treatment, over 90% of participants were satisfied with their skin texture, noted improved softness and smoothness of skin, and felt the product was suitable for their skin type. Additionally, over 80% of participants reported improved confidence and decreased embarrassment related to skin at the end of the treatment period, highlighting a potential opportunity to improve patient quality of life. During the 4-week study period, there were no adverse events reported, and a majority of participants reported that they would recommend or purchase the test product.

High-concentration urea preparations, such as this 20% urea cream, could feasibly address both skin barrier abnormalities and defective keratinization/hyperkeratosis that contribute to KP pathogenesis.[13] Urea is an endogenous humectant;[9] topical urea application improves skin hydration[9,11] and increases retention of water by the stratum corneum.[14] Additionally, urea stimulates epidermal differentiation, lipid synthesis, and gene transcription of skin barrier proteins (transglutaminase 1, involucrin, filaggrin, and loricrin).[15] Together, these effects contribute to improved skin barrier function; 20% urea has been shown to decrease transepidermal water loss, a measurement used as a proxy for barrier function.[15] Further, high-concentration urea exhibits keratolytic properties, facilitating skin desquamation by reducing cohesion of keratinocytes and breaking hydrogen bonds.[12] Urea also leads to thinning of hyperkeratotic epidermis

and reduction of basal epidermal cells.[10] These combined effects could explain the success of 20% urea preparations shown here and previously.[16,17] Nonetheless, future studies are required to validate the specific mechanism of 20% urea cream's effects on KP.

Limitations of this study include a relatively short follow-up period; this study's observation period of 4 weeks may not capture the full clinical effect of using this product. Future studies assessing this product over longer periods of time can assess the duration and extent of the effect, as well as long-term patient satisfaction and compliance. Other limitations include a small sample size and the absence of a control group testing vehicle alone without 20% urea.

CONCLUSION

In conclusion, this study contributes to growing knowledge on the clinical outcomes of KP treatment with urea. Application of this 20% urea cream did not cause adverse events during the 4-week treatment period and study participants' perspectives suggested general satisfaction with its effects. Future work should expand upon the long-term effects of high-concentration urea application and assess this cream in comparison to other topical treatments for KP to guide clinical recommendations.

DISCLOSURES

Ms McCormick, Dr Nussbaum, and Dr Friedman do not have any relevant conflicts to disclose. Ms Pham, Dr Meckfessel, and Dr Emesiani are employees of Galderma Laboratories, L.P.

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Integrated Short-Term and Long-Term Efficacy of Topical Clascoterone Cream 1% in Patients ≥12 years of Age With Acne Vulgaris

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ABSTRACT

Background: Clascoterone cream 1% is approved for the treatment of acne vulgaris in patients aged ≥12 years based on results from two identical pivotal Phase 3 trials. Integrated efficacy of clascoterone in patients aged ≥12 years with acne vulgaris from the pivotal trials (NCT02608450 and NCT02608476) and long-term extension (LTE) study (NCT02682264) is reported.

Methods: In the pivotal trials, patients with moderate-to-severe acne vulgaris were randomized 1:1 to twice-daily application of clascoterone cream 1% or vehicle for 12 weeks; they could then enter the LTE study, where all patients applied clascoterone to the face and, if desired, trunk for up to 9 additional months. Efficacy was assessed from treatment success based on Investigator's Global Assessment scores (IGA 0/1) in patients aged ≥12 years in the intention-to-treat population; lesion counts were assessed through week 12. Missing data were handled using multiple imputation in the pivotal studies and were not imputed in the LTE study.

Results: Of 1421 patients enrolled, 1143 (clascoterone, 576; vehicle, 567) completed week 12; 600 entered and 343 completed the LTE study. The treatment success rate and most lesion count reductions following clascoterone vs placebo treatment reached statistical significance at week 12; the overall treatment success rate increased to 30.2% for facial acne after 12 months and 31.7% for truncal acne after 9 months of treatment.

Conclusions: The efficacy of clascoterone cream 1% for the treatment of acne vulgaris continued to increase over time for up to 12 months in patients aged ≥12 years with acne vulgaris.

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INTRODUCTION

Acne vulgaris is the eighth most prevalent disease worldwide, affecting approximately 85% of adolescents and young adults aged 12 to 25 years.[1,2] Androgen inhibition is an effective strategy for treating acne in female patients.[3] However, treatment with systemic androgen inhibitors such as combined oral contraceptives and spironolactone is associated with side effects that restrict their use in male patients, pregnancy, and other high-risk conditions.[4]

Clascoterone is a first-in-class molecule that competitively binds to androgen receptors with high affinity and inhibits the transcription of androgen-responsive genes, including sebum components and inflammatory cytokines.[5] Clascoterone cream 1% is approved in the US for the treatment of acne vulgaris in patients aged ≥12 years.[6] In two identical pivotal Phase 3 trials in patients with facial acne vulgaris, treatment with clascoterone cream 1% resulted in a marked clinical improvement after 12 weeks, with a favorable safety profile during up to 12 months of treatment in the extension study; efficacy was also maintained in patients who completed the extension study per protocol.[3,7-9] Here, we present the integrated efficacy of clascoterone cream 1% in the intention-to-treat (ITT) population of patients aged ≥12 years with acne vulgaris in the pivotal and extension studies.

MATERIALS AND METHODS

Study Design and Patients

The Phase 3 trial designs were described previously (Figure 1).[3,7-9] Briefly, patients ≥9 years of age with moderate-to-severe acne vulgaris were randomized to twice-daily treatment of the face with clascoterone cream 1% or vehicle for 12 weeks; patients completing either pivotal study could enter a long-term extension (LTE) study in which all patients applied clascoterone cream 1% twice daily to the face and, if designated by the investigator and desired by the patient, truncal acne for up to 9 additional months.[3,7] Patients who achieved an Investigator's Global Assessment (IGA) score of 0 or 1 (IGA 0/1) could stop treatment and resume if/when acne worsened (IGA ≥2), as assessed by the investigator for each respective treatment area. Only patients aged ≥12 years were included in the current analysis.

The institutional review board or ethics committee approved the study protocols at each participating site. The studies were conducted in accordance with the principles of the Declaration of Helsinki, the current Good Clinical Practice guidelines as defined by the International Conference on Harmonization, and all applicable regulatory requirements. All patients provided written informed consent before participation in the trials. Patients under 18 years of age were accompanied by a parent or legal guardian at the time of consent signing.[3,7]

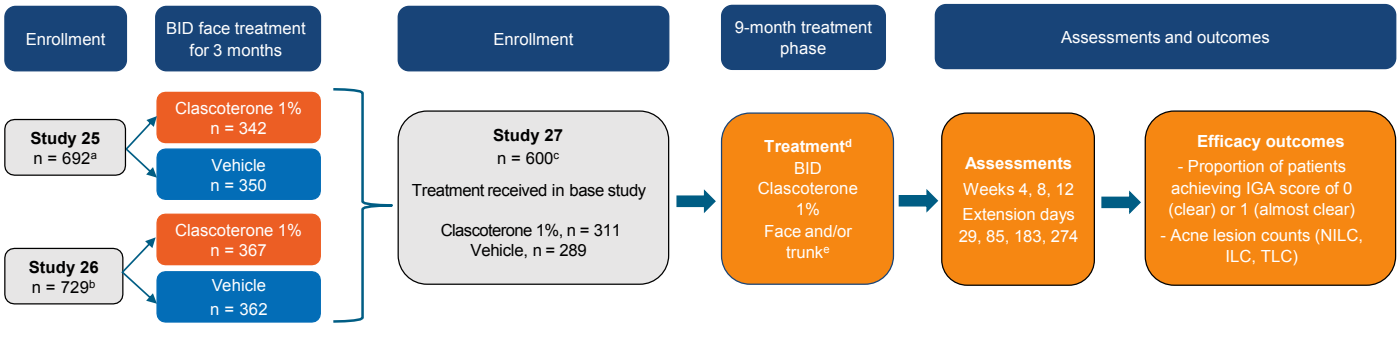
Assessments and Outcomes

The IGA was assessed at baseline and every 4 weeks in the pivotal studies and at extension days 0 (pivotal study week 12 visit), 29, 85, 183, and 274 in the LTE study using a 5-point scale (0 = clear to 4 = severe). Efficacy was assessed from the proportion of patients achieving treatment success (defined as IGA of 0 or 1 with a ≥2-point reduction in IGA score from baseline), assessed separately for the face and trunk in the long-term study. Noninflammatory (NILC), inflammatory (ILC), and total lesion counts (TLC) were obtained at each pivotal study visit, and the absolute and percent changes from baseline in NILC, ILC, and TLC were assessed through week 12.

Statistical Analysis

All statistical analyses were performed using SAS® for Windows, version 9.3 (SAS Institute, Cary, NC). The ITT patient population included all randomized individuals and was used for the analyses. For demographics, baseline characteristics, compliance, and efficacy analyses, continuous variables were described using descriptive statistics and categorical data by frequency counts and proportion of patients within each category. Efficacy comparisons between clascoterone and vehicle were performed using a logistic regression model as described previously.[3] Unadjusted and adjusted proportions and least squares means with associated 95% confidence intervals (CI) were analyzed, and two-sided *P*-values were reported. In the pivotal trials, missing data were handled using a multiple imputation method.[3] Missing data were not imputed in the LTE study.

FIGURE 1. Study design.



[a]Number of ITT patients ≥12 years of age enrolled in Study 25.
[b]Number of ITT patients ≥12 years of age enrolled in Study 26.
[c]Number of ITT patients ≥12 years of age enrolled in the long-term extension study (Study 27).
[d]Patients who achieved IGA score of ≤1 could stop treatment and resume if/when acne worsened.
[e]Total clascoterone treatment duration was up to 12 months for patients treated with clascoterone for 3 months in the pivotal studies.
BID, twice daily; IGA, Investigator's Global Assessment; ILC, inflammatory lesion count; ITT, intention-to-treat; NILC, noninflammatory lesion count; TLC, total lesion count.

TABLE 1.

Patient Disposition and Reasons for Discontinuation

Patients	Phase 3 pivotal studies						Long-term extension study		
	CB-03-01/25		CB-03-01/26		Total		CB-03-01/27		
	CLA (n = 342)	VEH (n = 350)	CLA (n = 367)	VEH (n = 362)	CLA (n = 709)	VEH (n = 712)	CLA (n = 311)	VEH-to-CLA (n = 289)	Total (N = 600)
Completed study	276 (80.7)	286 (81.7)	300 (81.7)	281 (77.6)	576 (81.2)	567 (79.6)	177 (56.9)	166 (57.4)	343 (57.2)
Discontinued	66 (19.3)	64 (18.3)	67 (18.3)	81 (22.4)	133 (18.8)	145 (20.4)	134 (43.1)	123 (42.6)	257 (42.8)
Reasons for discontinuation									
Adverse event	3 (0.9)	6 (1.7)	2 (0.5)	8 (2.2)	5 (0.7)	14 (2.0)	9 (2.9)	0 (0.0)	9 (1.5)
Lack of efficacy	0 (0.0)	3 (0.9)	3 (0.8)	1 (0.3)	3 (0.4)	4 (0.6)	12 (3.9)	16 (5.5)	28 (4.7)
Lost to follow-up	39 (11.4)	32 (9.1)	24 (6.5)	24 (6.6)	63 (8.9)	56 (7.9)	49 (15.8)	41 (14.2)	90 (15.0)
Noncompliance with study drug	0 (0.0)	2 (0.6)	1 (0.3)	5 (1.4)	1 (0.1)	7 (1.0)	1 (0.3)	4 (1.4)	5 (0.8)
Physician decision	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Pregnancy	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.3)	1 (0.3)	2 (0.7)	3 (0.5)
Progressive disease	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)
Recovery	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.7)	3 (0.5)
Technical problems	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)
Withdrawal by patient	21 (6.1)	15 (4.3)	30 (8.2)	37 (10.2)	51 (7.2)	52 (7.3)	55 (17.7)	46 (15.9)	101 (16.8)
Withdrawal by parent/guardian	2 (0.6)	2 (0.6)	5 (1.4)	4 (1.1)	7 (1.0)	6 (0.8)	5 (1.6)	7 (2.4)	12 (2.0)
Other	0 (0.0)	2 (0.6)	0 (0.0)	1 (0.3)	0 (0.0)	3 (0.4)	0 (0.0)	4 (1.4)	4 (0.7)

ITT population.
Data shown as n (%) unless otherwise specified.
CLA, clascoterone; ITT, intention-to-treat; VEH, vehicle.

RESULTS

Patients

Overall, 1421 ITT patients ≥12 years of age enrolled in Phase 3 pivotal studies; 709 were randomized to apply clascoterone and 712 to vehicle (Figure 1). Baseline characteristics were previously reported.[9] Patient disposition in the pivotal and LTE studies is summarized in Table 1. The patients' baseline demographic characteristics were generally balanced between the treatment arms in the pivotal study and between patients originally randomized to clascoterone vs vehicle who continued into the LTE study. Patients' baseline characteristics were similar between the pivotal and LTE study populations, except that the proportion of non-Hispanic patients was higher in the LTE study relative to the combined pivotal studies (Table 2).

Short-Term Efficacy

The adjusted proportion of ITT patients achieving treatment success in the pivotal studies was higher among those receiving clascoterone vs vehicle beginning at week 8 (5.5% vs 3.7%, $P = 0.13$) and reached significance at week 12 (19.9% vs 7.7%,

TABLE 2.

Patient Demographics

Characteristic	Phase 3 pivotal studies						Long-term extension study		
	CB-03-01/25		CB-03-01/26		Total		CB-03-01/27		
	CLA (n = 342)	VEH (n = 350)	CLA (n = 367)	VEH (n = 362)	CLA (n = 709)	VEH (n = 712)	CLA (n = 311)	VEH-to-CLA (n = 289)	Total (N = 600)
Sex, female	211 (61.7)	210 (60.0)	242 (65.9)	220 (60.8)	453 (63.9)	430 (60.4)	193 (62.1)	180 (62.3)	373 (62.2)
Race									
Caucasian	290 (84.8)	296 (84.6)	355 (96.7)	347 (95.9)	645 (91.0)	643 (90.3)	279 (89.7)	257 (88.9)	536 (89.3)
Asian	8 (2.3)	10 (2.9)	0 (0.0)	4 (1.1)	8 (1.1)	14 (2.0)	5 (1.6)	8 (2.8)	13 (2.2)
Black or African American	30 (8.8)	34 (9.7)	7 (1.9)	6 (1.7)	37 (5.2)	40 (5.6)	16 (5.1)	16 (5.5)	32 (5.3)
Other	14 (4.1)	10 (2.9)	5 (1.4)	5 (1.4)	19 (2.7)	15 (2.1)	11 (3.5)	8 (2.8)	19 (3.2)
Ethnicity									
Not Hispanic	253 (74.0)	271 (77.4)	348 (94.8)	353 (97.5)	601 (84.8)	624 (87.6)	285 (91.6)	274 (94.8)	559 (93.2)
Age, years									
Mean	20.3	20.0	19.4	19.0	19.8	19.5	19.3	19.3	19.3
SD	6.54	6.71	5.61	5.38	6.09	6.09	5.77	6.68	6.22

ITT population.
Data shown as n (%) unless otherwise specified.
CLA, clascoterone; ITT, intention-to-treat; SD, standard deviation; VEH, vehicle.

TABLE 3.

Proportion of Patients Achieving Treatment Success in Pivotal Studies

Treatment success	CB-03-01/25			CB-03-01/26			Pooled		
	CLA (n = 342)	VEH (n = 350)	Point estimate (95% CI) *P*-value	CLA (n = 367)	VEH (n = 362)	Point estimate (95% CI) *P*-value	CLA (n = 709)	VEH (n = 712)	Point estimate (95% CI) *P*-value
Week 4, n (%)	3 (0.9)	5 (1.4)	0.6 (0.14 to 2.58)	8 (2.2)	7 (1.9)	1.0 (0.36 to 2.78)	11 (1.6)	12 (1.7)	0.9 (0.41 to 2.13)
Adjusted proportion	1.0	1.6	*P* = 0.50	2.3	2.3	*P* = 1.0	1.8	1.9	*P* = 0.87
Week 8, n (%)	13 (3.8)	9 (2.6)	1.4 (0.61 to 3.22)	21 (5.7)	12 (3.3)	1.6(0.79 to 3.18)	34 (4.8)	21 (2.9)	1.5 (0.89 to 2.60)
Adjusted proportion	4.6	3.3	*P* = 0.42	6.5	4.2	*P* = 0.20	5.5	3.7	*P* = 0.13
Week 12, n (%)	55 (16.1)	24 (6.9)	2.3 (1.41 to 3.89)	69 (18.8)	17 (4.7)	3.7 (2.16 to 6.27)	124 (17.5)	41 (5.8)	3.0 (2.07 to 4.27)
Adjusted proportion	18.8	8.7	*P* = 0.001	20.9	6.6	*P* <0.0001	19.9	7.7	*P* <0.0001

ITT population.
CI, confidence interval; CLA, clascoterone; ITT, intention-to-treat; VEH, vehicle.

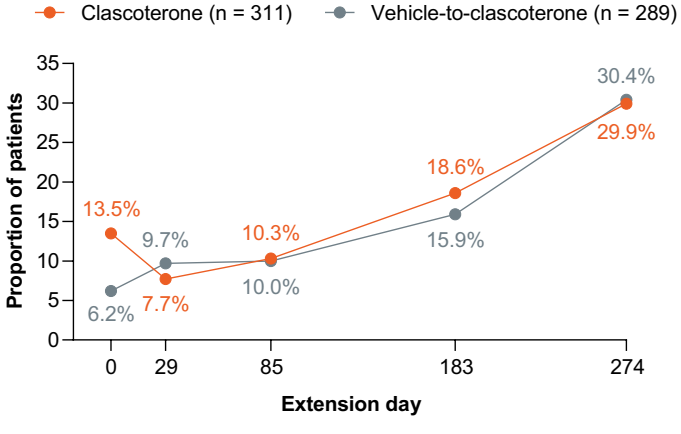
P<0.0001, Table 3), as previously reported.[9] Clascoterone treatment also resulted in significantly larger reductions in lesion counts compared with the vehicle at week 12 (Table 4), as previously reported.[9] The absolute and percent change from baseline in NILC reached statistical significance between patients treated with clascoterone vs vehicle at week 12. For ILC and TLC, the treatment difference for clascoterone vs placebo became significant starting at week 8 for absolute and percent change from baseline (Table 4).

Long-Term Efficacy

The unadjusted proportion of ITT patients previously treated with clascoterone who achieved facial IGA 0/1 increased from 42/311 (13.5%) at extension day 0 to 93/311 (29.9%) at extension day 274, with improvement observed at each visit from extension day 29. Similarly, the unadjusted proportion of ITT patients previously treated with vehicle and switched to clascoterone in the LTE study who achieved facial IGA 0/1 increased from 18/289 (6.2%) at extension day 0 to 88/289 (30.4%) at extension day 274, with improvement observed at each visit (Figure 2).

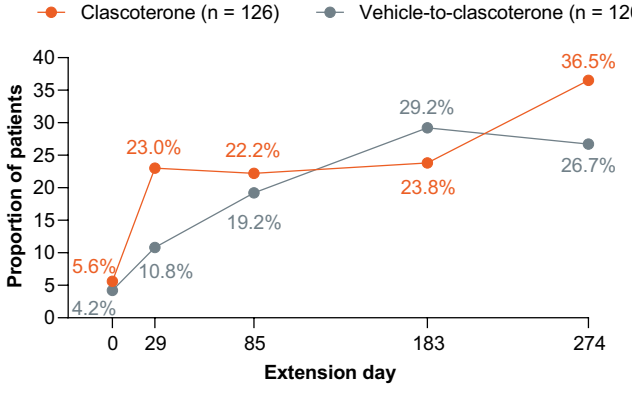
Among ITT patients who treated truncal acne, the unadjusted proportion with truncal IGA 0/1 increased from 12/246 (4.9%) at extension day 0 to 78/246 (31.7%) on extension day 274, with improvement observed at each visit beginning at extension day 29. Although patients were treated for truncal acne only in the LTE study, the unadjusted proportions achieving truncal IGA 0/1 were greater among patients previously treated with clascoterone vs vehicle in the pivotal studies at extension day 274 (46/126 [36.5%] vs 32/120 [26.7%], respectively; Figure 3).

FIGURE 2. Proportion of patients with facial IGA of 0/1 in the long-term extension study by visit.



ITT population.
IGA, Investigator's Global Assessment; ITT, intention-to-treat.

FIGURE 3. Proportion of patients with truncal IGA of 0/1 in the long-term extension study by visit.



ITT population.
IGA, Investigator's Global Assessment; ITT, intention-to-treat.

TABLE 4.

Absolute and Percent Changes From Baseline in Lesion Counts at Each Study Visit in Pivotal Studies

Change from baseline	CB–03–01/25			CB–03–01/26			Pooled		
	CLA (n = 342)	VEH (n = 350)	Point estimate (95% CI) *P*–value	CLA (n = 367)	VEH (n = 362)	Point estimate (95% CI) *P*–value	CLA (n = 709)	VEH (n = 712)	Point estimate (95% CI) *P*–value
NILC, absolute									
Week 4	–9.4	–9.2	–0.3 (–3.53 to 3.00) 0.87	–13.0	–11.5	–1.5 (–4.69 to 1.66) 0.35	–11.5	–10.2	–1.3 (–3.52 to 0.98) 0.27
Week 8	–15.8	–12.4	–3.4 (–6.95 to 0.23) 0.07	–15.3	–15.5	0.2 (–3.39 to 3.76) 0.92	–15.8	–14.0	–1.7 (–4.10 to 0.63) 0.15
Week 12	–20.4	–13.0	–7.3 (–11.10 to –3.50) 0.0001	–19.5	–10.8	–8.7 (–12.40 to –4.50) <0.0001	–19.8	–11.7	–8.1 (–10.78 to –5.44) <0.0001
NILC, percent									
Week 4	–14.7	–16.8	2.1 (–3.68 to 7.85) 0.48	–20.5	–17.4	–3.1 (–8.49 to 2.23) 0.25	–18.1	–16.8	–1.3 (–5.17 to 2.63) 0.52
Week 8	–24.7	–20.9	–3.9 (–10.13 to 2.38) 0.22	–23.7	–24.0	0.2 (–5.77 to 6.25) 0.94	–24.7	–22.5	–2.2 (–6.23 to 1.90) 0.30
Week 12	–32.6	–21.8	–10.8 (–17.60 to –3.90) 0.001	–29.6	–15.7	–13.8 (–20.10 to –7.50) <0.0001	–30.8	–18.3	–12.5 (–16.99 to –7.98) <0.0001
ILC, absolute									
Week 4	–12.5	–12.0	–0.5 (–2.53 to 1.56) 0.64	–14.6	–13.0	–1.6 (–3.66 to 0.53) 0.14	–13.8	–12.7	–1.1 (–2.53 to 0.33) 0.13
Week 8	–16.6	–15.0	–1.6 (–4.01 to 0.83) 0.20	–19.0	–16.3	–2.7 (–4.77 to –0.60) 0.01	–18.1	–15.6	–2.5 (–4.09 to –0.83) 0.003
Week 12	–19.3	–15.4	–3.9 (–6.50 to –1.30) 0.004	–20.1	–12.6	–7.5 (–9.90 to –5.20) <0.0001	–19.7	–13.8	–5.9 (–7.65 to –4.24) <0.0001
ILC, percent									
Week 4	–29.4	–28.5	–0.9 (–5.81 to 3.92) 0.70	–34.5	–30.7	–3.8 (–9.03 to 1.45) 0.16	–32.5	–29.9	–2.6 (–6.02 to –0.86) 0.14
Week 8	–38.9	–35.8	–3.1 (–8.81 to 2.61) 0.29	–45.0	–38.3	–6.6 (–11.77 to –1.52) 0.01	–42.6	–36.9	–5.7 (–9.60 to –1.90) 0.004
Week 12	–44.6	–36.3	–8.3 (–14.40 to –2.20) 0.007	–47.1	–29.8	–17.5 (–23.10 to –11.80) <0.0001	–46.2	–32.5	–13.7 (–17.62 to –9.69) <0.0001
TLC, absolute									
Week 4	–22.6	–21.4	–1.2 (–5.43 to 3.05) 0.58	–28.1	–24.8	–3.4 (–7.64 to 0.88) 0.12	–25.4	–23.2	–2.3 (–5.22 to 0.69) 0.13
Week 8	–33.3	–27.9	–5.4 (–10.16 to –0.63) 0.03	–34.8	–32.2	–2.7 (–7.50 to 2.18) 0.28	–34.2	–30.1	–4.1 (–7.52 to –0.75) 0.008
Week 12	–39.9	–28.5	–11.3 (–16.77 to –5.93) <0.0001	–40.2	–23.5	–16.7 (–22.20 to –11.29) <0.0001	–40.0	–26.1	–13.9 (–17.73 to –10.12) <0.0001
TLC, percent									
Week 4	–21.9	–21.5	–0.5 (–4.74 to 3.81) 0.83	–27.0	–23.2	–3.8 (–7.96 to 0.31) 0.07	–24.5	–22.4	–2.1 (–5.04 to 0.81) 0.15
Week 8	–31.9	–27.6	–4.3 (–9.04 to 0.44) 0.08	–33.3	–30.4	–2.9 (–7.72 to 1.92) 0.24	–32.8	–29.0	–3.8 (–7.14 to –0.50) 0.02
Week 12	–38.0	–28.3	–9.7 (–15.01 to –4.42) 0.0003	–37.6	–22.0	–15.5 (–20.84 to –10.23) <0.0001	–37.8	–25.1	–12.7 (–16.42 to –9.01) <0.0001

ITT population.
CI, confidence interval; CLA, clascoterone; ILC, inflammatory lesion count; ITT, intention–to–treat; NILC, noninflammatory lesion count; TLC, total lesion count; VEH, vehicle.

DISCUSSION

The present post hoc analysis was performed to assess the integrated efficacy of clascoterone in patients aged ≥12 years with moderate-to-severe facial and/or truncal acne vulgaris in the ITT populations across the pivotal and extension studies. The proportion of clascoterone-treated patients with facial IGA of 0/1 became significant at week 12 and continued to increase throughout the LTE study; the reductions in NILC, ILC, and TLC also reached significance at weeks 8 or 12. Efficacy also increased over time for patients reassigned from vehicle to clascoterone treatment and those who were treated for truncal acne.

Results from the current analysis align with the previously published results on the efficacy of clascoterone in patients with acne vulgaris.[3,8,9] This study expands the efficacy analyses to include time points before week 12 in the pivotal studies and the entire ITT population rather than the per-protocol population in the LTE study, allowing a comparison of success rates in the pivotal and extension studies. Although substantial numbers of patients did not complete the LTE study, as expected in a study of this duration, efficacy in the ITT population increased over time during treatment.

This analysis has some limitations. First, there was a high patient discontinuation rate before and during the LTE study, a common problem in studies with long-term follow-up. Therefore, the results of patients who entered and remained in the extension study may not be generalizable to the entire study population, which may further limit generalizability from the clinical studies to real-world patients. Second, the effect of clascoterone treatment on patients' quality of life was not assessed. Third, the majority of patients in the clinical trials were White (>84%) and not of Hispanic or Latino origin (>74%). Future studies should investigate the efficacy of clascoterone in a more diverse patient population.

CONCLUSION

The efficacy of clascoterone cream 1% for the treatment of acne vulgaris increased over time for up to 12 months in all treated patients aged ≥12 years with acne vulgaris. Clinicians may consider counseling patients that treatment persistence is required to maximize the efficacy of clascoterone treatment.

DISCLOSURES

LFE, AAH, and LSG were study investigators. LFE, AAH, and LSG were also compensated advisors to Cassiopea S.p.A. AAH is an employee of the McGovern Medical School of The University of Texas Health Science Center in Houston, Texas, which received compensation from Cassiopea S.p.A. for study participation; she also received an honorarium for serving on the Cassiopea advisory board; all research grant funds were paid to her institution. She also received personal fees for advisory, speaking, and consulting roles from Pfizer, Sun Pharma, Galderma, Arcutis, Incyte, and LEO Pharma. LFE is an employee of the University of California San Diego, which received compensation from Cassiopea S.p.A. for study participation; he also served as an investigator, advisor, or consultant for Almirall, Dermata, Galderma Laboratories, Ortho Dermatologics, and Pfizer. LSG is an employee of the Henry Ford Health System in Detroit, Michigan, which received compensation from Cassiopea S.p.A. for study participation; she also received personal fees for advisory, speaking, consulting, research, and/or other services from Almirall, Foamix, Galderma Laboratories, Novartis, Sol-Gel, and Sun Pharma. JH is an employee of Pharmapace, Inc. AM is employed as the chief medical officer for Cassiopea S.p.A. and holds stock options in the company; and has served as the chief medical officer of Cosmo Pharmaceuticals. LM is an employee of Cassiopea S.p.A. and holds stock options in the company. NS is an employee of Sun Pharmaceutical Industries, Inc. DT served in the past as a consultant to Cassiopea, Inc., and is an employee of the College of Medicine at The Pennsylvania State University in Hershey, which received compensation from Cassiopea S.p.A. for study participation; she also received honoraria from Galderma Laboratories and Novartis.

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ORIGINAL ARTICLE

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Validation of a Midfacial Scale and Its Use in a Randomized, Evaluator-Blinded Study of CPM-HA-V

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ABSTRACT

Background: Age-related loss of midfacial contour is frequently corrected using dermal fillers. A validated photonumeric scale is beneficial when evaluating post-treatment aesthetic improvement.

Objective: To present scale-development activities for the Merz Cheek Fullness Assessment Scale (MCFAS) and report pilot-study results of a hyaluronic-acid filler (Belotero® Volume with Lidocaine; CPM-HA-V) to treat midfacial volume loss.

Methods: A 5-point photonumeric scale was developed to objectively assess midface volume loss. Rater reliability was evaluated using live assessments. The clinical relevance of a 1-point difference in severity grade was evaluated using photographic comparisons. Pilot-study participants, with moderate-to-severe volume loss on the MCFAS, were randomized 2:1 to treatment or untreated control. Effectiveness was evaluated using the MCFAS, and adverse events were recorded.

Results: The MCFAS demonstrated substantial intra- and interrater agreement among physicians (weighted kappa > 0.6). The mean absolute difference (95% confidence interval) in scale ratings was 1.12 (1.00, 1.24) for photographic pairs differing by one grade and was 0.55 (0.48, 0.63) for pairs of the same grade, suggesting a 1-point difference is clinically relevant. In the pilot study, significant ($P < 0.0001$) differences were observed in MCFAS response rates between treatment and control. No safety concerns were identified.

Conclusion: The MCFAS is a validated, reliable, and clinically relevant photonumeric scale for rating midfacial volume loss in males and females of various ages and skin types. In a pilot study, CPM-HA-V was found to be safe and tolerable, and the MCFAS was able to detect clinically meaningful post-treatment changes.

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INTRODUCTION

Primary markers of facial aging include a noticeable, and often undesirable, lack of midfacial contour, generally characterized by a loss of cheek volume and a shift in soft tissue fullness from the midface to the lower facial regions.[1-3] Loss of volume and the ligamentous attachments of skin to bone results in specific patterns of deflation, ptosis, and shadowing, resulting in a heavier, rectangular-shaped face, rather than the preferred youthful, heart-shaped face.[3]

Minimally invasive treatments, including dermal fillers, are often used to reestablish cheek volume and contour. To demonstrate treatment effectiveness, regulatory agencies often require meaningful and measurable treatment-related improvements from baseline using scientifically valid photonumeric scales.

Consistent with other facial aesthetic scales intended for use in clinical trials,[4-11] the current work describes the validation of the Merz Cheek Fullness Assessment Scale (MCFAS) and establishes that a 1-point difference in scale-severity grade is clinically relevant. Furthermore, this manuscript presents the results of a pilot study in which a Cohesive Polydensified Matrix® (CPM) hyaluronic-acid filler (Belotero® Volume with Lidocaine; CPM-HA-V) was used for volume augmentation in the midface. The safety and effectiveness of CPM-HA-V, as well as the MCFAS's ability to detect clinically relevant post-treatment changes, are reported.

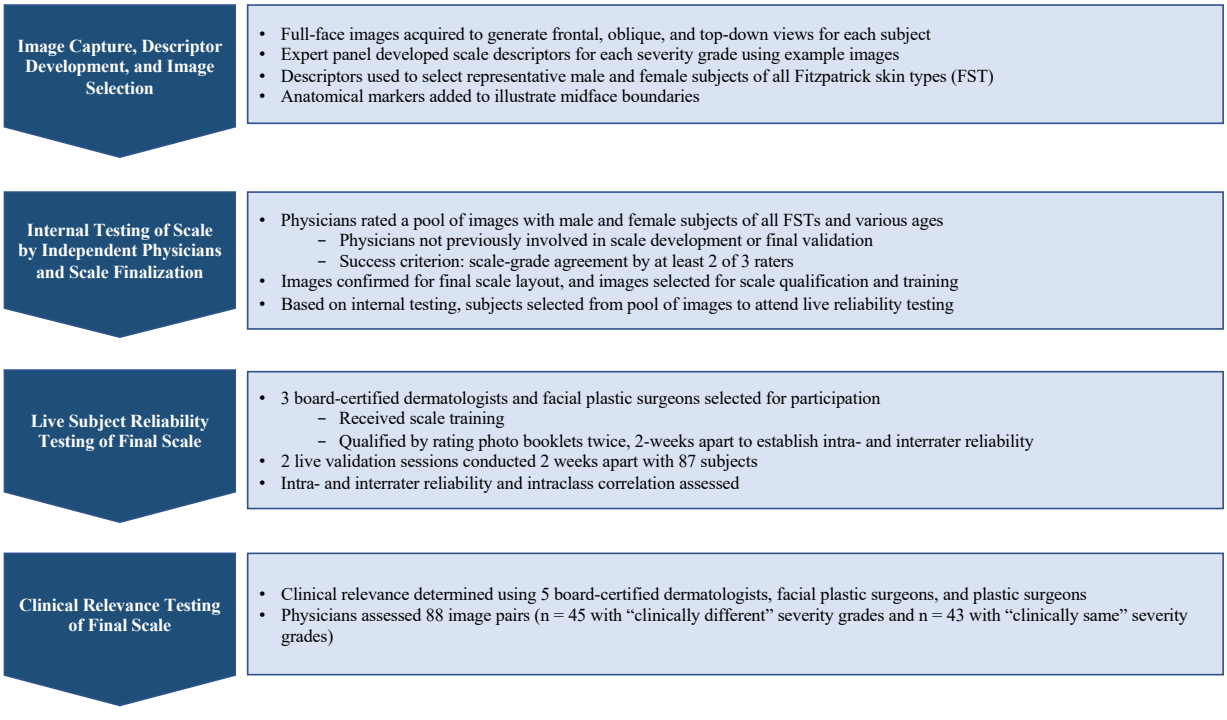
MATERIALS AND METHODS

The following subsections outline the: (1) MCFAS development, reliability, and clinical relevance and (2) design and analysis of a pilot study assessing the safety and effectiveness of CPM-HA-V and the ability of the MCFAS to detect clinically relevant post-treatment changes.

MCFAS Development

Development and layout of the MCFAS was similar to other published facial aesthetic scales.[4-6] Figure 1 describes the overall

FIGURE 1. Merz Cheek Fullness Assessment Scale (MCFAS) development and establishment of reliability and clinical relevance.



process for MCFAS development and establishment of its reliability and clinical relevance. Figure 2 illustrates the midface anatomical boundaries and treatment region used in the pilot study, and Figure 3 details the final MCFAS.

Statistical Methods for Reliability Testing and Establishing Clinical Relevance

For the live participant-reliability assessment, approximately 110 photographs were reviewed to ensure all MCFAS grades were represented by males and females of various Fitzpatrick skin types (FST) and ages. A total of 87 participants were selected to attend 2 live validation sessions, 2 weeks apart. Intrarater reliability between both sessions was evaluated using weighted kappa statistics and intraclass correlation coefficients (ICC). The same analyses were applied for interrater reliability for each individual session. Methods proposed by Fleiss and Cohen[12] and Shrout and Fleiss[13] were used to calculate weighted kappa statistics and ICCs, respectively. A threshold of 0.6 was selected for weighted kappa statistics and ICC as a criterion for satisfactory reliability.

To establish clinical relevance, 88 image pairs from 55 unique participants of all FST were selected and included in the side-by-side rating activity performed by 5 independent physician raters. Of the 88 pairs, 45 represented a 1-grade difference on the MCFAS (ie, *clinically different)* and 43 represented the same grade (ie, *clinically same*). The absolute difference in MCFAS scores between the 2 paired images was calculated using the actual scores from the independent raters and was summarized to the predetermined classifications of *clinically different* or *clinically same*. The mean and standard deviation (SD) of the absolute difference in scores are reported, along with the 95% confidence internal (CI) of the mean. To successfully establish the clinical relevance of a 1-grade difference, the 95% CI for the mean absolute difference in scores, among the predetermined clinically different and clinically same image pairs, should not overlap.

Pilot Study

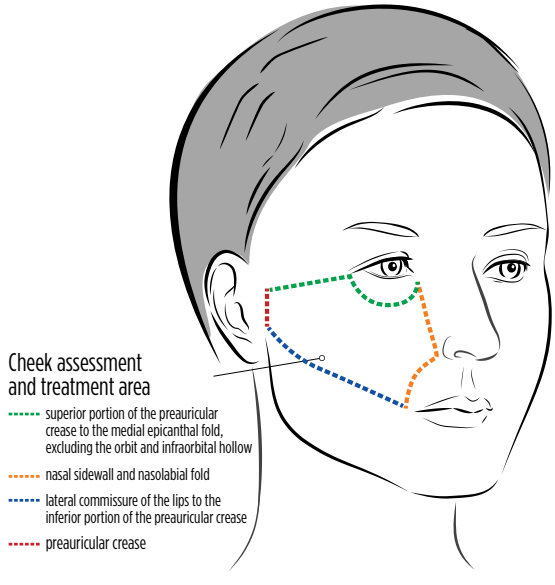
Study Design

Based on the scale-development findings, a pilot study was performed to confirm the reliability and clinical relevance of the MCFAS in a real-world setting where post-treatment changes must be observed. The safety and effectiveness of CPM-HA-V to treat midface volume loss was also evaluated.

This was a 4-week prospective, evaluator-blinded, multi-center, randomized-controlled study among participants with moderate-to-severe midface volume deficit (ClinicalTrials.gov: NCT03321825). All eligible participants were randomized (2:1) to either treatment with CPM-HA-V or untreated control.

Treated participants received an injection in the right and left cheeks, according to the anatomical midface treatment boundaries (Figure 2). Independent evaluators, who were blinded to randomization assignments, assessed cheek volume

FIGURE 2. Cheek anatomical boundaries and treatment region.



using the MCFAS at baseline and Week 4 for all participants (Figure 3).

Additional effectiveness assessments in the treatment group included comparison of baseline and post-treatment appearance using the Global Aesthetic Improvement Scale (GAIS) by treating investigators and participants. Untreated participants did not complete the GAIS assessment.

Safety outcomes were evaluated during all in-clinic visits and a 72-hour post-treatment telehealth visit.

Statistical Methods

The primary effectiveness endpoint was comparison of responder rates between the treated and untreated groups at Week 4, according to the MCFAS, as assessed by blinded evaluators. Treatment response was defined as a ≥ 1-point improvement on both cheeks compared to baseline. A Fisher's Exact Test was used to compare both proportions to test superiority of CPM-HA-V over untreated control.

Treating investigator and participant GAIS scores were summarized into 3 categories: *improvement*, classified as participants with rating of +1 (improved), +2 (much improved), or +3 (very much improved); *worsening*, classified as participants with rating of -1 (worse), -2 (much worse), or -3 (very much worse); and *no change*, classified as score of 0.

To support the MCFAS's ability to detect clinically relevant post-treatment changes, 3x2 cross-tabulations were performed between whether a participant had a ≥ 1-point MCFAS improvement on both cheeks, as assessed by blinded evaluators, vs treating investigator and participant GAIS categorizations (*improvement, worsening, no change*). A proportion of ≥ 70% agreement between participants classified as having a ≥ 1 point MCFAS improvement on both cheeks and having an improvement rating on the investigator and participant GAIS was used to establish the objective MCFAS assessment, performed by the blinded evaluator, was consistent with the perspective of an aesthetically pleasing outcome from the treating investigator and participant.

Safety findings were descriptively summarized for all participants treated with CPM-HA-V.

RESULTS

Establishing MCFAS Reliability Prior to Clinical Application

Three physicians rated 87 participants; 4 participants did not return for Session 2. Most participants were Caucasian (69.0%) females (66.7%), with a median age of 39 years (age range: 22 to 85 years). Twenty-six percent (25.9%) of participants were in the upper FST group (IV-VI).

Intrarater agreement between the 2 live-participant sessions conducted 2 weeks apart was excellent (median weighted kappa and ICC = 0.92 and 0.92, respectively). Interrater agreement was substantial across both rating sessions (median weighted kappa range = 0.76 to 0.93; median ICC range = 0.76 to 0.93). These estimates indicate the MCFAS is reliable for multiple assessments of the same participant, within the same rater and across different raters.

Establishing Clinical Relevance Between MCFAS Grades

The mean (95% CI) absolute difference in MCFAS scores was 1.12 (1.00, 1.24) for the *clinically different* image pairs (eg, 1 grade apart) and 0.55 (0.48, 0.63) for the *clinically same* image pairs (Table 1). The 95% CI of the mean absolute difference did not overlap between the 2 categories, confirming that a 1-point difference in MCFAS-grading categories is clinically significant.

Pilot Study

Demographics and Baseline Severity

A total of 66 participants were screened and randomized (44 treated and 22 untreated). The majority of participants (n = 54, 81.8%) were female. The mean (SD) age was 55 (9.5) years (range: 33 to 76 years). Regarding FST categories, 49 (74.2%) participants were classified as having FST I, II, or III, and 17 (25.8%) had FST IV, V, or VI. The population enrolled was representative of those seeking midfacial aesthetic treatment.

Of the 44 participants randomized and treated, 25 (56.8%) had a MCFAS score of 2 (moderately sunken) on both cheeks, and 19

FIGURE 3. Merz Cheek Fullness Assessment Scale (MCFAS).

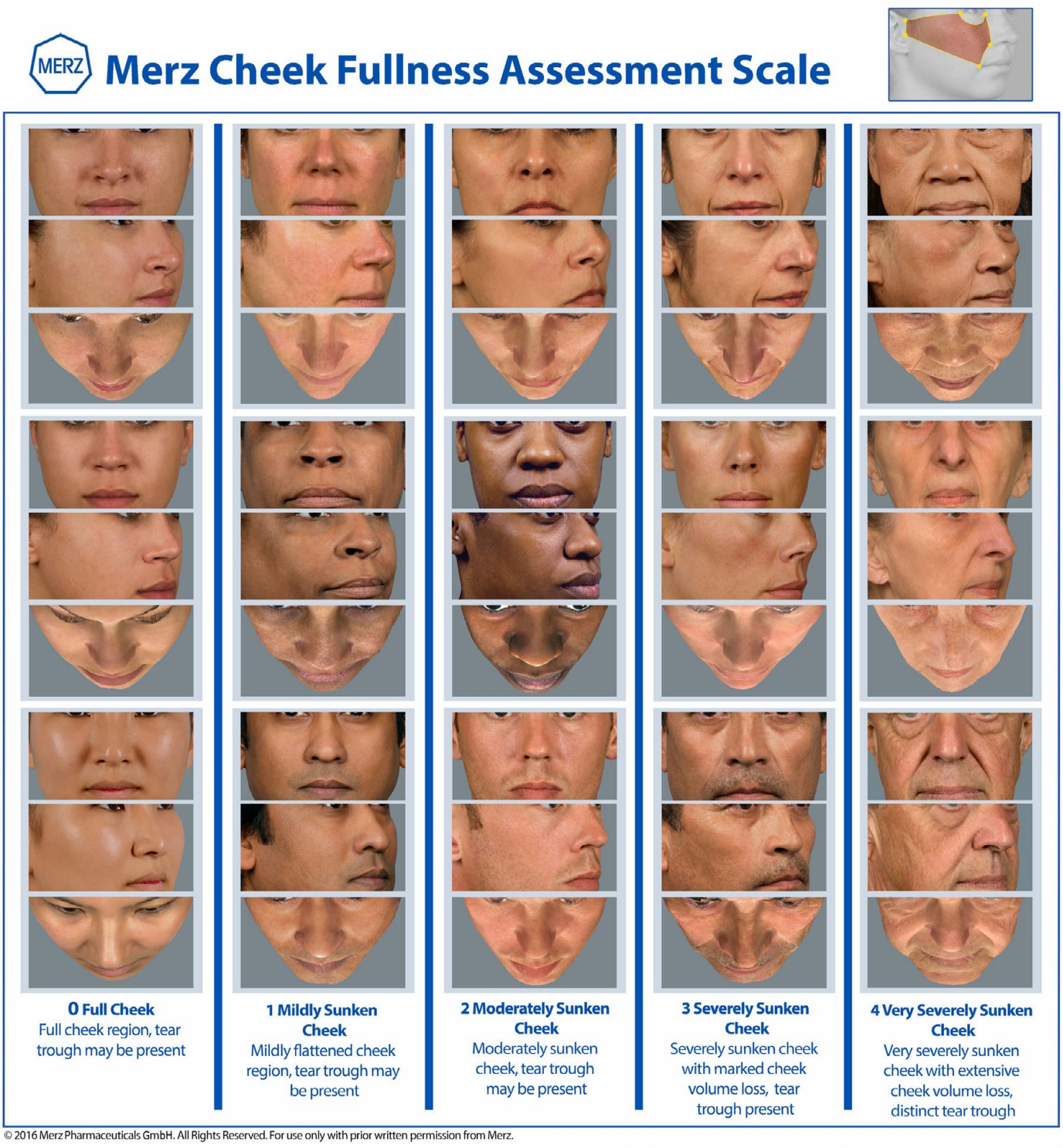


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TABLE 1.

Differences in MCFAS Scores for Image Pairs Deemed "Clinically Different" or "Clinically Same"

	Absolute Difference in MCFAS Scores			
	n[1]	Mean (SD)	Range	95% CI of Mean
"Clinically different" pairs	225	1.12 (0.88)	0 – 4	(1.00, 1.24)
"Clinically same" pairs	215	0.55 (0.57)	0 – 2	(0.48, 0.63)

[1]N = 440 = 88 pairs x 5 raters
CI, confidence interval; n, number of image pairs rated by 5 independent panel reviewers in each category; SD, standard deviation

(43.2%) had a score of 3 (severely sunken) on both cheeks. For the 22 participants randomized to untreated control, 12 (54.5%) had a MCFAS score of 2 on both cheeks, and 10 (45.5%) had a score of 3 on both cheeks (Table 2).

Treatment

All 44 (100%) participants randomized to treatment received a single injection in both cheeks. Volumes administered in both cheeks were similar, ranging from 0.6 mL to 3.0 mL (mean [SD] = 1.4 [0.51] mL) in the right cheek and 0.6 mL to 2.4 mL (mean [SD] = 1.4 [0.45] mL) in the left cheek. Total volume injected in both cheeks ranged from 1.4 mL to 4.7 mL (mean [SD] = 2.7 [0.89] mL).

Effectiveness

A significant difference (P<0.0001; Fisher's Exact Test) in response rates was noted when comparing the treatment group to untreated controls (Table 2). All treated participants (n = 44; 100%) and only 7 (31.8%) untreated controls demonstrated a ≥ 1-point improvement on the MCFAS, as assessed live by blinded evaluators, for both cheeks at Week 4 when compared to baseline. The risk difference (95% CI) between the treatment group and the untreated control group was 0.68 (0.49, 0.88). The CPM-HA-V responder rate was statistically significant when compared to the control group, and the lower bound of the risk difference was greater than zero.

TABLE 2.

Summary of MCFAS Response Between The CPM-HA-V Treatment and Untreated Control Groups When Comparing Baseline to Week 4

Visit	CPM-HA-V (N=44)	Control (N=22)
MCFAS Rating	n (%)	n (%)
Baseline		
Full cheek	0	0
Mildly sunken cheek	0	0
Moderately sunken cheek	25 (56.8%)	12 (54.5%)
Severely sunken cheek	19 (43.2%)	10 (45.5%)
Very severely sunken cheek	0	0
Week 4		
Full cheek	6 (13.6%)	0
Mildly sunken cheek	26 (59.1%)	6 (27.3%)
Moderately sunken cheek	12 (27.3%)	7 (31.8%)
Severely sunken cheek	0	9 (40.9%)
Very severely sunken cheek	0	0
Response: ≥ 1-point MCFAS improvement from baseline to Week 4	44 (100%)	7 (31.8%)
P-value*	< 0.0001	

CPM-HA-V = Belotero Volume with Lidocaine; N = number of participants in CPM-HA-V or control groups;
n = number of observations
*P-value from Fisher's Exact Test of no difference in response between CPM-HA-V and control groups

FIGURE 4. Oblique midfacial photographs before (left) and after (right) treatment with CPM-HA-V, a hyaluronic acid filler with lidocaine.

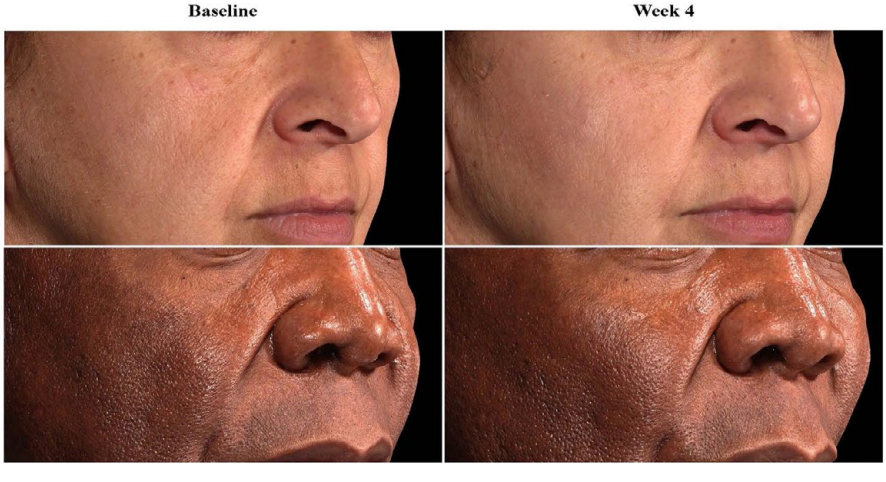

TABLE 3.

Summary of Treating Investigator and Participant GAIS at Week 4

Global Aesthetic Improvement Scale	Treating Investigator Assessment (N=44)	Participant Assessment (N=44)
	n (%)	n (%)
GAIS Score		
+3 = Very much improved	17 (38.6%)	13 (29.5%)
+2 = Much improved	20 (45.5%)	12 (27.3%)
+1 = Improved	7 (15.9%)	18 (40.9%)
0 = No change	0	0
-1 = Worse	0	0
-2 = Much worse	0	1 (2.3%)
-3 = Very much worse	0	0
GAIS Categorization		
Any improvement	44 (100%)	43 (97.7%)
No change	0	0
Any worsening	0	1 (2.3%)

N = number of participants in CPM-HA-V or control groups; n = number of observations

Representative before and after treatment photographs are shown in Figure 4.

Comparing post-treatment and baseline photographs, treating investigators reported that all treated participants (n = 44; 100%) were improved on the GAIS (Table 3). The majority of treated participants (n = 43; 97.7%) confirmed GAIS improvement when comparing post-treatment and baseline photographs; 1 (2.3%) participant reported a post-treatment GAIS score of *much worse*.

All 44 (100%) treated participants achieved a ≥ 1-point MCFAS improvement on both cheeks, according to the blinded evaluator's ratings, and a level of improvement on the treating investigator GAIS. Additionally, 43 of 44 (97.7%) treated participants, achieved a ≥ 1-point MCFAS improvement on both cheeks, via the blinded evaluator's ratings, and a level of improvement on the participant GAIS. One treated participant achieved a ≥ 1-point improvement on both cheeks, via the blinded evaluator MCFAS ratings; however, this participant reported a level of worsening on the participant GAIS (Table 4). These results surpassed the predefined threshold of 70% agreement between participants who achieved a ≥ 1-point MCFAS improvement on both cheeks, according to the blinded evaluator's ratings, and a level of improvement on the treating investigator and participant GAIS.

The cross-tabulation analysis demonstrated the objective clinical outcome from the MCFAS, as assessed by blinded evaluators, was consistent with the treating investigator's and participant's perspective of aesthetic post-treatment improvements on the GAIS. The findings reinforced the aesthetically pleasing MCFAS

TABLE 4.

Summary of Cross-Tabulation of MCFAS Results Via Blinded Evaluators for Changes From Baseline to Week 4 vs Treating Investigator and Participant GAIS Results at Week 4

	≥ 1-Point MCFAS Improvement on Both Cheeks (N=44)	No ≥ 1-Point MCFAS Improvement on Both Cheeks (N=44)	Total (N=44)
	n (%)	n (%)	n (%)
Investigator GAIS			
Improvement[1]	44 (100%)	0	44 (100%)
No change from baseline	0	0	0
Worsening[2]	0	0	0
Total	44 (100%)	0	44 (100%)
Participant GAIS			
Improvement[1]	43 (97.7%)	0	43 (97.7%)
No change from baseline	0	0	0
Worsening[2]	1 (2.3%)	0	1 (2.3%)
Total	44 (100%)	0	44 (100%)

N = number of participants exposed to treatment; n = number of observations
[1]Including "improved", "much improved", "very much improved" on the GAIS
[2]Including "worse", "much worse", "very much worse" on the GAIS

outcomes from the blinded evaluator, were clinically relevant and were consistent with other aesthetic assessment scales.

Safety

CPM-HA-V was found to be tolerable and safe among participants treated for midface volume loss. No unexpected safety concerns were identified during treatment, immediately after treatment, or during the 4-week follow-up period.

Eight (18.2%) of 44 participants treated with CPM-HA-V experienced 12 adverse events (AEs) related to injection procedure and/or CPM-HA-V. Reported AEs by most-common incidence included hypoesthesia (n=3; 6.8%); injection-site mass (n=2; 4.5%); facial pain (n=2; 4.5%); headache (n=2; 4.5%); injection-site bruising (n=1; 2.3%); injection-site discoloration (n=1; 2.3%); and skin exfoliation (n=1; 2.3%). In 2 participants, a specific event (injection-site mass or facial pain) was reported as related to both injection procedure and CPM-HA-V. Most AEs were mild in intensity, except for skin exfoliation and 1 case of headache, which were reported as moderate. All events resolved/recovered prior to study conclusion. No serious AEs were reported.

DISCUSSION

Based on results of a pilot study, the validated MCFAS successfully detected clinically meaningful aesthetic improvements following a single, safe, and effective CPM-HA-V treatment for midface volume loss in males and females of various ages and skin types.

Patients are increasingly seeking minimally invasive, nonsurgical alternatives for the midface region; therefore, it is important for clinicians and patients to agree on post-treatment expectations. A treat-to-goal approach, which begins with establishing practical, results-oriented expectations before the patient is treated, increases the likelihood of satisfaction. Furthermore, a patient's understanding of appropriate outcomes significantly increases when standardized scales are used during initial consultation.[14] The MCFAS was initially developed to be a valid, reliable, clinically relevant assessment tool for use in assessing clinically meaningful post-treatment results; however, it can also be helpful in facilitating discussions related to patient outcomes.

Prior to use in a clinical setting, the MCFAS was tested to ensure it is reliable for multiple assessments of the same participant, within the same rater and across different raters. It demonstrated exceptional reliability when used by trained clinicians to evaluate live male and female participants of various ages and FST. Excellent intra- and interrater agreement was demonstrated, with all weighted kappa coefficients exceeding the predefined 0.6 threshold. Additionally, during development, the MCFAS was tested for clinical meaningfulness by demonstrating that a 1-point difference between severity grades could be detected. Clinicians were able to successfully identify image pairs with the same MCFAS severity score vs image pairs with a 1-point difference in severity scores. The reliability and clinical relevance methods and results reported herein are consistent with other published facial studies.[4,7-11]

Many published aesthetic scale studies only use untreated participants to evaluate the scale's reliability and to establish the clinical relevance of a 1-grade difference.[4,7-11] Whether these scales can detect clinically meaningful differences when comparing pre- and post-treatment outcomes remains uncertain. To address this concern, the current work reports results of MCFAS-development activities, along with results of a pilot study in which CPM-HA-V was used for volume augmentation in the midface. In addition to CPM-HA-V's favorable safety profile, its effectiveness was demonstrated by utilizing the MCFAS in a clinical setting where participants were assessed for clinically relevant post-treatment changes.

Primary effectiveness results showed the MCFAS was able to detect clinically meaningful changes (ie, ≥ 1-grade) when comparing live, blinded rater scores at Week 4 to baseline. Differences (P<0.0001) in response rates between the CPM-HA-V-treated group and untreated controls indicated the MCFAS was successfully able to detect aesthetic improvements in the treatment group, while the majority of untreated participants had the same MCFAS score at baseline and Week 4.

An important aspect to consider during aesthetic-scale development and testing is the ability of a scale to have a correlation with another commonly used measure of similar concept (ie, post-treatment aesthetic improvement).[15] To further demonstrate MCFAS results from the primary effectiveness endpoint were clinically meaningful, cross tabulations were performed between the blinded evaluator's rating of ≥ 1-point MCFAS improvement on both cheeks and GAIS scores reported by the treating investigator and the participant. These cross-tabulations indicated 100% concordance between the blinded evaluator's MCFAS ratings and improvement on the treating investigator GAIS, as well as nearly 98% agreement between the blinded evaluator's MCFAS ratings and improvement on the participant GAIS. Findings suggest MCFAS's objective clinical outcome, as assessed by blinded evaluators, is consistent with the treating investigator's and participant's perspective of post-treatment aesthetic improvements on the GAIS, thus supporting the MCFAS outcome is clinically meaningful.

The current findings indicate that treatment with CPM-HA-V is a safe and effective option to improve volume deficits in the midface. AEs reported in the study were minimal or moderate, resolved prior to study end, and typical for midface-injection procedures.[16-18]

With respect to study limitations, while a 1-point difference was determined to be clinically meaningful during MCFAS validation and pilot-study testing, in-clinic patients may seek more subtle aesthetic improvements (ie, <1-point change). Additionally, the MCFAS was not designed to assess severity between grades (eg, 0.5 and 1.5). Given the variability in patient expectations, other measures, including validated patient-reported outcome scales, are more appropriate for evaluating patient satisfaction.[19] Although the MCFAS was able to detect clinically meaningful changes in a 4-week pilot study, robust studies are needed to test its reproducibility in a larger study population.

CONCLUSION

The Merz Cheek Fullness Assessment Scale demonstrated excellent intra- and interrater reliability, and a 1-point difference in scale severity was found to be clinically meaningful. The scale maintained its reliability and clinical relevance when tested across participants of representative ages and FST and can be considered a valuable tool in a clinical setting. Results of a pilot study supported the MCFAS's utility, while also demonstrating CPM-HA-V is a safe and effective treatment option for moderate to severe midface-volume loss.

DISCLOSURES

Drs Moradi and Bloom received an honorarium for scale development and have provided expert consultancy and advisory input to Merz North America. The remaining authors had no conflict-of-interest disclosures.

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ORIGINAL ARTICLE

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A Retrospective Analysis of Patient Satisfaction With a Graft-Based Non-Surgical Rhinoplasty Procedure Using a Modified Surgical Rhinoplasty Module

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ABSTRACT

Non-surgical rhinoplasty, also known as liquid or injection rhinoplasty, utilizes hyaluronic acid-based fillers to offer a minimally invasive alternative to surgical rhinoplasty. Patient goals for injection rhinoplasty includes improving various aspects of their nose, including the bridge of the nose, tip of the nose, shape of the nose in profile, and how well the nose suits the face. The purpose of this study is to use a modified surgical rhinoplasty questionnaire to analyze patient satisfaction and adverse complication rates of the author's non-surgical injection rhinoplasty technique using a hyaluronic acid-based filler. A retrospective data analysis of 56 patients who had received a graft-based non-surgical rhinoplasty procedure between January 2019 and December 2019 was conducted. All procedures were performed at a single center by the primary investigator. Participants completed a questionnaire to assess for preoperative and postoperative satisfaction with their nose using a visual analogue scale and modified "FACE-Q" module. Two-tailed paired t-tests and confidence intervals were calculated using bootstrapping/resampling techniques. Visual analogue scale results depict a paired median difference of 4, yielding a *P*-value of 0.00001. Results illustrate that using a graft-based non-surgical rhinoplasty technique presents a promising alternative to surgical rhinoplasty that significantly improves patient satisfaction with their nose while ensuring minimal complication rates. Over 98% of patients indicated feeling "somewhat" or "very likely" to repeat the procedure.

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INTRODUCTION

Surgical rhinoplasty has been the gold standard for nasal reshaping for the past century, with over 726,000 procedures performed internationally in 2018 alone.[1] However, this number has been declining due to the rise in popularity of minimally invasive, non-surgical rhinoplasty alternatives: which offer comparable results at a lower cost and less downtime. In the U.S., surgical rhinoplasty procedures were down 3% between 2018 and 2019, with 213,780 and 207,284 procedures performed respectively,[2] these trends offer insight on the newfound prominence of non-surgical cosmetic procedures utilizing hyaluronic acid based fillers, which saw a 27.9% increase between 2014 and 2018.[1] Although non-surgical rhinoplasty trends were not explicitly recorded by these surveys, the primary investigator has noted an increased demand for injection rhinoplasty over the last years.

In order to evaluate patient satisfaction with non-surgical rhinoplasty and adverse complications rates, a questionnaire should be developed to assess the efficacy and success of the procedure. We looked at the FACE-Q module which has been utilized by Kalaaji et al to assess surgical rhinoplasty outcomes amongst 243 patients.[4] Most notably, patients from this study reported feeling "very" or "somewhat" dissatisfied with the nasal bridge (85.7%), nasal tip (83.7%), nasal profile (91.8%), and the appearance from every angle (93.8%) prior to their surgical rhinoplasty procedure.[4] Post-operatively, patient dissatisfaction among these categories decreased substantially: 45%, 51.7%, 43.4%, 55% respectively.[4] The FACE-Q module also assessed for quality of life improvements such as ability to breathe through the nose and adverse complications experienced.[4]

Comparative to surgical rhinoplasty, discourse regarding patient satisfaction with liquid rhinoplasty is limited due to its newfound prevalence in the aesthetic community. Few studies evaluate patient satisfaction with injection rhinoplasty to the same degree of specificity as that of surgical rhinoplasty. Although there are several studies that provide insight on complication rates and visual assessment scores from a surgeon's perspective, ultimately the patient's satisfaction should be the highest consideration when determining the efficacy and success of the procedure.[5,6]

Finally, the author employs a "graft-based technique" similar to that explained by Segreto et al by creating a shield graft structure using filler in the tip of the nose.[7] Cartilage grafts are normally used to correct for tip drooping, nasal asymmetries, and other irregularities that require volume to be added to the nose. A similar effect can be achieved utilizing a high G' hyaluronic acid-based filler, by creating a graft with filler that structurizes and lifts the tip of the nose as seen in Figure 1. As this non-surgical rhinoplasty technique is being more widely implemented by surgeons and injectors, the resultant impact towards patient satisfaction and complication rates is further explored by this retrospective study.

MATERIALS AND METHODS

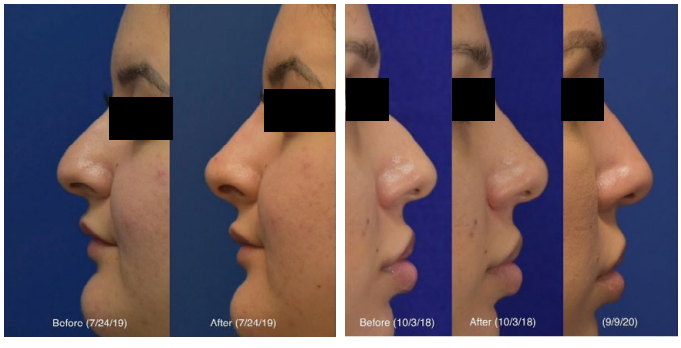
Patients

All non-surgical rhinoplasties described by the data were performed by the author. A total of 208 patients received a liquid rhinoplasty in 2019. Only 129 were reachable by email and received the questionnaire, of which 56 responded and were enrolled in the study. Surveys were sent via email in July of 2020 and data was collected until August of 2020. All data results were collected and processed anonymously.

Questionnaire

This study's survey consisted of questions from the FACE-Q rhinoplasty module, which was developed by Memorial Sloan Kettering Cancer Center (New York, N.Y.). Questions measuring patient satisfaction with their nose preoperatively and postoperatively were included from the FACE-Q module. This includes patient satisfaction with nasal width, nasal length, nasal bridge, nasal tip, straightness of nose, appearance of nose in photos, nasal profile, appearance of nose from every angle, overall nasal size, and how well the nose suits the face. Satisfaction was measured using a Likert scale between 0 and 4 (0, "very dissatisfied"; 1, "somewhat dissatisfied"; 2, "neutral"; 3, "somewhat satisfied"; 4, "very satisfied"). Pre-operative and post-operative visual analogue scale results measuring the patient's overall satisfaction with their nose were collected as well (scale from 0 to 10; 0= very dissatisfied; 10= very satisfied). The "Adverse Effects" questions were modeled after those used by the FACE-Q rhinoplasty module, measuring the degree of complication that patients experience following the procedure. Questions regarding nasal and breathing functionality were omitted as they are more specific to surgical rhinoplasties. Instead, adverse complications such as bruising, swelling, tenderness, infection, bumps, and asymmetry were incorporated. Adverse complications were measured using a Likert scale between 0 and 3 (0, "not at all"; 1, "a little"; 2, "moderate"; 3, "extreme"). Patients were also asked to rate the level of pain they experienced during the procedure from 1 to 10 (1= no pain, 10= extreme pain).

FIGURE 1. Preoperative and postoperative non-surgical rhinoplasty photos of two separate patients.



Statistical Analyses

All statistical analyses were conducted using Colaboratory by Google. All paired t-test results utilized bootstrapping and resampling techniques, since most distributions were nonuniform, not normally distributed, and had differing variances.[8] One hundred thousand (100,000) simulations were performed per paired t-test. The Null Hypothesis, that the median differences between the paired preoperative and postoperative ratings for each FACE-Q module question and Visual analogue scale were 0, was tested using bootstrapping and resampling methods. Paired differences were calculated and resampled (with replacement) to find simulated median differences. This was repeated 100,000 times, and the 0.5% and 99.5% cutoffs were used to calculate statistical significance (*P*-value). Only *P*-values less than 0.01 were considered "statistically significant."

RESULTS

Patients

Of the 208 patients that received an injection rhinoplasty in 2019 at our clinic, only 129 were reachable by email. The questionnaire was completed by 56 (2 male and 54 female) patients (response rate: 43.4%). Patient ages ranged from 18 to 59 years old, with a median patient age of 33.5 (99% CI of 29.5 - 36 years).

TABLE 1.

Visual Analogue Scale Pre- and Postoperative Results						
	Median Preoperative Score	Median Postoperative Score	Paired Median Difference	99% CI for Paired Median Difference	*P*-value (paired t-test)	Reject null? (alpha=0.01)
VAS ("How much I liked the overall appearance of my nose")	4	9	4	(3, 5.5)	1.00E-05	Y

TABLE 2.

FACE-Q Questionnaire Pre- and Postoperative Scores					
	Very Dissatisfied	Somewhat Dissatisfied	Neutral	Somewhat Satisfied	Very Satisfied
Q1 preoperative (width of nose)	14.29%	30.36%	30.36%	16.07%	8.93%
Q1 postoperative	3.57%	3.57%	26.79%	28.57%	37.50%
Q2 preoperative (length of nose)	23.21%	28.57%	28.57%	10.71%	8.93%
Q2 postoperative	1.79%	5.36%	25.00%	21.43%	46.43%
Q3 preoperative (bridge of nose)	42.86%	25.00%	16.07%	10.71%	5.36%
Q3 postoperative	3.57%	1.79%	5.36%	19.64%	69.64%
Q4 preoperative (tip of nose)	55.36%	19.64%	16.07%	5.36%	3.57%
Q4 postoperative	3.57%	1.79%	3.57%	33.93%	57.14%
Q5 preoperative (straightness of nose)	48.21%	21.43%	19.64%	3.57%	7.14%
Q5 postoperative	3.57%	1.79%	7.14%	23.21%	64.29%
Q6 preoperative (nose appearance in photos)	60.71%	26.79%	1.79%	7.14%	3.57%
Q6 postoperative	1.79%	3.57%	3.57%	19.64%	71.43%
Q7 preoperative (shape of nose in profile)	64.29%	17.86%	8.93%	7.14%	1.79%
Q7 postoperative	1.79%	3.57%	3.57%	23.21%	67.86%
Q8 preoperative (nose appearance from every angle)	46.43%	37.50%	8.93%	5.36%	1.79%
Q8 postoperative	3.57%	1.79%	10.71%	37.50%	46.43%
Q9 preoperative (overall size of nose)	28.57%	35.71%	23.21%	7.14%	5.36%
Q9 postoperative	3.57%	5.36%	12.50%	30.36%	48.21%
Q10 preoperative (how well nose suits face)	32.14%	35.71%	21.43%	7.14%	3.57%
Q10 postoperative	3.57%	1.79%	12.50%	39.29%	42.86%

Visual Analogue Scale

The median preoperative satisfaction rating for the "overall appearance of the nose" was 4. The median postoperative satisfaction rating was 9. The paired median difference between postoperative and preoperative satisfaction ratings with the "overall appearance of the nose" was 4. Calculated P-value and confidence intervals are presented in Table 1.

Satisfaction With Nose

Following the injection rhinoplasty treatment, patient satisfaction ("somewhat satisfied" or "very satisfied") increased significantly relative to their pretreatment satisfaction ratings. Substantial increases in patient satisfaction can be seen with their nasal bridge (16.1% vs 89.2%), tip (8.9% vs 91.1%), profile appearance (8.9% vs 91.1%), straightness of their nose (10.7% vs 87.5%), appearance of the nose in photos (10.7% vs 91.1%), nasal appearance from every angle (7.15% vs 83.9%), overall size of the nose (12.5% vs 78.6%), how well the nose suits the face (10.7% vs 82.2%), nasal width (25% vs 66.1%), and nasal length (19.6% vs 67.9%).

Most notably, patient dissatisfaction ("somewhat" or "very dissatisfied") prior to the procedure decreased in every category including the appearance of their nose in photos (87.5% vs 5.4%), nasal profile (82.2% vs 5.4%), nasal tip (75% vs 5.4%), appearance from every angle (83.9% vs 5.4%), and how well the nose suits the face (67.9% vs 5.4%). Furthermore, patients chose liquid rhinoplasty over surgical rhinoplasty due to less downtime (66.1%), less costly (51.8%), fear of surgery (37.5%), and temporary results (25%). Complete pre- and postoperative satisfaction ratings are presented in Table 2.

P-values were calculated for each question regarding patient satisfaction with their nose, using bootstrapping paired t-test methods between preoperative and postoperative ratings. Only two of the questions failed to reject the null assuming $\alpha=0.01$ ("length of the nose," *P*-value= 0.0299; "appearance of nose in photos", *P*-value= 0.0204). All other questions regarding patient satisfaction with their nose had a P-value less than $\alpha=0.01$, thus allowing us to conclude that there is statistical significance between the paired preoperative and postoperative ratings for these questions. 99% confidence intervals for paired median difference and *P*-values are summarized in Table 3.

Adverse Effects

Patients reported a median pain level of 2, on a scale from 1 (no pain) to 10 (extreme pain). Over 89% of the surveyed patients reported pain from 1 to 4. No patient reported experiencing pain from 8 to 10.

TABLE 3.

FACE-Q Questionnaire Statistical Analysis Results						
	Median Preoperative Score	Median Postoperative Score	Paired Median Difference	99% CI for Paired Median Difference	*P*-value (paired t-test)	Reject null? (alpha=0.01)
Q1 (width of nose)	2	3	1	(0, 2)	0.0042	Yes
Q2 (length of nose)	1	3	1	(0, 1)	0.0299	No
Q3 (bridge of nose)	1	4	3	(2, 4)	0	Yes
Q4 (tip of nose)	0	4	3	(2, 4)	0	Yes
Q5 (straightness of nose)	1	4	3	(2.5 , 4)	0	Yes
Q6 (nose appearance in photos)	0	4	3	(2, 3)	0.02042	No
Q7 (shape of nose in profile)	0	4	3	(2, 3)	0.00623	Yes
Q8 (nose appearance from every angle)	1	3	3	(3, 4)	0	Yes
Q9 (overall size of nose)	1	3	2	(2, 3)	0.00012	Yes
Q10 (how well nose suits face)	1	3	2	(1, 2.5)	0.00075	Yes

TABLE 4.

Adverse Effects Following Non-Surgical Rhinoplasty Procedure				
	Severity Rating			
	0 (not at all)	1 (a little)	2 (moderate)	3 (extreme)
Bruising	51.79%	35.71%	8.93%	3.57%
Swelling	35.71%	44.64%	17.86%	1.79%
Tenderness	32.14%	46.43%	19.64%	1.79%
Infection	100.00%	0.00%	0.00%	0.00%
Bumps	98.21%	1.79%	0.00%	0.00%
Asymmetry	82.14%	12.50%	3.57%	1.79%

Adverse complications following the non-surgical rhinoplasty procedure were generally low. Patients reported little to no complications within 2 weeks after the procedure with bruising (87.5%); swelling (80.3%); tenderness (78.6%); asymmetry (94.6%). There were no reported instances of skin necrosis, vascular occlusion, or blindness. The adverse effects data is summarized in Table 4.

Strengths

Because this draws upon a large, diverse population, the results of this study are applicable to the general population. All patient survey responses were conducted anonymously and are representative of the general population, thereby providing a basis to determine statistical significance. The use of bootstrapping, resampling statistical techniques for t-test analyses are more indicative than traditional T-test statistical analyses using formulas.[8] This bypasses the need for normally distributed data with similar variances and utilizes more representative forms of central tendency (ex. median). The paired design of this study also eliminates individual variability between patients and provides accurate satisfaction differences before and after receiving the non-surgical rhinoplasty procedure.

Limitations

Because this was a retrospective review of non-surgical rhinoplasty patients from 2019, true patient satisfaction may not have been accurately expressed due to the time delay following the initial procedure. Greater accuracy would be observed if survey results were taken immediately prior to the procedure, and 2 weeks after the procedure. Furthermore, volunteer response bias should be considered in this retrospective study, as patients with strong sentiments (whether positive or negative) are more inclined to complete the survey, resulting in the expression of mainly extreme opinions. This study could be improved through obligatory participation, randomizing patient selection (nullifying volunteer response bias), and collecting survey results closer to pre- and postoperative dates for greater degrees of accuracy. Furthermore, patient satisfaction towards the beginning of 2019 may have varied from patient satisfaction towards the end of 2019, as the surgeon (Kay Durairaj MD FACS) self-reports her techniques improved and experience increased during that time frame.

DISCUSSION

The safety and efficacy of non-surgical rhinoplasty can be evaluated relative to surgical rhinoplasty outcomes using our modified questionnaire. Patients reported high satisfaction ratings ("somewhat" or "very satisfied") with their nasal bridge (89.2%), tip (91.1%), straightness (87.5%), profile appearance (91.1%), appearance from every angle (83.9%), overall size (78.6%), how well the nose suits the face (82.2%), and nasal width (66.1%). Aspects such as the nasal bridge, tip, straightness, profile, and appearance from every angle saw paired median differences of 3. Furthermore, we found statistical significance ($P<0.01$) between pre- and postoperative patient satisfaction amongst all these categories, allowing us to reject the null

hypothesis that there is no difference between paired pre- and post-treatment satisfaction with each respective aspect of the nose. According to the visual analogue scale results, the paired median difference between pre- and postoperative patient satisfaction with the overall appearance of their nose was 4. This is a statistically significant paired median difference (*P*-value = 0.00001), meaning that only 1 simulation out of 100,000 observed a paired median difference equal to or more extreme than 4. Therefore, on average, the injection rhinoplasty procedure will increase patient satisfaction with the overall appearance of their nose by 4 points on a Likert scale.

Although we observed increases in patient satisfaction ("somewhat" or "very satisfied") with the length of their nose (19.6% vs 67.9%) and how their nose appears in photos (10.7% vs 91.1%), we did not find any statistical significance between the pre- and postoperative satisfaction among these categories. This is expected given that non-surgical rhinoplasty does not directly impact these aspects. Characteristics such as the nasal bridge, tip, and profile are relevant to the expectations of the non-surgical rhinoplasty procedure, thus resulting in statistically significant findings. Therefore, a modified questionnaire should be used to assess patient satisfaction given the differing expectations between surgical and non-surgical rhinoplasties.

Generally non-surgical rhinoplasty procedures are associated with little downtime and only minor side effects.[9] Most of the patients from this study experienced little to no bruising (87.5%), swelling (80.4%), and tenderness (78.6%) within 2 weeks after the procedure. These minor complications are expected within 48 hours following the procedure but subside fairly quickly leaving the patient with little downtime. Furthermore, none of the study patients experienced more adverse complications such as white skin discoloration due to blanching, skin necrosis, or blindness associated with vascular occlusion. With a skilled injector that has extensive knowledge on the anatomy and planes of the nose, the incidence of adverse reactions can be reduced. This includes staying in the midline of the nose, injecting sub-superficial musculoaponeurotic system (SMAS) with less than 0.05 mL aliquots, and aspiration before injection.[10] By following these guidelines, the likelihood of retrograde embolization of a blood vessel and blindness due to vascular occlusion is reduced dramatically.[11]

Given the temporary duration of the filler, patients who desire a surgical rhinoplasty look without the expenses and risks of surgery should consider injection rhinoplasty. Over 98% of our study patients indicated feeling "somewhat likely" or "very likely" to repeat the non-surgical rhinoplasty procedure. Rare occurrences of extreme complications, low pain ratings, and minimal downtime allow the procedure to be highly repeatable over 6–12-month periods. Patients with a prior history of surgical rhinoplasty also seek this treatment to correct imperfections that do not meet their expectations following the surgery. A study published in 2015 by the Aesthetic Surgery Journal indicated that amongst dissatisfied surgical rhinoplasty patients, residual dorsal hump, under-rotated tip, and bulbous tip were the highest rated reasons for dissatisfaction.[12] The graft-based injection method for non-surgical rhinoplasty allows surgical results using minimally invasive techniques with filler.

CONCLUSION

Based on the questionnaire results, it is evident that non-surgical rhinoplasty with filler can achieve similar satisfaction as surgical rhinoplasty, in all categories of the FACE-Q module excluding the length of the nose and its appearance in photos. It was also evident that the procedure significantly improved the patient's subjective perception of the overall appearance of their nose. The results of this study provide support that hyaluronic dermal filler can be used as an alternative to surgical nasal reconstruction to achieve symmetrical features in the nasal region, immediately and non-invasively, with rare incidences of moderate to extreme complications. Future studies incorporating a larger sample size, randomization of patient selection, and data collection immediately before and after the procedure can offer greater accuracy of true patient satisfaction with non-surgical rhinoplasty.

DISCLOSURES

There is no conflict of interest per each author.

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ORIGINAL ARTICLE

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Effectiveness and Safety of Sculptra Poly-L-Lactic Acid Injectable Implant in the Correction of Cheek Wrinkles

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ABSTRACT

Background: The current study evaluated the effectiveness and safety of Sculptra® injectable poly-L-lactic acid (PLLA-SCA) treatment in correcting cheek wrinkles compared with a no-treatment control.

Methods: Male/female immune-competent adults (aged >21 years) with moderate/severe cheek wrinkles, graded using the Galderma Cheek Wrinkle Scale (GCWS) at rest, were randomized 2:1 to receive PLLA-SCA injections (150 mg; 8 mL reconstitution in sterile water for injection) + 1 mL lidocaine hydrochloride (2%), administered immediately after reconstitution, or no treatment (control). Up to 3 additional treatments were allowed at monthly intervals and follow up was at months 7, 9, and 12. The primary endpoint was ≥1-grade improvement in GCWS at rest for both cheeks at month 12.

Results: GCWS at rest responder rate was significantly higher with PLLA-SCA treatment versus the no-treatment control at months 7 (66.2% versus 38.6%; P=0.0043), 9 (70.6% versus 31.1%; P<0.0001), and 12 (71.6% versus 26.1%; P<0.0001). Treating investigators reported improvements in skin radiance (>95%), tighter appearance (>88%), and jawline contour (>85%). PLLA-SCA recipients reported high satisfaction levels regarding improvements in skin radiance (≥90%), sagging (≥84%), and firmness (≥91%) as well as natural looking results (≥85%) and a desire for repeat treatment (≥84%). Treatment-related adverse events were mostly mild in severity with no serious events related to PLLA-SCA injections.

Conclusion: Injectable PLLA-SCA treatments were well tolerated and significantly reduced the severity of moderate/severe cheek lines and wrinkles, while improving skin quality. Effectiveness was durable over the 12-month study period with high subject-reported satisfaction, natural looking appearance, and enthusiasm for repeat treatments.

Clinical trial registry number: NCT04124692

J Drugs Dermatol. 2024;23(1):1297-1305. doi:10.36849/JDD.7729

INTRODUCTION

Sculptra® poly-L-lactic acid injectable implant (PLLA-SCA; Galderma, Sweden) is a plant-derived alpha-hydroxy-acid polymer.[1–4] When used for soft tissue augmentation, PLLA-SCA gradually stimulates collagen formation, over the course of several treatments, to provide semi-permanent correction of facial volume loss associated with aging.[1–4]

Injectable PLLA-SCA has demonstrated durable and natural looking results in randomized studies, with most recipients (80%) maintaining aesthetic correction of contour deficiencies until the 25-month data cut-off.[5,6] Growing experience has driven an improved understanding of optimal PLLA-SCA injection techniques to achieve high levels of treatment satisfaction and good safety outcomes.[2,7–9] PLLA-SCA studies

have demonstrated skin quality improvements and recipient-reported emotional and functional benefits, including elevated self-esteem and confidence.[10–12] Based upon current evidence, expert recommendations support the use of PLLA-SCA for facial rejuvenation, according to the approved indication.[13–15]

Since 2004, this product has been approved in the US for restoration and/or correction of signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus, and since 2009 also for correction of shallow to deep nasolabial fold contour deficiencies and other facial wrinkles in immune-competent individuals.[5] Recently (2023), the US FDA approved an extension of the indication to include the correction of fine lines and wrinkles in the cheek region for use in immune-competent subjects, based on the study results presented here.

This study evaluated the effectiveness and safety of the PLLA-SCA injectable implant in the correction of cheek wrinkles compared with a no-treatment control, using the preparation and administration protocol published by Palm et al (2021), in which treatment was administered immediately after PLLA-SCA reconstitution in sterile water for injection (SWFI; 8 mL) + 1 mL lidocaine solution (2%), rather than waiting the standard 2 hours before injection.[5,16–18] The adapted protocol was intended to support safety and tolerability outcomes with PLLA-SCA, and to aid convenience for physicians.

MATERIALS AND METHODS

Study Design

A randomized, evaluator-blinded, no-treatment controlled study was conducted between November 2019 and August 2021 at 13 sites in the US to assess the effectiveness and safety of PLLA-SCA injections for the correction of cheek wrinkles (NCT04124692). The study was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice as applicable for medical devices. Subjects gave written informed consent and ethical approval was obtained from each relevant institutional review board.

Live study assessments were conducted by blinded evaluators and treating investigators, and subject self-assessment data were reported via questionnaires and subject diaries. During screening and throughout the study, the validated 5-point Galderma Cheek Wrinkles Scale (GCWS; none, mild, moderate, severe, or very severe) was used to grade the severity of wrinkles in repose (GCWS at rest) and when adopting a closed maximum smile (GCWS dynamic).

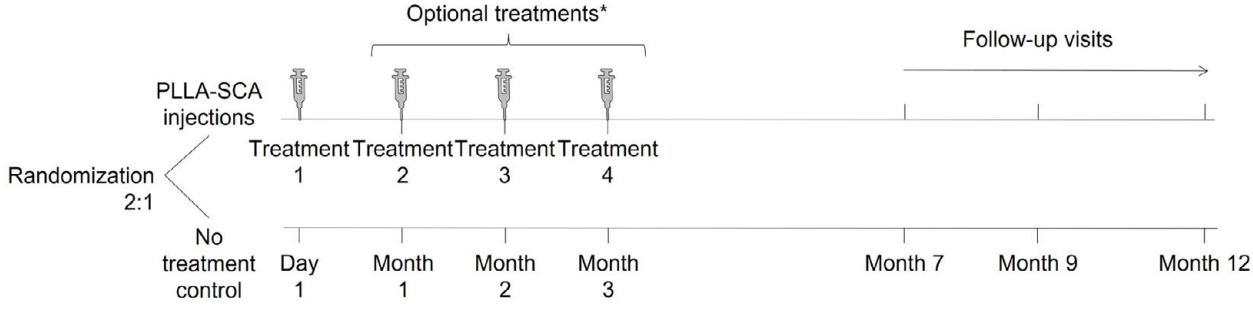
Study Population

The study included male/female immune-competent adults (aged >21 years) with cheek wrinkles graded as moderate or severe on each side of the face according to GCWS at rest assessments (blinded evaluator and treating investigator). The difference in wrinkle severity was no more than 1-grade between sides. Individuals who had known allergy to injectable PLLA-SCA or lidocaine had undergone previous tissue augmentation, contouring, resurfacing, or similar therapies, or had facial lesions in the treatment area were excluded. Subjects who were pregnant, planning a pregnancy, or breastfeeding were not allowed to enter the study.

Study Treatment

Figure 1 shows the study schedule. Eligible subjects were randomized 2:1 to receive either PLLA-SCA injections (PLLA-SCA group) or no treatment (control group). PLLA-SCA injections were administered on day 1/baseline (Treatment 1). Up to 3 additional treatments were allowed at monthly intervals (Treatments 2, 3, and 4). Follow up visits were conducted at months 7, 9, and 12 (taking place 3, 5, and 8 months after the fourth treatment session, respectively). Each vial containing sterile, freeze-dried,

FIGURE 1. Study schedule.



*Treatment in both cheeks until optimal results were achieved.

Subjects were randomized 2:1 to receive PLLA-SCA or no treatment (control). A maximum of 9 mL PLLA-SCA was administered by subdermal injection in each cheek on Day 1. Up to 3 additional treatments were allowed at monthly intervals until Month 3. Follow up visits were conducted at Months 7, 9 and 12.

injectable PLLA-SCA (150 mg) was reconstituted in SWFI (8 mL) and 1 mL lidocaine hydrochloride (2%) was added immediately prior to injection. PLLA-SCA solution (9 mL maximum) was administered sub-dermally into each cheek using a 25 G needle. The treated area was defined according to the superior, medial, inferior, and lateral anatomical cheek borders. The superior border comprised the area from the topmost part of the tragus to top of alar crease. The medial border encompassed the top of the alar crease, along the nasolabial fold to the inferior border of the mandibular ramus. The inferior border ran from the medial border at the mandibular ramus to the angle of mandibular ramus and the lateral border comprised the area from the angle of the mandibular ramus to the top of the tragus.

Effectiveness Endpoints

The primary effectiveness endpoint was the responder rate based on a blinded evaluator assessment of GCWS at rest at month 12 after baseline. A responder was defined as a subject with ≥1-grade GCWS improvement from baseline in both cheeks concurrently.

Secondary and exploratory endpoints included responder rate for GCWS at rest at months 7 and 9, and responder rate for GCWS dynamic at months 7, 9, and 12 (blinded evaluator assessments). Treating investigators assessed the combined improvement on both sides of the face using the 7-point Global Aesthetic Improvement Scale (GAIS: very much improved, much improved, improved, no change, worse, much worse, very much worse) at all visits for the PLLA-SCA group and at months 7, 9, and 12 for the control group. GAIS responders scored very much improved, much improved, or improved from baseline. Treating investigators also assessed the change from baseline regarding skin radiance, tightness, and jawline contour at months 7, 9, and 12.

PLLA-SCA recipients completed the subject satisfaction questionnaire at all visits, following treatment. Participants rated overall treatment results using a 5-grade scale: excellent, very good, good, satisfactory, or not satisfied. Subjects also indicated the extent to which they agreed with statements relating to the effectiveness of treatment using a 5-grade scale: strongly agree, agree, neither agree nor disagree, disagree, strongly disagree. The satisfaction with cheeks FACE-Q™ questionnaire examined subject-assessed outcomes regarding the change in symmetry, smoothness, attractiveness, contour, and youthful fullness. Subjects indicated their level of satisfaction with treatment outcomes using a 4-grade scale: very satisfied, somewhat satisfied, somewhat dissatisfied, very dissatisfied. The control group completed the satisfaction with cheeks FACE-Q questionnaire at months 7, 9, and 12. FACE-Q responses were converted to Rasch-transformed total scores. Subject diaries recorded the time to return to social engagement for 28 days after each treatment.

Safety Endpoints

Adverse events (AEs) were reported by the treating investigator throughout the study and included any abnormal findings from an evaluation of cheek firmness, symmetry, function, mass formation and palpability, cheek sensation, and visual function performed at all study visits. Subject diary cards were used to collect expected post-treatment symptoms (for 28 days after each treatment).

Statistical Analysis

All statistical analyses used the SAS® software. Confidence intervals (CIs) were 2-tailed and at a level of 95%. The intention-to-treat (ITT) and safety populations comprised all randomized subjects. Effectiveness analyses examined the ITT population. The per-protocol (PP) population comprised all ITT subjects completing baseline and month 12 visits without deviations considered likely to impact the primary effectiveness outcome. The primary endpoint analysis used Fisher's exact test with multiple imputations of missing data instead of baseline observation carried forward (defined in the study protocol) to manage the increased risk of premature study discontinuation or missed month 12 visits during the COVID-19 pandemic. Month 12 responder rate CIs used multiple imputations, but sensitivity analysis of the primary and secondary endpoints used the planned Clopper-Pearson intervals.

RESULTS

Study Population

Baseline demographics and characteristics are presented in Table 1. Overall, 149 subjects were included in the study, with 97 randomized to the PLLA-SCA group and 52 to the control group. Most subjects were female (96.6%), White (90.6%), and not of Hispanic/Latino origin (91.9%). Mean age was 60.7 (range: 41–89) years and subjects were typically aged ≥55 years (77.9%). All subjects had moderate or severe cheek wrinkles at baseline (blinded evaluator GCWS at rest assessments). Additional PLLA-SCA treatments were required at months 1, 2, and 3 for 95 (97.9%), 86 (88.7%), and 67 (69.1%) subjects, respectively. Injection volumes for each treatment are shown in Table 2.

Effectiveness Outcomes

Figure 2 shows the GCWS at rest responder rate at months 7, 9, and 12 (live blinded evaluator assessment). Concerning the primary endpoint, the GCWS at rest responder rate was significantly higher in the PLLA-SCA group (70.7% estimated; 71.6% observed cases), compared with the control group (25.9% estimated; 26.1% observed cases) at month 12 (P<0.0001 for both comparisons). GCWS responder rate was also significantly greater in the PLLA-SCA group, versus the control, at month 7 (66.2% versus 38.6%; P=0.0043) and at month 9 (70.6% versus 31.1%; P<0.0001).

TABLE 1.

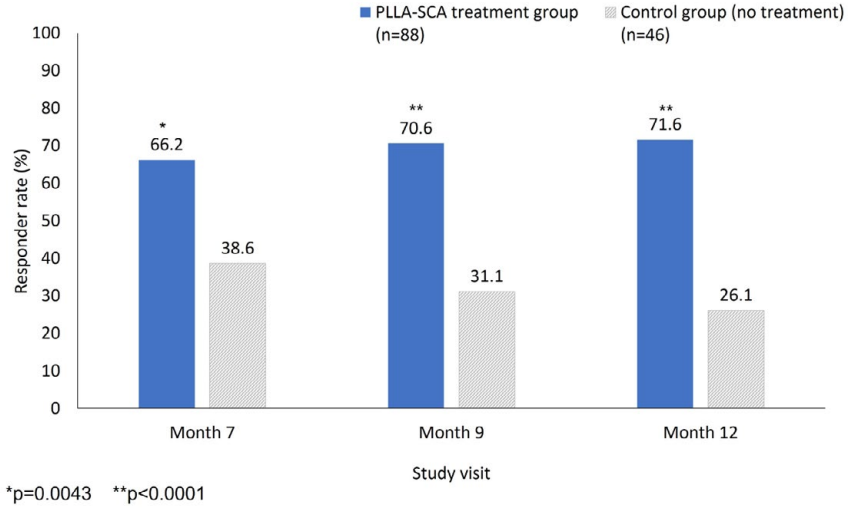
Baseline Demographics and Characteristics (ITT Population)				
	Control group (N=52)		PLLA-SCA group (N=97)	Total (N=149)
Age (years)				
Mean (range)	60.4 (45–88)		60.9 (41–89)	60.7 (41–89)
≥55 years	39 (75.0)		77 (79.4)	116 (77.9)
Gender, n (%)				
Female	50 (96.2)		94 (96.9)	144 (96.6)
Male	2 (3.8)		3 (3.1)	5 (3.4)
Race, n (%)				
American Indian/Alaska Native	0		1 (1.0)	1 (0.7)
Asian	1 (1.9)		1 (1.0)	2 (1.3)
Black/African American	4 (7.7)		7 (7.2)	11 (7.4)
White	47 (90.4)		88 (90.7)	135 (90.6)
Ethnicity, n (%)				
Not Hispanic or Latino	47 (90.4)		90 (92.8)	137 (91.9)
Hispanic or Latino	5 (9.6)		7 (7.2)	12 (8.1)
Fitzpatrick Skin Type, n (%)				
I	2 (3.8)		4 (4.1)	6 (4.0)
II	18 (34.6)		25 (25.8)	43 (28.9)
III	21 (40.4)		47 (48.5)	68 (45.6)
IV	6 (11.5)		12 (12.4)	18 (12.1)
V	4 (7.7)		5 (5.2)	9 (6.0)
VI	1 (1.9)		4 (4.1)	5 (3.4)
Baseline body mass index (kg/m2)				
Mean (SD)	23.93 (4.0)		24.74 (4.9)	24.46 (4.6)
GCWS – At Rest, Blinded Evaluator, n (%)	Left	Right	Left	Right
None	0	0	0	0
Mild	0	0	0	0
Moderate	28 (53.8)	37 (71.2)	50 (51.5)	60 (61.9)
Severe	24 (46.2)	15 (28.8)	47 (48.5)	37 (38.1)
Very severe	0	0	0	0
GCWS – At Rest, Treating Investigator, n (%)				
None	0	0	0	0
Mild	0	0	0	0
Moderate	28 (53.8)	33 (63.5)	49 (50.5)	62 (63.9)
Severe	24 (46.2)	19 (36.5)	48 (49.5)	35 (36.1)
Very severe	0	0	0	0
GCWS – Dynamic, Blinded Evaluator, n (%)				
None	0	0	0	0
Mild	0	0	1 (1.0)	0
Moderate	18 (34.6)	23 (44.2)	24 (24.7)	39 (40.2)
Severe	30 (57.7)	24 (46.2)	57 (58.8)	45 (46.4)
Very severe	4 (7.7)	5 (9.6)	15 (15.5)	13 (13.4)
GCWS – Dynamic, Treating Investigator, n (%)				
None	0	0	0	0
Mild	1 (1.9)	0	0	0
Moderate	15 (28.8)	17 (32.7)	21 (21.6)	30 (30.9)
Severe	25 (48.1)	25 (48.1)	56 (57.7)	48 (49.5)
Very severe	11 (21.2)	10 (19.2)	20 (20.6)	19 (19.6)

Abbreviations: GCWS, Galderma Cheek Wrinkles Scale; ITT, intention-to-treat; N, number of subjects in ITT population; n, number of subjects in specific category; SD, standard deviation.

TABLE 2.

Injection Volume Administered Per Subject (Safety Population)					
	Injection volume per subject by treatment (left + right sides of the face)				Total injection volume (All treatments) (n=97)
	Treatment 1 (Day 1) (n=97)	Treatment 2 (Month 1) (n=95)	Treatment 3 (Month 2) (n=86)	Treatment 4 (Month 3) (n=67)	
Injection volume (mL)					
Mean (SD)	15.29 (3.04)	15.26 (3.03)	15.10 (3.57)	15.17 (3.34)	54.11 (15.30)
Median	16.00	16.00	16.00	16.00	58.50
Minimum, maximum	7.5, 18.0	8.0, 18.0	3.0, 18.0	6.1, 18.0	18.0, 72.0

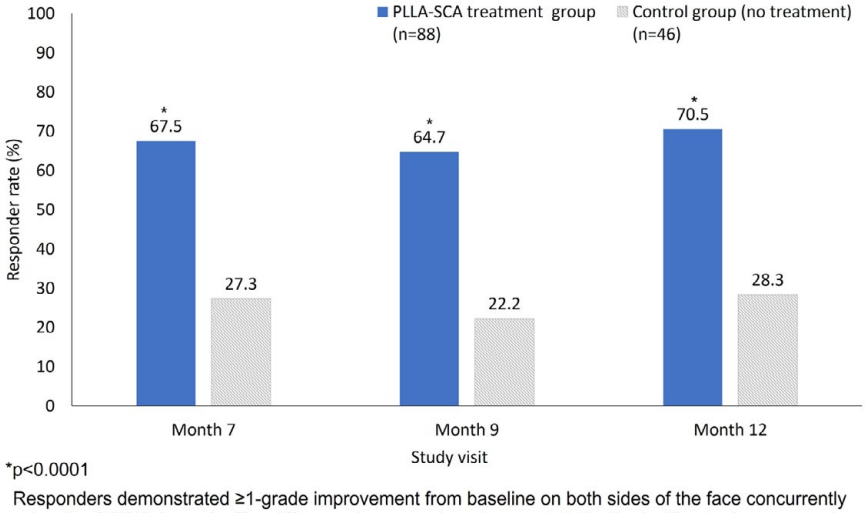
FIGURE 2. GCWS at rest responder rate, based on blinded evaluator assessment, by study visit (observed cases, ITT population).



*p=0.0043 **p<0.0001

Responders demonstrated ≥1-grade improvement from baseline on both sides of the face concurrently using the GCWS at rest. The difference in responder rate was statistically significant when comparing the PLLA-SCA and control groups at Month 7 (p=0.0043) and at Months 9 and 12 (p<0.0001). Two-sided p-value as calculated via Fisher's exact test. A p-value <0.05 was considered statistically significant

FIGURE 3. GCWS dynamic responder rate, based on blinded evaluator assessment, by study visit (observed cases, ITT population).



*p<0.0001

Responders demonstrated ≥1-grade improvement from baseline on both sides of the face concurrently using the GCWS dynamic. The difference in responder rate was statistically significant when comparing the PLLA-SCA and control groups at Months 7, 9 and 12 (p<0.0001). Two-sided p-value as calculated via Fisher's exact test. A p-value <0.05 was considered statistically significant.

TABLE 3.

Treating Investigator Assessment of Change From Baseline Concerning Skin Radiance, Tightness, Jawline Contour, and Dermal Thickness By Study Visit (ITT population)

	Control group		PLLA-SCA group	
	N	n (%)	N	n (%)
Improved skin radiance				
Month 7	44	2 (4.5)	77	75 (97.4)
Month 9	45	0	85	81 (95.3)
Month 12	46	0	88	85 (96.6)
Tighter skin appearance				
Month 7	44	2 (4.5)	77	73 (94.8)
Month 9	45	0	85	75 (88.2)
Month 12	46	0	88	84 (95.5)
Improved jawline contour				
Month 7	44	2 (4.5)	77	66 (85.7)
Month 9	45	1 (2.2)	85	73 (85.9)
Month 12	46	0	88	79 (89.9)

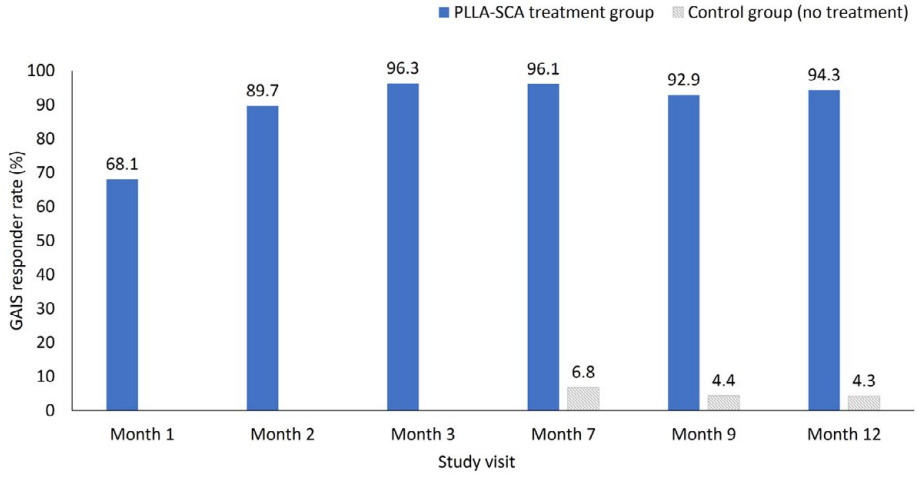
Abbreviations: ITT, intention-to-treat; N, number of subjects in ITT population; n, number of subjects in category

GCWS dynamic responder rate (live blinded evaluator assessment) was significantly higher in the PLLA-SCA group versus the control at months 7 (67.5% versus 27.3%; *P*<0.0001), 9 (64.7% versus 22.2%; *P*<0.0001), and 12 (70.5% versus 28.3%; *P*<0.0001; Figure 3).

Treating investigator-reported GAIS responder rate was 68.1% at month 1 and >92% from month 7 onwards in the PLLA-SCA group and <7% throughout the study period in the control group (Figure 4). After the PLLA-SCA injection, treating investigators agreed/strongly agreed that skin radiance was improved (>95%), skin appeared tighter (>88%) and the jawline contour was improved (>85%;Table 3).

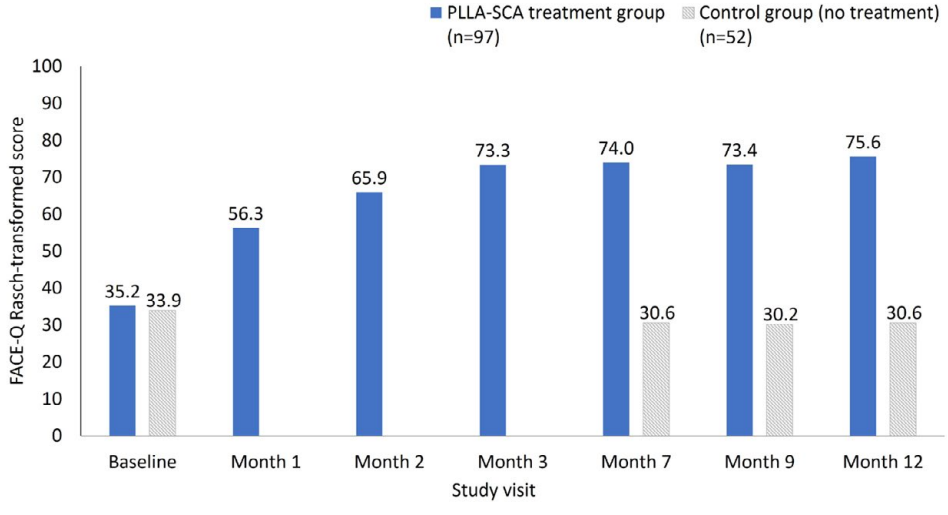
From month 7 through month 12, subject satisfaction questionnaires revealed that most PLLA-SCA recipients reported treatment results to be excellent, very good, good, or satisfactory regarding improvement in skin radiance (≥90%), sagging (≥84%) and firmness (≥91%). Most PLLA-SCA subjects saw improvements regarding looking younger (≥90%) and skin appearing more refreshed (≥91%). The majority reported improved overall satisfaction with their appearance (≥92%), natural looking results (≥86%), and a desire to have the same PLLA-SCA treatment again (≥84%). PLLA-SCA recipients indicated that they would recommend the treatment to a friend (≥88%). Other key satisfaction outcomes included feeling better about yourself (≥92%) and improved self-confidence (≥90%).

FIGURE 4. GAIS responder rate, based on treating investigator assessment, by study visit (ITT population).



GAIS responders were defined as subjects with cheek wrinkles that were very much improved, much improved or improved on both sides of the face (treating investigator assessment).
PLLA-SCA recipients were assessed at all study visits and control groups assessments were at Months 7, 9 and 12.

FIGURE 5. FACE-Q questionnaire Rasch-transformed scores regarding subject satisfaction, by study visit (ITT Population).



Rasch-transformed total scores were based on 5 FACE-Q questionnaire items assessing cheek symmetry, smoothness, attractiveness, contour and youthful fullness.

Speed of recovery, denoted by the median time to return to social engagement after PLLA-SCA treatment, ranged between 3.9 hours (after treatment 1) and 7.1 hours (after treatment 4).

Mean FACE-Q Rasch-transformed score was increased in the PLLA-SCA group from 35.2 at baseline to >73 (mean increase: 37.9–40.0) at months 7 through 12, indicating increased satisfaction, whereas mean scores decreased by 3.6–4.1 during the study period in the control group, indicating that satisfaction was not increased (Figure 5).

Subject photographs illustrating the improvements from baseline to month 12 are shown in Figure 6.

TABLE 4.

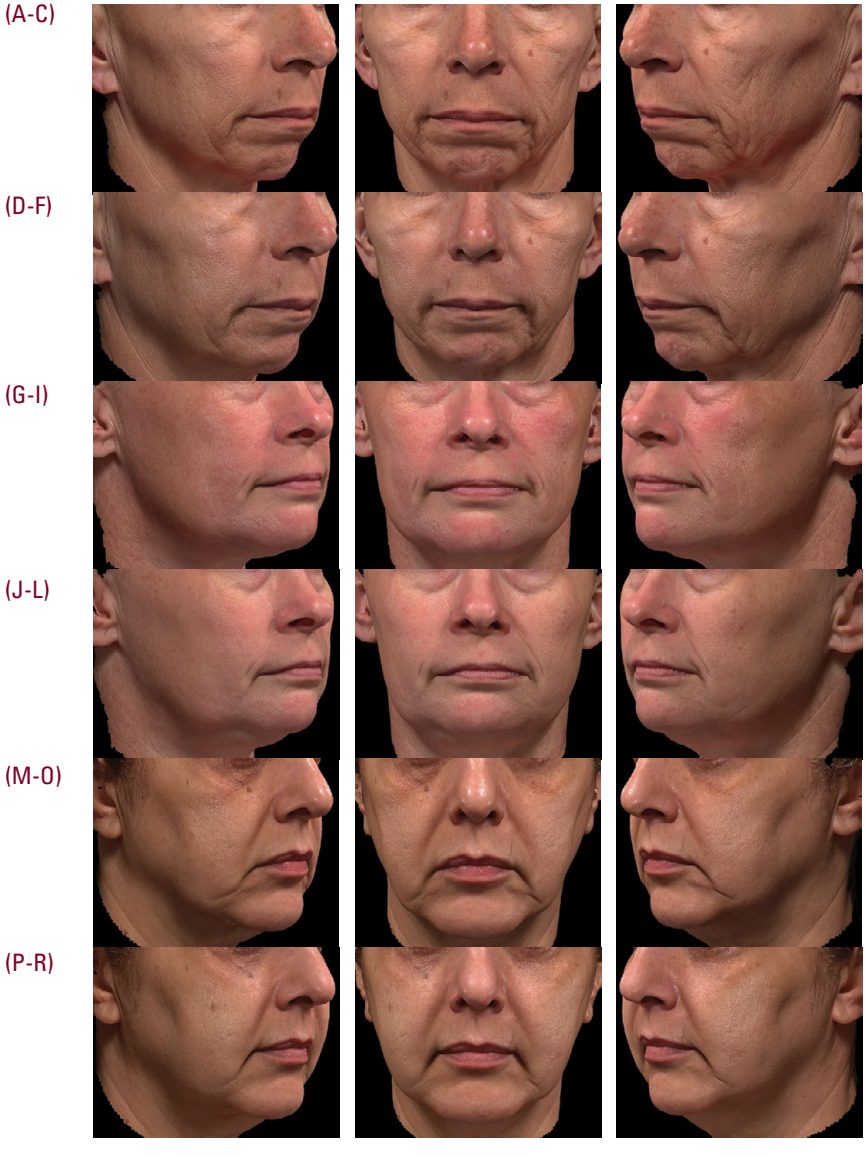
Treatment-Related Adverse Events (Safety Population)	
Preferred Term	**PLLA-SCA Group (N=97) n (%)**
Subjects with ≥1 related adverse event	20 (20.6)
Injection site bruising	11 (11.3)
Dizziness	2 (2.1)
Headache	2 (2.1)
Abnormal sensation in eye	1 (1.0)
Injection site erythema	1 (1.0)
Injection site irritation	1 (1.0)
Injection site nodule	1 (1.0)
Injection site pain	1 (1.0)
Injection site discolouration	1 (1.0)
Injection site swelling	1 (1.0)
Skin mass (small lump)[a]	1 (1.0)

[a]One subject experienced 2 events: small lump on lower left cheek, near corner of mouth; small lump below left corner of mouth. Subjects reporting more than 1 event in a category were counted only once in that category.
Abbreviations: N, number of subjects in safety population; n, number of subjects in specific category

Safety Endpoints

The most common self-reported (diary card) post-treatment symptoms were tenderness (93.5%), bruising (93.5%), swelling (87.1%), and pain (83.9%), most of which were mild/moderate in intensity (97.8%). Among the 97 subjects randomized to receive PLLA-SCA, 20 (20.6%) experienced treatment-related/injection procedure-related AEs (Table 4). Seventeen subjects (17.5%) in the PLLA-SCA group experienced mild treatment-related AEs and 3 (3.1%) had events that were moderate in severity. No serious treatment-related AEs were reported. The most common treatment-related AEs in the PLLA-SCA group were injection site bruising (11.3%), dizziness (2.1%), and headache (2.1%), all of which resolved within 1–13 days.

FIGURE 6. Subject photographs at baseline and month 12. All subjects were administered PLLA-SCA at 4 treatment sessions. The GCWS scores were assessed at rest by blinded evaluators. Subject 1) 54-year-old female with moderate (right)/severe (left) GCWS at baseline (A-C) had a 2-grade GCWS improvement to month 12 (D-F). Subject 2): 46-year-old female, with moderate (right)/severe (left) GCWS at baseline (G-I), had a 1-grade (right)/2-grade (left) GCWS improvement to month 12 (J-L). Subject 3): 59-year-old female, with moderate GCWS at baseline (M-O) had a 1-grade GCWS improvement to month 12 (P-R).



DISCUSSION

This study demonstrated that PLLA-SCA injections, given as up to 4 individual treatments (approximately 1 month apart), are effective and well tolerated in correcting the appearance of moderate and severe cheek wrinkles. Improvements in wrinkle severity were durable, with significant reductions in severity observed from month 7 (P=0.0043) that were sustained over the 12-month study period (P<0.0001) alongside enhancements in key indicators of skin quality. These outcomes are aligned with previous studies examining wrinkle correction with PLLA-SCA injections and reflect published data regarding the safety and effectiveness of the adapted protocol for immediate administration of reconstituted PLLA-SCA (approved by the US FDA) and support its use moving forward.[6,16,17]

Blinded evaluator-assessed GCWS responder rates (at rest and dynamic) were significantly greater in the PLLA-SCA group compared with controls throughout the study period. These data build upon the effectiveness outcomes previously reported concerning PLLA-SCA injections and provide an indication of the treatment outcomes that clinicians may expect to see in their clinics.[16,17] GAIS scores were high from month 1 (4 weeks after treatment 1) and endured for most PLLA-SCA recipients (>96%) through month 12. Again, this magnitude of treatment effectiveness as well as durability of treatment outcomes corresponds with the data reported for the adapted PLLA-SCA reconstitution protocol in nasolabial fold studies.[16,17] Treating investigators considered skin quality parameters, skin radiance, and firmness (tightness), to be increased following

PLLA-SCA treatment with improved jawline contour. These outcomes were corroborated by subject self-assessment data reporting improvements in skin quality (skin radiance, sagging, and firmness) following PLLA-SCA treatment (≥84%) and also mirrored published data demonstrating statistically significant increases in skin elasticity, radiance, and smoothness among individuals receiving repeated PLLA-SCA injections, compared with saline injections.[11]

Subjects recovered rapidly after each treatment, feeling confident enough to return to social engagement after approximately 4–7 hours. Treatment satisfaction was high throughout the study with PLLA-SCA recipients self-reporting natural looking results, younger looking and refreshed appearance, and improved self-confidence. Most (≥84%) said that they would choose to receive PLLA-SCA treatment again and would recommend it to others. Longer study periods may be of benefit for future investigations exploring cheek wrinkle improvement with PLLA-SCA treatments as nasolabial fold studies have demonstrated effectiveness, safety, and treatment satisfaction at 25 months, following the last treatment.[6]

PLLA-SCA injections were generally well tolerated with mainly mild treatment-related AEs, typically occurring at the injection site. The incidence of injection site nodule and papule formation was lower compared with previous trials examining PLLA-SCA and other dermatological fillers, potentially due to the increased reconstitution volume used in the current study.[6,16,17] Other investigations examining higher administration volumes showed comparable incidences of treatment-related AEs.[6,16,17] Improved safety outcomes may also be associated with enhanced administration techniques, informed by advances in the understanding of the anatomy of aging and the availability of expert recommendations and consensus.[3,8,13–15]

CONCLUSION

Injectable PLLA-SCA treatments, administered using an immediate injection protocol, were well tolerated and provided significant reductions in the severity of moderate or severe cheek wrinkles. Durable effectiveness and improvements in skin radiance, firmness (tightness), and jawline contouring were observed over the 12-month study period. PLLA-SCA recipients reported high satisfaction and natural looking appearance and most expressed a desire to have repeat PLLA-SCA treatments.

DISCLOSURES

Sabrina Fabi is an investigator and consultant for Galderma, Merz, Revance and Allergan. Tiffani Hamilton is an investigator for Galderma. Brenda LaTowsky is an investigator for Galderma. Rebecca Kazin is an investigator and trainer for Galderma. Keith Marcus is an investigator for Galderma, a speaker for Galderma, Allergan, and Evolus, a trainer for Galderma, and Merz, and an advisory board member for Galderma, Allergan, Merz, and Evolus. Flor Mayoral is an investigator for Galderma. John Joseph is an investigator and paid speaker for Galderma. Deirdre Hooper is an investigator, speaker, and trainer for Galderma, investigator consultant and trainer for Allergan, an advisory board member for Evolus, and a consultant for Revance. Sachin Shridharani is an investigator for Galderma, Merz, Revance, and Allergan. Jessica Hicks, Daniel Bråsäter, Felipe Weinberg, and Inna Prygova are employed at Galderma. **Funding:** This study was funded by Galderma R&D, LLC.

Selected data from the current study have been presented in the form of abstracts/posters at the following congresses: American Society for Dermatologic Surgery Annual Meeting, Denver CO, USA, 6-10 Oct 2022; Fall Clinical Dermatology Congress, Wynn Las Vegas, NV, USA, 20-23 Oct 2022; Maui Derm, Maui, Hawaii, USA, 23-27 Jan 2023; International Master Course on Aging Science, Paris, France 26-28 Jan 2023; AMWC North America, Miami, FL, USA, 23-25 Feb 2023, Annual Meeting of the American Academy of Dermatology, New Orleans, LA, USA, 17-21 Mar 2023; Aesthetic & Anti-aging Medicine World Congress, Monte Carlo, Monaco, 30 Mar-1 Apr 2023.

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

The Importance of Photoaging Prevention in All Skin Types: An Update on Current Advancements

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ABSTRACT

Light from across the electromagnetic spectrum, including ultraviolet, visible, and infrared light, can cause detrimental cutaneous effects including photocarcinogenesis and photoaging. Traditional and broad-spectrum sunscreens offer protection against ultraviolet radiation. However, visible and infrared light may not always be covered by traditional sunscreens. These forms of solar radiation have been shown to cause photodamage and may have particular importance in the effects induced in skin of color. This article aims to review the mechanisms of photoaging from various light forms, the implications of these damaging effects on skin of color, and innovative approaches that can advance the way patients practice photoprotection. We will expand upon the latest innovations in photoprotection that hold the potential to increase patient adherence and improve skin health across all skin types.

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INTRODUCTION

Light from across the electromagnetic (EM) spectrum can cause detrimental cutaneous effects including photocarcinogenesis and photoaging. Prevention strategies can help reduce malignancy risk and clinical manifestations of photoaging such as rhytides.[1] Increased education about skin health, photodamage, and the impact photoaging has on aesthetics drives demand for sun care products.

The optical spectrum portion of light includes ultraviolet (UV) with wavelengths of 10 to 400 nm; visible light (VL) with wavelengths of 400 to 700 nm; and infrared (IR) with wavelengths of 700 nm to 1 mm.[2] Commercial organic and inorganic sunscreens are designed to protect up to wavelengths of 380 nm.[2] However, UV only accounts for approximately 5% of the solar radiation reaching earth's surface.[3] The remaining solar radiation is approximately 50% IR and 45% VL.[3]

It is well established that exposure to ultraviolet radiation (UVR) can cause skin cancer and photoaging. While traditional sunscreens can block much of this UVR, recent studies have shown that skin damage is also induced by other forms of radiation. VL and IR may not always be covered by current, traditional sunscreens. Research in this area is notably important for skin of color (SOC), which may be particularly sensitive to the photodamaging effects of these other forms of radiation. This article will review established photoaging prevention strategies and examine innovative products beyond traditional sunscreens and their potential role in photoprotection in all skin types.

Importance of Photoaging Prevention

Cumulative solar radiation can lead to skin cancers, including melanoma, basal cell carcinoma, and squamous cell carcinoma. Treating these malignancies and other pre-cancers can cause scarring and deformities in the skin. Additionally, photoaging can manifest as unwanted aesthetic concerns including rhytides, atrophy, laxity, dyspigmentation, telangiectasias, roughness, and mottled appearance of the skin.[1] Preventative photoprotection strategies are essential to thwarting the risk of developing such conditions.

Established Photoaging Prevention: Sunscreen and UV

Most current sunscreen products protect against UVB and, to a lesser extent, UVA solar radiation.[2] Sunscreen is graded by sun protection factor (SPF). SPF measures the amount of UVR needed to induce erythema, or burn, on protected skin relative to unprotected skin.[4] SPF does not distinguish between protection against UVB and other forms of radiation.[5] The Food and Drug Administration (FDA) and the United States Preventive Services Task Force (USPSTF) recommend broad-spectrum filters with an SPF of 15 or above. The American Academy of Dermatology (AAD) recommends using an SPF of 30 and above.

SPF 15 and SPF 30 allow 6.7% and 3.3%, respectively, of UVR to be transmitted to the surface of the skin.[2]These values are based on the ideal application of sunscreen, which is 2 mg/cm^2.[6] In reality, people tend to apply much smaller amounts of product, around 0.5 to 1 mg/cm^2.[2]

UV filters in sunscreens are broadly classified as organic (chemical) or inorganic (mineral). Organic sunscreens consist of carbon-based chemicals that filter or absorb UVR, thus preventing it from reaching the skin.[7] The main types of organic filters include para-aminobenzoic acid (PABA) derivatives, benzophenones, salicylates, and cinnamates.[7] Inorganic sunscreens consist of minerals and metal oxides that absorb, reflect, or scatter UVR and create a barrier that blocks UV from the skin. The main filters are zinc oxide and titanium dioxide.[8] Inorganic sunscreens sometimes produce a chalky white appearance when applied. Thus, historically inorganic sunscreens have been limited by consumer cosmetic preferences, especially in users who have SOC.[2] This article will review the mechanisms of photoaging from various light forms, the implications of these damaging effects for SOC, and innovative approaches that can advance the way patients practice photoprotection.

PHOTOAGING ACROSS THE EM SPECTRUM

Laboratory and clinical studies demonstrate that IR and VL contribute to skin damage and photoaging. VL can induce hyperpigmentation, photoaging, and erythema in the skin.[2] The primary source of VL damaging exposure is from the sun and secondary sources from electronic devices including screens from smartphones, laptops, computers, and tablets.[2,9,10] It is widely established that UVB causes photoaging by direct DNA damage leading to thymine dimers or cyclobutane pyrimidine dimers (CPDs). It is now understood that UVA, IR, and VL similarly increase reactive oxygen species (ROS), collagen degrading enzymes, and other inflammatory cytokines that also induce DNA damage and photoaging.[11]

Traditional sunscreens mainly target UVB, however, UVA contributes to over 80% of premature aging of the facial skin.[1] Only broad-spectrum sunscreens specifically offer protection against UVA radiation in addition to the standard UVB radiation. Additionally, the ozone absorbs UVR, including UVC and UVB, but does not absorb UVA or VL, further exposing individuals to these radiations.[2]

Implication for SOC

Understanding the role of UV, VL, and IR in the photoaging process is particularly important for persons of color. SOC may be more sensitive to VL.[12] In one clinical trial evaluating the cutaneous effects of light emitting diode-red light, individuals with SOC had lower maximum tolerated dose, suggesting increased photosensitivity to VL compared to those with lighter skin.[12] Individuals with SOC experienced more adverse effects of VL at lower doses, such as dyspigmentation and blistering.[12] VL may contribute to melasma, post inflammatory hyperpigmentation, and photodermatoses, particularly in SOC.[2,13] This highlights the need for products that prevent damage from light across the spectrum, especially for individuals who have SOC.

Clinical studies of combination sunscreens with UV and VL protection showed greater improvement in the Melasma Area and Severity Index, colorimetric values, and melanin assessments compared to sunscreens that were only UV protective.[2,14] Sunscreen containing iron oxide alone or with zinc oxide and titanium dioxide improved melasma lesions after 8 weeks and prevented relapses after 6 months.[15,16] This demonstrates the value of incorporating VL and IR protection into UV protective agents. Further research is needed to develop effective treatments that have minimal negative cosmetic side effects like the white cast often associated with mineral sunscreen and of particular concern to people with SOC. Herein we will expand upon the latest innovations in photoprotection that hold the potential to increase patient adherence and improve skin health across all skin types.

Antioxidants

Antioxidants hold tremendous potential to prevent photoaging by scavenging ROS and thwarting the harm induced by solar radiation.[17] Studies evaluating the use of antioxidants with or without sunscreen demonstrated photoprotection against VL in epidermal keratinocytes in vitro.[11] It has further been shown that antioxidants provide a significant reduction in ROS, interleukin (IL)-1a, and matrix metalloproteinases (MMPs) after exposure to VL.[11] These antioxidant combination therapies consisted of feverfew (*Tanacetum parthenium*) extract, soy (*Glycine saja*) extract, and gamma tocopherol.[11] In contrast, UVA/UVB sunscreen alone did not provide any protection against VL. Furthermore, research demonstrates that adding antioxidants to sunscreen reduces ROS by 2.4-fold for SPF 15.[2]

Naturally derived antioxidants, including vitamin E, vitamin C, and licochalcone, may offer additional photoprotection while also meeting the growing consumer demand for natural, organic skincare products.[17]Vitamins C and E scavenge free radicals that are induced by damaging radiation. Licochalcone A induces Nrf2, which regulates antioxidant defenses and signaling in cellular redox cascades.[17] Innovative combination antioxidant therapies have shown promising clinical results in preventing VL-induced erythema and hyperpigmentation.[17-19]

Clinical studies have demonstrated that antioxidant combination therapy applied to human skin before VL exposure decreases ROS production compared to VL exposure without antioxidant use.[11] Thus, sunscreens with antioxidants significantly reduce VL damage.[11] One study demonstrated that sunscreen containing a combined antioxidant formulation of vitamin E,

vitamin C, diethylhexyl syringylidene malonate, licochalcone A, and glucyrrhetinic acid resulted in a significant decrease in hyperpigmentation caused by VL exposure compared to sunscreens without antioxidants.[19]

Complexes of antioxidants and additional naturally derived products have further shown promise in photoaging treatment. Studies have shown that vitamins C and E combined with green tea polyphenols produce positive outcomes in the treatment of photoaging.[20] Green tea polyphenols reduce ROS and H_2O_2 free radicals in fibroblasts.[21] Green tea polyphenol was shown to additionally stimulate keratinocyte proliferation.[22] In combination, the vitamins and polyphenols work synergistically to improve photodamage, wrinkles, hyperpigmentation, firmness, smoothness, radiance, and erythema of the skin.[15] These products also increase skin density as measured by ultrasound, signifying photoaging reversal.[20]

New oral options, such as gummies with antioxidant properties, claim to protect skin from photodamage, potentially offering innovative photoprotective therapy.[23] There is an opportunity for further research to explore the precise mechanisms of VL photoprotection and treatments targeting these pathways and to study these effects in large clinical trials.

Inorganic Tinted Sunscreens

Inorganic sunscreens formulated with zinc oxide, iron oxide, and/or titanium dioxide offer protection against VL.[3,17] However, these sunscreens typically leave a white cast that can appear particularly stark on SOC. Recent advancements in sunscreen development have led to micro- or nano-sized ingredients that help mitigate white cast. While the smaller particles are effective at absorbing UV radiation, they are limited in their ability to reflect VL.[17] To maintain optimal protection with minimal undesired cosmetic appearance, inorganic sunscreens have been formulated with a mix of particle sizes and tinted pigments. This innovation offers a novel approach to sun protection.

Tinted (colored) sunscreens contain iron oxide and titanium dioxide pigments that block both UV and VL radiation.[2] These minerals induce a barrier function that also helps to block IR radiation.[2] This physical barrier protection is beneficial for all skin types. Tinted sunscreens reduce VL radiation at the skin by 93% to 98%.[2] With the ability to reflect long UVA and VL radiation, tinted sunscreens have also demonstrated efficacy in preventing and treating dyspigmentation.[17,24] This may carry important implications for SOC, which may be particularly sensitive to dyspigmentation and can benefit from products with a minimal white cast.

Tinted sunscreens appear yellow, red, or black. The adoption of these products can be increased by incorporating them into cosmetic products. These compounds, when combined with makeup, can serve to both cover blemishes and protect the skin from further dyspigmentation induced by sunlight.[2] For all sunscreens, it is important to educate patients about the proper application as it is often underapplied.[2]

Light Emitting Diodes

Light emitting diode (LED) devices have become popular, commercially available products in the skincare market. Studies show that blue and red light treatments can reduce the effects of photoaging.[7,25] Red light therapy is an FDA-approved treatment that has demonstrated restorative effects such as decreased fibrosis and wrinkles and increased skin tightness.[26-28] Blue light-induced photolyases in combination with topical antioxidants may have synergistic effects in the prevention of photodamage.[2] Additionally, it has been discovered that VL induces a biphasic response where lower doses are photoprotective in contrast to the photoaging effects induced by higher doses.[2,29-31] In addition to its established role as a photoaging treatment, there may be a place for low-level light therapy in the prevention of photoaging that can be explored through further research. Special consideration should be given to the use of light treatment in patients with SOC as they are more prone to hyperpigmentation from this type of therapy.[32,33]

Minerals

Minerals represent additional naturally occurring substances that may have a role in photoaging prevention. Mineral imbalances are associated with intrinsic and extrinsic aging.[34] Studies show that mineral-containing products, like volcanic water, contribute to photoprotection and the treatment of photoaging.[35] Emerging products incorporating these ingredients may offer patients unique and targeted benefits.

Balneotherapy, or bathing in mineral baths, is a practice that has been used throughout history for therapeutic effects.[36] It has been used to treat a variety of dermatologic conditions including inflammation, psoriasis, atopic dermatitis, and wound healing.[36,37] Bathing regimens high in minerals, such as magnesium, calcium, potassium, and bromine, can filter UV rays and offer photoprotection.[37] Naturally derived hydrated magnesium aluminum silicate fibrous clays from traditional balneotherapies have been reimagined as topical agents that offer photoprotection in addition to a wide range of dermatologic benefits.[37] Future studies are needed to explore the role of these products as the demand for natural products and skin damage prevention continues to rise.

Nicotinamide

Nicotinamide (NAM), or vitamin B3, demonstrates preventative and restorative effects on photoaging.[38] Filaggrin and loricrin are markers of late differentiation and are normally decreased by UVR, resulting in increased cellular senescence.[38] Clinical studies demonstrate that NAM application prior to UV exposure

prevents the decrease of these markers.[38] The result is decreased cell senescence and improved photodamage prevention.[38] The use of NAM prior to UVR also showed reduced effects of DNA damage, decline in energy metabolism, and inflammatory markers induced by UVR in keratinocytes. Together these findings support NAM's role as a photoprotective agent.

Photolyases

Photolyases are enzymes that repair CPDs upon exposure to blue light (400-500 nm wavelength).[2] Advances in photoprotection innovation have led to the inclusion of these enzymes in sunscreens. Clinical studies demonstrate that adding photolyases to sunscreens and antioxidants reduces markers of photoaging.[39] Sunscreens with photolyases applied following photodynamic therapy (PDT) result in fewer new actinic keratoses compared to the use of sunscreen alone.[39] Photolyases are also associated with decreased MMP-1 expression.[40,41]

A systematic review considering the use of photolyases in sunscreen and its impact on photoaging found promise for these products to enhance DNA repair mechanisms.[41] Clinical trials have shown that when photolyases are added to sunscreens, there was a significant decrease in DNA damage and apoptosis resulting from UV radiation.[42,43]

Photolyases may also demonstrate a synergistic effect with antioxidants offering further UV photoprotection.[39] Tinted sunscreen with zinc oxide, Q10 antioxidant, and photolyase shows both protective and regenerative effects of photoaging clinically.[44] Photolyases are limited in their ability to protect against damage simultaneously across the spectrum as they require blue light for activation, thus VL blockers inhibit its protective effects.[2] However, there may be a role for photolyases in photoaging prevention, which further studies can help elucidate.

Retinoids

Commercial retinoids include natural and synthetic derivatives of vitamin A. Natural derivatives include tretinoin, isotretinoin, and alitretinoin. Synthetic derivatives include tazarotene and adapalene. Topical retinoids treat photoaging by increasing collagen synthesis, reorganizing collagen fibers, and increasing extracellular matrix anchoring fibrils.[45] Retinoids bind nuclear receptors and activate the expression of genes involved in keratinization.[14] These findings demonstrate the ability of retinoids to address visible signs of photoaging. There may be additional roles for retinoids earlier in the process related to the prevention of photoaging.[14]

Sun Avoidance

Innovations in photoprotection are essential to providing adequate options for persons of all skin types. Beyond these advancements, traditional means of minimizing solar exposure remain important for preventing damage from radiation across the spectrum. Avoiding the sun, seeking shade, and wearing protective clothing/hats are effective strategies to minimize solar radiation.[2] UV protection factor measures protection against UVR offered by clothing and can be used to assess the effectiveness of an apparel's photodamage prevention.[2] These strategies should be encouraged among patients to prevent the damage induced by solar radiation.

LOOKING AHEAD

Future Regulations and Guidelines

Further regulations and guidelines are needed to address photoaging beyond UVB induced damage. The FDA currently has no guidelines regarding VL or IR. The US has 16 approved UV filters while Europe and other countries have 29 UV filters approved.[2] These additional filters offer superior UVA protection demonstrating the need for these types of approved products in the US.[2]

In other ways, the US can benefit from more stringent guidelines against certain molecules in photoprotective products. For example, oxybenzone is a major contributor to sunscreen allergy and has concerning environmental side effects. Oxybenzone is allowed in the US but is not commonly used outside of this country.[2] Benzene is another harmful molecule that has been classified as a carcinogen by the Environmental Work Group. Systemic absorption of benzene can lead to decreased red blood cell levels, increased risk of leukemia, and harm to other systems including the central nervous system and reproductive organs. Benzene was recently found in certain sunscreens, demonstrating the importance of monitoring sun-protection safety.[46]

In 2019, the FDA proposed updates to sunscreen requirements, including maximum SPF labeling, broad-spectrum requirements, and updates to required ingredients.[47] However, the 2020 Coronavirus Aid, Relief, and Economic Security Act (CARES Act) in response to the pandemic altered the FDA regulation process and these provisions never became mandated.[47]

Through a modified Delphi method, a panel of dermatologists and photobiologists recommended a standard rating for UVA and VL protection as many sunscreens lack coverage for these radiation types. The panel also agreed that physicians should recommend photoprotection that is personalized and tailored to a patient's specific skin type, preferences, and exposure.[13]

CONCLUSION

Traditional sunscreens offer protection against UVB radiation. Broad-spectrum products offer additional protection against UVA radiation. However, it is now understood that VL and IR make up a significant portion of solar radiation that reaches

earth's surface and contributes to photoaging of the skin. This is of particular importance to people with SOC who may be sensitive to the damage induced by radiation in these wavelengths. Continued research can help elucidate products that will offer protection against these forms of radiation. Current research has already demonstrated the promising effects of antioxidants, inorganic tinted sunscreens, LEDs, minerals, NAM, photolyases, and retinoids. Future studies and regulations are needed to further our understanding and meet the growing demands for products that prevent photoaging from across the spectrum in all skin types.

DISCLOSURES

The authors report no relevant conflicts of interest.

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ORIGINAL ARTICLE

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A Two-Staged Injection Technique and Dose-Ranging Study Using High Dose AbobotulinumtoxinA for Treating Platysmal Bands

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ABSTRACT

Background: AbobotulinumtoxinA (AboBoNT-A) is useful for the treatment of platysmal banding. This study evaluated the efficacy and safety of a standardized 2-staged injection technique using high doses of AboBoNT-A for treating platysmal banding.

Methods: This was a randomized, double-blinded, dose-ranging prospective study. Subjects included adults with moderate-to-severe platysmal bands (grade 3 or 4 on the validated 5-point photographic scale), who received either 120 U (Cohort 1) or 180 U (Cohort 2) of aboBoNT-A, followed by an optional 90 U touch-up. The relatively higher on-label concentration of AboBoNT-A was used (1.5 mL/300 unit) to reduce the volume injected and the risk of spread to adjacent muscles. Subjects were followed for 5 months, with safety and efficacy endpoints evaluated by the Investigator Live Assessment (ILA) and Subject Live Assessment (SLA).

Results: Twenty women were included in the analysis. Cohort 1 and Cohort 2 had 100% and 90% responder rates (achieved grade 1 or 2) during maximal contraction at month 1 with ILA. Cohort 2 had more subjects with ≥2 grade improvement at maximal contraction using both ILA and SLA. Cohort 2 also had longer time to loss of grade 1 or 2 at maximal contraction compared with Cohort 1. No major adverse reactions occurred, but 3 subjects experienced transient positional neck weakness.

Conclusion: We demonstrate a standardized 2-staged injection technique using aboBoNT-A for effectively treating moderate-to-severe platysmal banding. We used relatively higher doses while maintaining a good safety profile by using the more concentrated on-label volume of reconstitution for aboBoNT-A and by including a touch-up.

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INTRODUCTION

Botulinum toxin type-A (BoNT-A) injections are the most popular cosmetic procedure in the world.[1] By blocking acetylcholine neurotransmitter presynaptic release, this neurotoxin can reduce muscle contraction and lead to functional benefits in spasticity and cosmetic effects in minimizing wrinkles. There are several different preparations of BoNT-A available for aesthetic use worldwide, each with different manufacturing processes and properties.

AbobotulinumtoxinA (aboBoNT-A; Dysport®, Ipsen Biopharm Ltd., Wrexham, UK; Azzalure®, Galderma Ltd., Lausanne, Switzerland) is currently approved in the United States of America for treating moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adult patients younger than 65 years of age for aesthetic purposes.[2] The current US Food and Drug Administration (FDA)-recommended dosing is 50 U injected intramuscularly in 5 equal aliquots of 10 U each using a reconstitution involving 2.5 mL saline added to a 300 U vial. A reconstitution involving 1.5 mL saline added to a 300 U vial is also used on-label.

AboBoNT-A is commonly used to treat wrinkles and lines in other areas of the face, neck, and chest for cosmetic purposes in an off-label manner.[3] One area of increasing interest is treating the platysma as an effective non-surgical option for reducing platysmal bands and for improving jawline and neck contour. Treatment of the platysma with onabotulinumtoxinA (onaBoNT-A; Botox®, Allergan, Irvine, CA, USA) has been well studied, and the mean dose for injection typically ranges between 10 U and 50 U.[4]

Several total face rejuvenation studies have included treating the platysma with aboBoNT-A, using doses ranging from 40 U to 180 U and concentrations of 10 U to 12 U per 0.1mL.[4-8] A study by Jabbour et al evaluated the "Nefertiti Lift," which focused on injecting aboBoNT-A into platysmal bands and along a line below the inferior mandibular border.[9] Each injection involved 5 U of aboBoNT-A, which had been reconstituted to a concentration of 20 U per 0.1 mL. The maximum dose allowed was 125 U and the mean dose used was 114.3 U. A touch-up treatment was performed using the same protocol for any

platysmal bands that were present during the day 15 follow-up visit (mean dose 31.7 U).

In a subsequent crossover study, these same subjects were treated using a microbotox technique extending from the anterior neck to the lower face.[10] This study involved injecting a mean dose of 154 U aboBoNT-A distributed among approximately 150 injection points into the superficial dermis using a concentration of 7 U per 0.1 mL. Both of these studies cautioned against injecting over 125 U in the neck area in one session due to increased risk of adverse events (AEs). Out of the 55 subjects in both studies, the most common side effect reported was ecchymosis. Only one patient (in the Nefertiti Lift study) reported mild transient dysphagia and neck muscle weakness that lasted 2 weeks.[9]

It has been previously recommended to limit aboBoNT-A dosing in the neck to 50 U to 100 U in one session to minimize the risk of toxin diffusing to the deeper neck muscles and causing dysphagia, dysphonia, dysarthria, or breathing difficulties.[11-12] In a case report by Obagi et al, only 60 U of aboBoNT-A (reconstitution of 2.5 mL in 300 U) was injected into the platysmal area across 6 sites, but the patient developed dysphagia with liquids that lasted for more than a month with incomplete resolution.[13]

No trial yet has studied higher doses of AboBoNT-A at a higher concentration for the treatment of platysmal banding, and this study was designed to address this insufficiency when combined with a standardized 2-staged protocol. To reduce the diffusion of AboBoNT-A and the potential for associated side effects, we use a higher concentration of AboBoNT-A so that lower injection volumes are needed. The goal of this research study is to design a standardized and reproducible approach to effectively yet safely treat the platysma with aboBoNT-A.

MATERIALS AND METHODS

Study Design and Population

This was a randomized, double-blinded, dose-ranging prospective US study that was conducted in accordance with the International Conference on Harmonization, Good Clinical Practice guidelines, and the Declaration of Helsinki. The study received approval from an institutional review board and was registered and posted on ClinicalTrials.gov (NCT 04886167) on May 13th, 2021. All subjects gave informed and written consent before any study procedure was performed.

Subjects were assessed using the Photographic Platysma Bands Scale. This validated, 5-point photonumeric assessment scale defined dynamic and at-rest platysmal bands. For at-rest platysmal bands, the scale ranges from 0 (no visible platysmal bands) to 5 (platysmal bands extremely visible). For dynamic platysmal bands, the scale ranges from 0 (barely visible and minimally raised platysmal bands) to 5 (all platysma bands are severely raised and extend from the clavicle to the mandible). The scale was used by both investigators and subjects for the evaluation of platysmal bands.

The target population for inclusion was adults from 18 to 65 years of age, with moderate to severe platysmal bands (grade 3 or 4 on the Photographic Platysma Bands Scale) at maximal contraction.

Subjects who met all inclusion/exclusion criteria were randomized into one of 2 sequential treatment cohorts receiving aboBoNT-A. The first cohort received a total dose of 210 U (Cohort 1) and the second cohort received 270 U (Cohort 2). During the baseline treatment visit, Cohort 1 received 120 U, and Cohort 2 received 180 U. A touch up was allowed at the day 14 follow-up visit for both cohorts, during which time an additional 90 U of aboBoNT-A was used. Both cohorts had a sample size of 10 subjects and followed the same schedule of follow-up appointments and touch-up injections. All subjects had a baseline visit with treatment, a day 2 telephone visit, and in-office follow-up visits on day 7, day 14, and months 1 to 5. After a safety evaluation was conducted by the Data and Safety Monitoring Committee (DSMC) after the month 1 follow up visit for Cohort 1, the study continued with Cohort 2. Of note, there were originally plans for assessing a third sequential cohort at a higher dosage of 360 U (240 U baseline, 120 U touchup), but this was not performed because the 270 U dose was found to be highly efficacious.

Treatment

For both cohorts, 1.5 mL of sterile preservative free 0.9% sodium chloride (injection) was used to reconstitute each 300 U vial of aboBoNT-A, resulting in a concentration of 20 U per 0.1 mL. A lower volume of diluent (1.5 mL) than that indicated on the product label (2.5 mL) was used in an attempt to mitigate potential AEs that could be created due to local diffusion of the toxin from the muscle into the surrounding tissues. Each cohort received intramuscular injections of aboBoNT-A into the anterior and posterior platysma bands at the baseline visit (day 0) regardless of their presentation, and was offered an optional touch-up treatment 14 days later to provide optimal aesthetic correction. Both cohorts received 24 injections (6 injections per each of 4 platysmal bands) during the baseline visit. A touch up was performed if there was significant persistence of the original bands or if new bands had formed. The touch up for all cohorts included an additional 90 U (18 injection points) using the same dosing as the initial treatment.

Injection Technique

The treating physician injected the abobotulinumtoxinA using a 30 G needle subdermally along the vertical muscular cord such that a soft wheal was formed. Injection points were placed at

least 2 cm apart, starting superiorly 2 cm below the body of the mandible. To reduce potential AEs, care was taken to avoid deep intramuscular injections. Using a sharp needle with an oblique angle of insertion may help reduce the risk of extending beneath the platysma.

Safety Endpoints

The primary safety objective of this study was to evaluate the safety of treating platysmal bands using a standardized 2-staged approach for the injection of the plastyma with larger doses of abobotulinumtoxinA than had previously been reported. A safety assessment collecting all AEs and focused physical examination findings on Cohort 1 was conducted at the screening visit and at all subsequent follow up visits. Cohort 1 data were reviewed by the Data and Safety Monitoring Committee to help determine eligibility before continuing onto Cohort 2. The safety population included all subjects who received at least 1 injection of the study treatment. The safety endpoints were the incidence and severity of treatment emergent AEs (TEAEs) and unexpected serious adverse reactions.

Efficacy Endpoints

Efficacy evaluations were conducted using the Photographic Platysma Bands Scale at all subsequent follow up visits after baseline visit on day 7, day 14, and months 1 to 5. Investigators used the scale for direct, live assessment of subjects termed the Investigator Live Assessment (ILA). Subjects evaluated their platysmal bands using the scale termed the Subject Live Assessment (SLA).

The primary objective of this study was to evaluate the efficacy of a 2-staged standardized injection protocol using escalating dosing cohorts in the treatment of moderate to severe platysmal bands. The primary endpoint was the percentage of responders, defined as subjects achieving a grade of 1 or 2 in platysmal bands severity, on ILA at maximum contraction at 1 month within each cohort. Secondary endpoints for this objective included: the percentage of responders at maximum contraction at all time points using the ILA and SLA scales; the percentage of subjects with at least a 2-grade improvement in platysmal bands severity using the ILA and SLA scales; and time to loss of a grade 1 or 2 at maximum contraction using the ILA and SLA scales.

Statistical Analysis

Continuous variables were summarized using mean and standard deviation (SD), and differences between treatment arms were assessed using Wilcoxon Rank-sum tests. The categorical variables were summarized using counts and percentages, and differences between groups were evaluated using Fisher's exact test. The correlation between ILA-assessed scores at rest and dynamic states were calculated using the Spearman correlation. The Kaplan-Meier method was constructed to plot time to event outcomes and to estimate the median time to loss of grade 1 or 2 level and median time to return to baseline for each treatment arm; the differences between the 2 treatment arms across time were evaluated using the log-rank test. Univariable Cox proportional hazard models were developed to estimate associations between treatment (Cohort 1 vs Cohort 2) and calculate the time to loss of grades 1 and 2. The results were summarized using hazard ratios (HRs) and their 95% confidence intervals (CIs). All tests are 2-sided and *P*-value $P<0.05$ is considered a statistically significant result. All the analyses were performed using R version 4.2.1.

RESULTS

Study Population

Twenty female subjects were enrolled in the United States. The mean age in Cohort 1 and Cohort 2 was 56.0 ± 3.7 and 56.3 ±

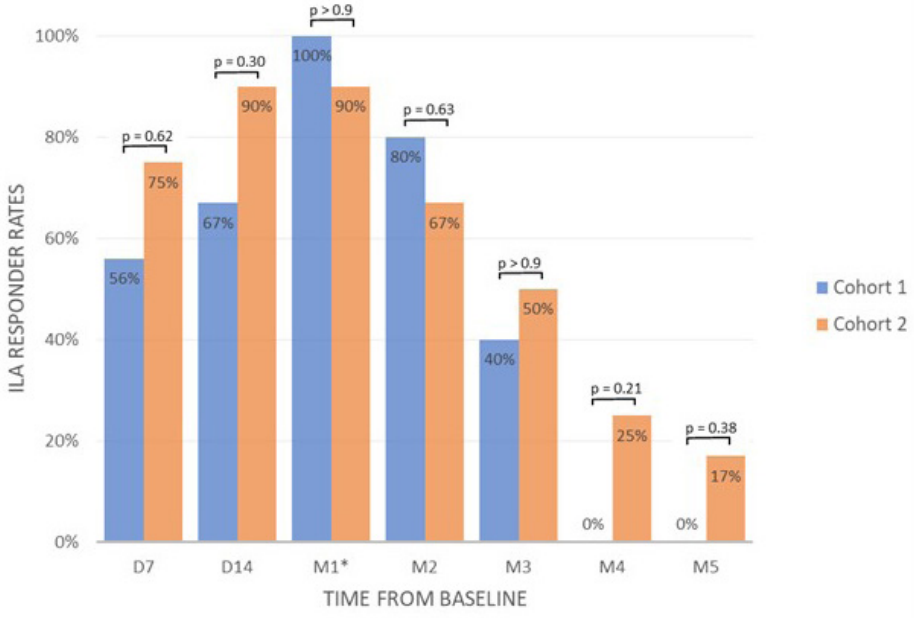
TABLE 1.

Demographic and Baseline Data for Enrolled Cohorts

		Cohort 1, n = 10	Cohort 2, n = 10	*P*-value
Age, mean (SD) years		56.0 (3.7)	56.3 (4.7)	0.9
Race and ethnicity, n (%)		--	--	0.5
White – not Hispanic		6 (60%)	5 (50%)	--
Asian – not Hispanic		1 (10%)	0 (0%)	--
Hispanic		2 (20%)	1 (10%)	--
Did not respond		1 (10%)	4 (40%)	--
Baseline platysmal grade at rest	ILA, mean (SD)	3.2 (0.42)	2.7 (0.43)	0.032*
	SLA, mean (SD)	3.1 (0.57)	3.0 (0.47)	0.69
Baseline plastymal grade at maximum contraction	ILA, mean (SD)	3.6 (0.52)	3.6 (0.52)	>0.9
	SLA, mean (SD)	3.8 (0.42)	3.7 (0.48)	>0.9

*denotes a statistically significant result
ILA, Investigator Live Assessment; SD, standard deviation; SLA, Subject Live Assessment.

FIGURE 1. Responder rate at maximum contraction using the Investigator Live Assessment platysmal grade across all post-treatment visits.



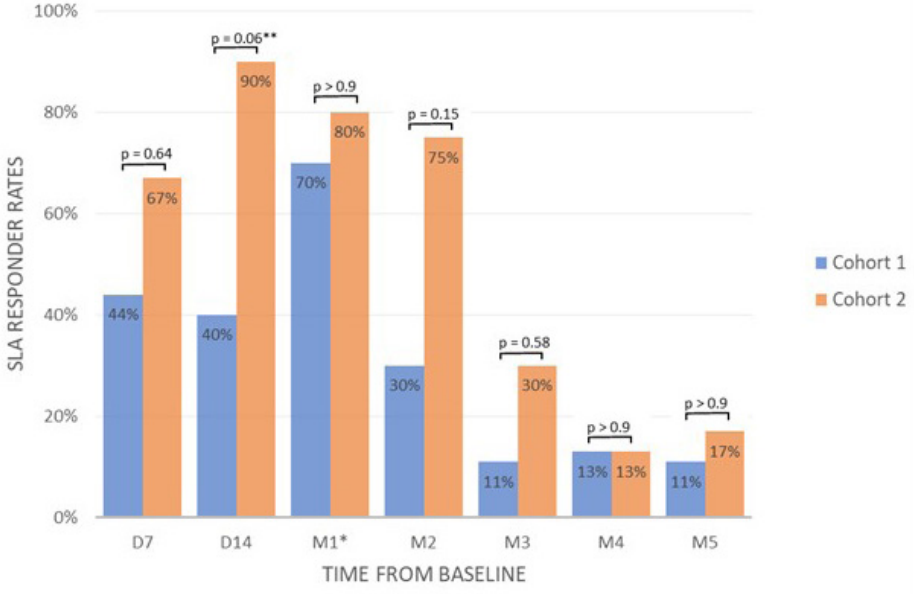
*denotes primary endpoint of the study.

4.7, respectively. Baseline ILA and SLA scores at maximum contraction (dynamic) did not differ significantly between the 2 cohorts. While baseline SLA scores at rest did not differ significantly between groups, baseline ILA scores at rest did differ significantly (P=0.032). Table 1 summarizes the baseline characteristics of both groups.

Responder Rate

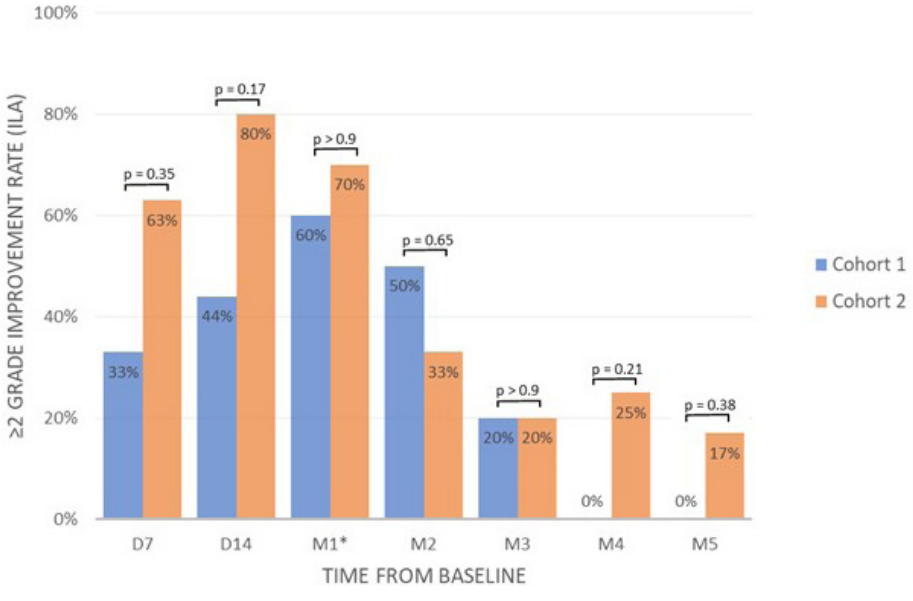
At 1-month post-treatment, there was no significant difference between the 2 cohorts. Cohort 1 had a 100% responder rate (mean ILA of 1.8 ± 0.42) and Cohort 2 had a 90% responder rate (mean ILA of 1.7 ± 0.67) at maximum contraction.

FIGURE 2. Responder rate at maximum contraction using the Subject Live Assessment platysmal grade across all post-treatment visits.



*denotes primary endpoint of the study.
**denotes a statistically significant difference in responder rate using SLA.

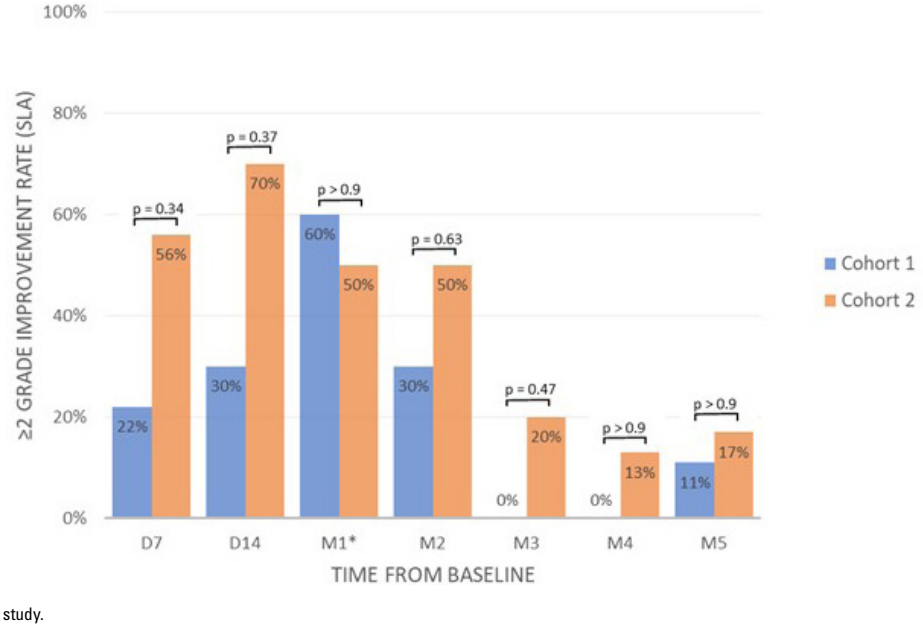
FIGURE 3. Percent of subjects with ≥2 grade improvement on maximum contraction using the Investigator Live Assessment platysmal grade across all post-treatment visits.



*denotes primary endpoint of the study.

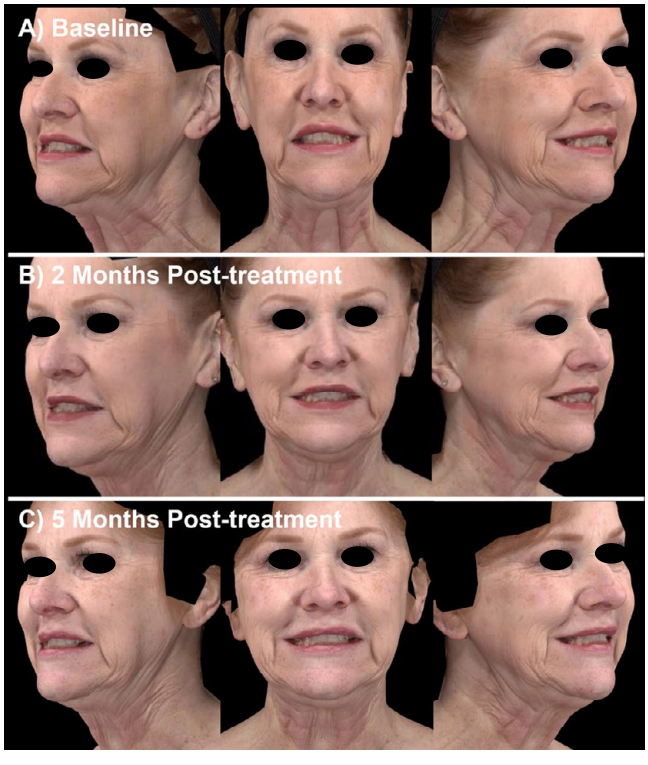
Figure 1 demonstrates the percentage of responders using ILA scale at maximum contraction at all post-treatment time points for both cohorts. The greatest number of responders occurred at month 1 for Cohort 1 and between day 14 and month 1 for Cohort 2. The responder rate dropped to 0% at month 4 for Cohort 1 but was still at 17% at month 5 for Cohort 2. However, there was no statistical significance between the 2 groups at each of the post-treatment time points. Figure 2 demonstrates the percentage of responders using the SLA scale at maximum contraction at all post-treatment time points for both cohorts. At day 14 (prior to touch up), Cohort 2 had a 90% responder rate and Cohort 1 had a 40% responder rate, which neared a significant difference

FIGURE 4. Percent of subjects with ≥2 grade improvement on maximum contraction using the Subject Live Assessment platysmal grade across all post-treatment visits.



*denotes primary endpoint of the study.

FIGURE 5. Clinical photographs of a subject in Cohort 2 at maximum contraction in the right 3-quarter view, front view, and left 3-quarter view at (A) baseline, (B) month 2 post-treatment, and (C) month 5 post-treatment demonstrating a sustained, significant decrease in platysmal banding.



(*P*=0.057). With both the ILA and SLA, there was a much greater responder rate at day 7 and day 14 for Cohort 2; however, this was not statistically significant.

Level of Improvement in Grade

At Maximal Contraction

Figure 3 and Figure 4 show the percentage of subjects with a 2-or-more grade improvement from baseline at maximum contraction across all time points using the ILA scale and SLA scale, respectively. A visual example of such an improvement in a subject from Cohort 2 is demonstrated in Figure 5. Overall, Cohort 2 had a greater percentage of subjects with a 2 or more grade improvement from baseline across the majority of time points with both the ILA and SLA scales. Over 50% of patients in Cohort 2 showed this improvement under both scales from day 7 to month 2.

At Rest

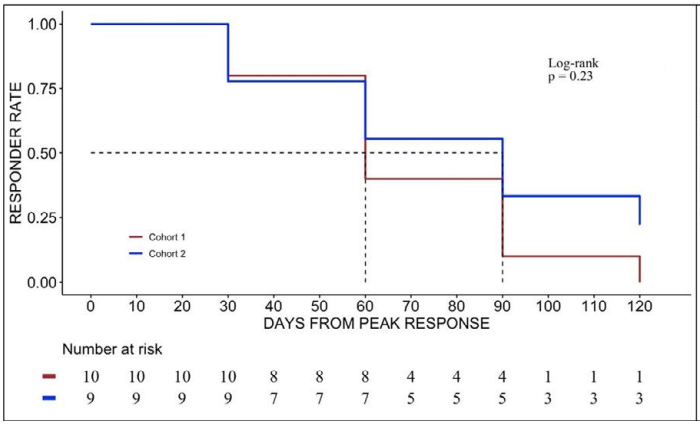
When evaluating the platysmal bands at rest at month 1 using the SSA, Cohort 1 and Cohort 2 had 80% and 60% of subjects with a 1 point or greater improvement, respectively. When evaluating the platysmal bands at rest at month 1 using the ILA, Cohort 1 and Cohort 2 had 60% and 20% of subjects with a 1 point or greater improvement, respectively.

Duration of Response

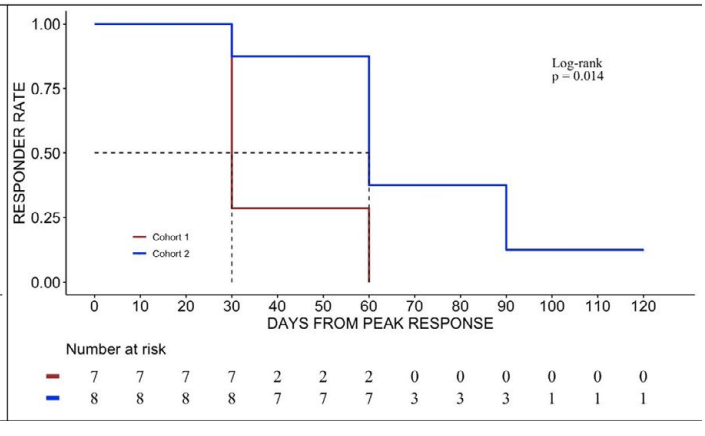
The time to loss of a grade of 1 or 2 was greater in Cohort 2 when compared with Cohort 1 at maximal contraction for both ILA and SLA (Figure 6). When measured from the peak time and using the ILA score at maximum contraction, Cohort 2 had an average of 80 days before loss of grade 1 or 2 compared with 63.3 days

FIGURE 6. Kaplan-Meier curve showing average days to loss of responder status (grade 1 or grade 2) at maximum contraction using the (A) Investigator Live Assessment and (B) Subject Live Assessment platysmal grades.

(A)



(B)



for Cohort 120; however, this was not a statistically different result, (Hazard Ratio: 0.54, 95% CI: 0.20 - 1.45, *P*=0.22). Using the SLA at maximum contraction, Cohort 1 had an average of 38.6 days before loss of grade 1 or 2 compared with 71.2 days for Cohort 2; Cohort 2 was significantly less likely to lose the grade of 1 or 2 compared with Cohort 1 (hazard ratio: 0.24, 95% CI: 0.07 - 0.80, *P*=0.02).

Safety Endpoints

No major or emergent serious adverse reactions occurred. Three subjects (one in Cohort 1 and two in Cohort 2) experienced transient neck weakness only during head flexion while in the supine position that resolved with no intervention in less than 1 month. This weakness did not occur with neck movement in any other directions or in any other positions. No subjects developed dysphagia or facial weakness, or experienced visual or neurologic symptoms.

DISCUSSION

This publication reports the first study evaluating the efficacy and safety of a standardized injection protocol using higher doses of aboBoNT-A for the treatment of moderate to severe platysmal bands.

Previous studies have shown that standard dosing up to 120 U of aboBoNT-A can decrease platysmal banding at maximal contraction.[9] Our data support this finding, such that 90% or greater of our subjects were responders. In addition, our study reveals a trend that higher dosing using 270 U of aboBoNT-A into the platysma can potentially achieve a stronger and longer-lasting effect while still maintaining minimal AEs. On both ILA and SLA, a greater number of subjects were responders for Cohort 2 (270 U group) compared with Cohort 1 (210 U group) at day 7 and day 14. However, this was not statistically significant, potentially due to a small sample size. Additionally, there was a longer lasting peak effect with Cohort 2, with the majority of subjects in Cohort 2 maintaining their grade 1 or 2 scores longer during maximal contraction on both ILA (a 17 day difference) and SLA (a 43 day difference) compared with their counterparts. The difference in SLA scores at maximum contraction was significantly different, showing that Cohort 2 was less likely to lose their grade of 1 or 2 once achieved.

Kane et al[14] in 1999 and Jabbour et al[9] in 2017 found statistically diminished platysmal banding at rest using botulinum toxin injections (Jabbour used an average of 114.3 U aboBoNT-A). Our results agreed with previous studies, as there was improvement at rest across both ILA and SLA in both cohorts. A greater number of subjects at rest had improving platysmal scores at month 1 using SLA when compared with ILA, which suggests that patients themselves may see more improvement at rest compared with the injectors treating them. Although Cohort 2 had less improvement in platysmal scores at rest at month 1 compared with Cohort 1 for both ILA and SLA, this could be explained by the statistically significant difference in their baseline characteristics.

Neuromodulator injection into the neck area has been found to be very safe with a minimal side effect profile. Still, because the neck muscles and viscera are directly underneath the platysma, any toxin interference with the deeper areas of the neck could lead to serious symptoms affecting neck mobility and swallowing. Case reports have discussed side effects of dysphagia and neck weakness with doses as low as 60 U. Because of this, a theoretical concern with higher dosing of aboBoNT-A in the neck area is that this would lead to a wider diffusion pattern with more AEs. In our study, we found that higher dosing of up to 270 U (180 U plus an additional 90 U touch up) of aboBoNT-A was very well tolerated with minimal side effects. There were only 3 cases of transient neck weakness that self-resolved quickly. This occurred in subjects treated earlier in the study, and it may be that greater experience with improving injection technique helped reduce the incidence of neck weakness later in the study. Importantly, this weakness only occurred in the supine position and there were no cases of neck weakness in the upright position. It is the senior author's opinion that these subjects may have normally recruited the platysma to perform head flexion in the supine position. When this minor contribution to flexion of the neck was reduced, this weakness was noticed but did not compromise their ability to perform this function. All these subjects had a complete resolution of symptoms in less than 1 month. There were no issues with swallowing, speech, facial weakness, or vision. There were no emergent or serious adverse reactions that occurred.

We believe there are a few methods and techniques that helped provide the safest treatment environment for our subjects. Reconstitution standards for aboBoNT-A advocate for using 0.6 mL to 3 mL of saline to create a strength of 10 U to 50 U per 0.1 mL. For the head and neck area, we have found that prescribers advocate for more dilute doses closer to 10 U to 12 U per 0.1 mL.[15] In our study, we used a more concentrated dose of 20 U per 0.1 mL for all injections; this relatively higher concentration helps decrease the risk of diffusion of the neurotoxin to the deeper critical neck areas by controlling the field of effect. Combined with the proper injection technique described in this study, the risk to this 2-staged standardized approach was found to be very safe and effective.

All 20 subjects in the study opted for the touch-up dose of 90 U at day 14. We felt that this touch up was very important, if not mandatory, because all patients had at least some degree of persistent banding or the formation of new bands. The new bands were not foreseeable at the initial session. The touch-up injection was used efficiently in this manner to treat the new bands or any resilient bands that had been initially injected.

Study limitations included the participation of only female subjects with no male subjects. In addition, our sample size was relatively small. Although we detected trends between the 2 cohort groups, we may not be showing statistical significance due to the limited sample size.

CONCLUSION

This study demonstrates a standardized method with higher doses of aboBoNT-A to achieve an excellent reduction in platysmal bands for a long duration. These effects were seen in both subject self-evaluations and the investigator evaluations using a validated photographic platysma scale. Higher dosing of aboBoNT-A is very safe with minimal side effects. Using proper injection technique and higher concentration reconstitutions are important for maintaining safety with higher dosages. A touch-up injection is critical to reduce persistent bands and new bands that appeared after the initial injection. Overall, injectors should feel comfortable using this standardized injection protocol to reduce platysmal bands.

DISCLOSURES

John H. Joseph is a consultant and speaker for Galderma, and conducts clinical trials for them. Allen Foulad, Victor Hsue, Tahmineh Romero, and Patrick Davis have no conflicts of interest to declare.

Statement of Contribution: John H. Joseph: conceptualization, methodology, software, investigation, writing – review & editing, supervision. Allen Foulad: conceptualization, methodology, software, investigation, writing – review & editing, supervision. Victor Hsue: formal analysis, writing – original draft, visualization. Tahmineh Romero: formal analysis, writing – review & editing, visualization. Patrick Davis: formal analysis, writing – review & editing, visualization.

Ethical Statements: The study received approval from an institutional review board (US IRB, Inc.) and was registered and posted on ClinicalTrials.gov (NCT 04886167) on May 13th, 2021. Informed written consent was obtained from all subjects. Consent for photographic documentation was obtained for all included photographs.

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ORIGINAL ARTICLE

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Validating the Reliability and Clinical Relevance of a Nasolabial Fold Photonumeric Scale

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ABSTRACT

Background: The use of tissue fillers to treat age-related deepening of the nasolabial fold (NLF) has increased and become the standard clinical approach, creating a need for evidence-based, objective evaluation for pre- and post-procedure assessment of the NLF.
Methods: A 5-point rating scale was developed to assess the NLF, specifically the presence of depression and shadowing. Live validation of the scale was performed with a total of 73 participants representing the full range of NLF severities. Physicians board-certified in a core aesthetic specialty (3 trained raters) performed the scale validation over 2 rounds, 2 weeks apart. Training was carried out, and test-retest reliability was quantitated through the determination of intra- and inter-rater reliability by percentage of agreement, weighted kappa statistic with 95% confidence interval (CI), and intraclass correlation coefficient with 95% CI. To evaluate the clinical relevance of a 1-grade difference, rater assessments of 90 photo pairs were compared with previous designations of *clinically different* or *not clinically different*.
Results: The NLF scale achieved near-perfect intra- and inter-rater reliability when utilized by trained raters to assess a diverse group of live participants. Furthermore, clinically relevant differences between grades were established, and a 1-point difference was detectable by trained evaluators using the NLF scale.
Conclusion: The clinically relevant and highly reliable validated NLF scale provides a standardized grading system with a user-friendly design for objectively assessing NLF in clinical practice and as a research tool for clinical approval studies of new aesthetic products and technologies.

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INTRODUCTION

Formation of wrinkles and folds due to age-related loss of fat, muscle, and bone mass, and changes in skin characteristics can have a negative impact on an individual's appearance, and in some cases affect psychological and social well-being.[1–3] The nasolabial folds extend symmetrically from the ala nasi, cheek, and upper lip junction to below the lateral corner of the mouth, following a straight, convex, or concave path. In the midface, loss of deep fat volume and muscle contour, in combination with age-related bone absorption in the malar area as well as flattening of the central mid-cheek, exaggerates the depth of the nasolabial folds (NLFs).[3–5] Deepening of the NLF is a common complaint in the aesthetics practice, and has been rated among the more bothersome facial defects for which more mature patients are likely to seek aesthetic treatment.[5–7] Over the past 2 decades, soft tissue augmentation using fillers has become the standard clinical approach for treating NLF, and innovations in filler and device technology continue to give rise to new tools to address this concern.[3,5,6] With the evolution in the treatment of NLF comes the need for evidence-based, objective evaluation. To meet this demand, several scales have been developed to assess wrinkle depth and NLF severity, improving over time with the integration of photonumeric scales using standardized methods of photography.[8–14] For adoption in clinical practice, rating scales should be clinically relevant and have high test-retest reliability, which can be quantitated through intra- and inter-rater reliability using Cohen's weighted kappa coefficient and intraclass correlation coefficient (ICC). These coefficients are numbers between 0 and 1, where 1 corresponds to exact reproducibility and 0 represents an agreement that occurs by chance.[15,16] The purpose of this study is to validate a newly developed, high-quality, 5-point photonumeric scale that includes photometric modelling of scale images (Table 1), for the assessment of NLF. Assessments establish test-retest reliability and clinical relevance and the scale itself may serve as a tool for the objective measure of the effect of aesthetic procedures, both in clinical practice and in the development of novel devices, which require regulatory approval.

TABLE 1.

Descriptors for Nasolabial Fold Scale		
Grade	**Term**	**Descriptor**
0	None / Minimal	None to minimal nasolabial fold Minimal shadowing or slight depression may be present
1	Mild	Mild apparent nasolabial fold Some shadowing may be present
2	Moderate	Moderate nasolabial fold Early visible shadowing present
3	Severe	Severe nasolabial fold Severe shadowing may extend to oral commissure No skin redundancy
4	Very Severe	Very severe nasolabial fold Extreme shadowing Evidence of skin redundancy

MATERIALS AND METHODS

The NLF scale is a 5-point rating scale to assess nasolabial fold, the presence of depression, and shadowing. The NLF scale was developed by a team consisting of a board-certified plastic surgeon and a board-certified dermatologist (*developers*) and separately validated using a different group of board-certified clinicians (*raters*), consisting of 2 dermatologists and 1 plastic surgeon. Raters were trained to use the NLF scale prior to validation.

Scale Development

A total of 126 adult men and women representing various races, ethnicities, and Fitzpatrick skin types consented to and participated in the image collection without cosmetics, jewelry, or facial hair (ie, beard/mustache). Scale developers independently reviewed the right and left oblique and frontal images, one participant at a time, and scored the NLF severity by designating them as none/minimal, mild, moderate, severe, and very severe in the absence of descriptors.

The final NLF scale consists of 3 components: 1) textual descriptors, 2) morphed images using facial artificial intelligence (AI) averaging, and 3) actual patient images representing different sexes and Fitzpatrick skin types (Figure 1).

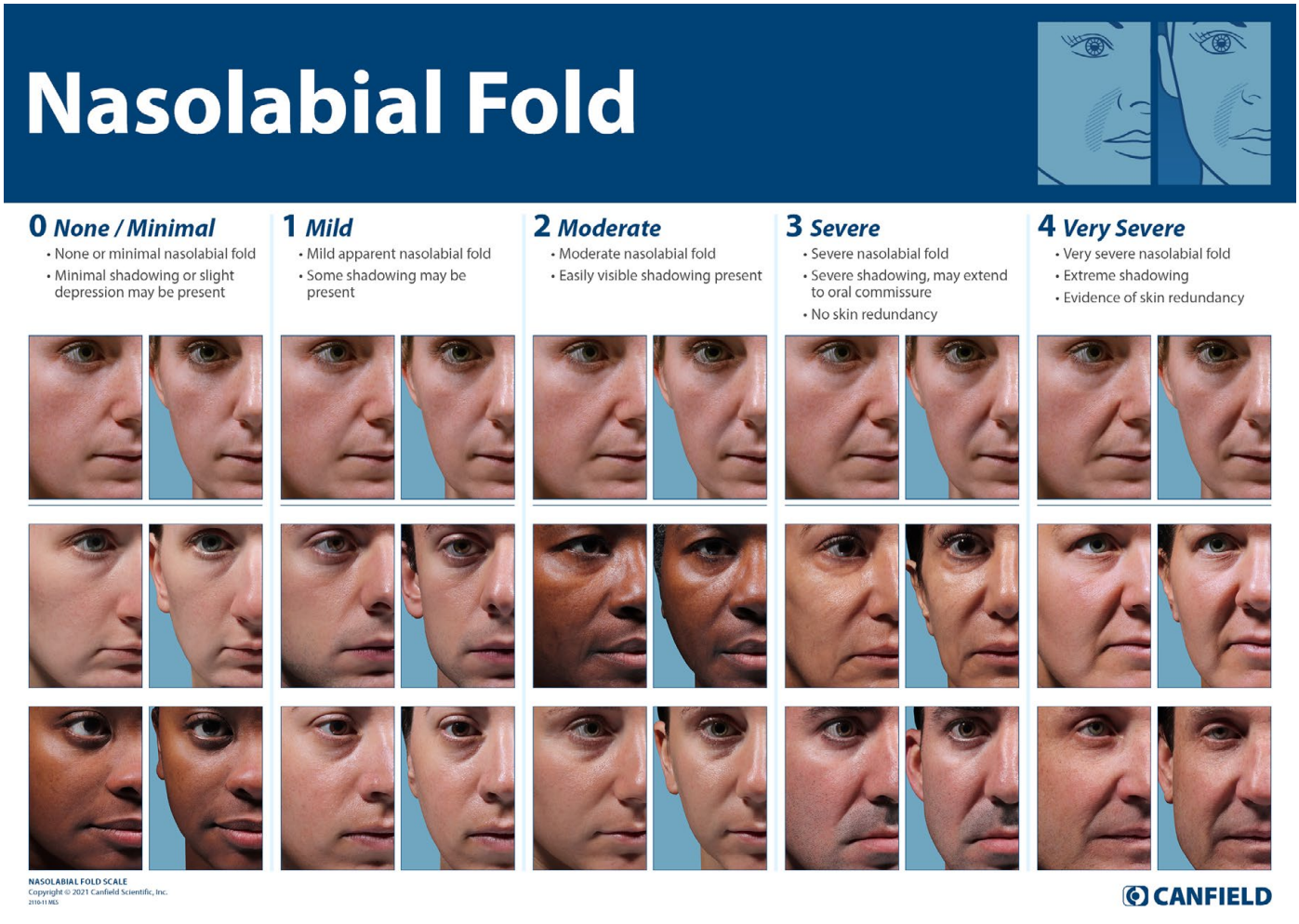
For participant images, scale developers selected 2 representative images of each grade, thereby compiling a diverse set of actual patient images for the scale. Textual descriptors for each grade were written by the scale developers.

Morphed images were developed through AI facial averaging technology.[17] The goal of this component was to statistically model grade-based differences across the 5 points of the scale to permit model-based "morphing" of the relevant appearance on a base image of 1 individual, selected from among the participants by the scale developers. First, all participant images were bucketed according to their respective grades. Next, the images were annotated with anatomical landmarks and aligned to the common base image of grade 0 using thin-plate spline warping. Statistical color and topography models were then built using the NLF grade of each image as the independent variable.[17–19] These models allowed for accurate image-based prediction of facial appearance for every pixel in the image given a desired target grade on the 5-point NLF scale. Note that the models were not just limited to the NLF region but predict the full face including any other facial feature correlated with the NLF grade. By taking the difference between the predictions for grade 0 and each of the grades 1 through 4, these relative differences were applied to the base image of grade 0 to produce simulated, morphed images for grades 1, 2, 3, and 4. These morphed images maintain the identity of the base participant but include the appearance of the higher NLF grades based entirely on the real graded dataset and the statistical models they generated. The result is a realistic, data-based NLF scale on a single base individual.

Scale Validation

Trained raters performed live validation of the NLF scale over 2 live validation rounds, conducted 2 weeks apart. A total of 73 participants were selected to represent the full range of different NLF depression levels and were instructed to arrive at the sessions clean-shaven, without cosmetics or jewelry, and maintain their usual routine (eg, facial care, sleep, and hydration routines), abstaining from tanning sessions or extensive sun exposure between sessions. Participants presented themselves at a rating station with standardized lighting and participant and rater positioning, where a scale validator used a printed copy of the photonumeric scale to assign an integer rating of 0 through 4 to each participant, separately assessing their right and left nasolabial folds, and recording the score through electronic data capture. Each scale validator proceeded from 1 rating station to the next until all participants had been evaluated by the 3 scale validators. The same participants were randomized into a different sequence before validators performed the second round of assessments at the rating stations.

FIGURE 1. The Nasolabial Fold Scale illustrates each severity grade with 3 sets of vivid images framed as cropped right and left oblique and corresponding detailed descriptions. The top-line photographs were morphed from a base image to represent each grade using facial averaging, whereas the rest of the scale was populated with unmorphed, actual patient images selected for each grade of NLF severity.



Evaluation of Clinical Relevance

The clinical relevance of the NLF scale was assessed by evaluating whether trained raters could detect differences between grades. A set of photographs was selected to represent all grades on the scale. The ratings were determined based on the most frequently assigned score during scale development. From these designated photographs, 90 photo pairs were selected that covered all scale grades, each pair being either *not clinically different* (34 pairs) or *clinically different* (36 pairs with 1-point difference, 10 pairs with 2-point difference, 6 pairs with 3-point difference, and 4 pairs with a 4-point difference).

The 3 scale validators performed a side-by-side evaluation of the 90 photo pairs and determined if there was a clinically significant difference in the NLF depression of the 2 participants. Following the side-by-side evaluation, each validator used the scale to assign individual scores to the same randomly sequenced photos.

Data Analysis and Statistical Methods

Statistical analyses were performed using SAS Version 9.4. Test-retest reliability was determined by measuring intra- and inter-rater reliability. Intra-rater reliability between round 1 and round 2 was evaluated for each rater, the median of all raters, and all raters combined by the percentage of agreement (exact and ≥ 1-grade difference), weighted kappa statistic with 95% confidence interval (CI), and ICC with 95% CI. Inter-rater reliability was determined for each pair of raters and each rater against the median rater score using the same 3 calculations. Weighted kappa statistics and ICC were determined using established methods, and reliability was determined based on the following criteria: > 0 and ≤ 0.2 indicates slight agreement, > 0.2 and ≤ 0.4 indicates fair agreement, > 0.4 and ≤ 0.6 indicates moderate agreement, > 0.6 and ≤ 0.8 indicates substantial agreement, and > 0.8 and ≤ 1.0 indicates almost perfect agreement.[15,20,21]

To evaluate clinical relevance, absolute differences in rating scores were determined between each paired photo. The absolute differences were calculated from the rater-assigned grades and separately summarized using descriptive statistics for the photo pairs initially deemed as clinically different and not clinically different. The mean, standard deviation, and 95% CI of the mean were reported. The proportion of agreement between the rater's assessments vs the original assessments of the photo pairs was also determined as a supportive analysis. The agreement was defined as at least 2 out of 3 raters giving the same assessment (ie, *clinically different* vs *not clinically different*). Frequency counts and percentages of agreement were summarized for *clinically different* photo pairs, *not clinically different* photo pairs, and all photo pairs.

RESULTS

Live-Participant Scale Validation

Patients participating in the live validation included men and women of a wide range of ages, self-reported races and ethnicities, and clinical-rater-assessed Fitzpatrick skin types (Table 2). Fitzpatrick skin types III and IV were most prevalent in the evaluated population. A broad range of heights and weights were represented, with the mean values representing a healthy body mass index.

Intra-rater reliability for assessing the NLF between round 1 and round 2 was evaluated for each rater through the percentage of exact matches, reproducibility within 1 grade, weighted kappa coefficients (95% CI), and ICC (95% CI) (Table 3). Among the 73 participants, ratings for the NLFs were comparable, reaching an almost perfect intra-rater agreement for combined weighted kappa coefficients (right NLF: 0.893 [0.862, 0.923] and left NLF: 0.876 [0.844, 0.909] and ICC (right: 0.943 [0.894, 0.967] and left: 0.934 [0.841, 0.967]). The percentage of exact grading agreement for each rater between the 2 rounds ranged from 56% to 75%, whereas the percentage of assigned grades within 1 grade was 95% to 100%.

Near-perfect inter-rater agreement was achieved among the 3 validators when the NLF scale was used to separately rate the 73 participants (total of 146 NLFs, left and right). Comparable weighted kappa coefficients were calculated across all rater pairs, ranging from 0.849 to 0.874 for round 1 and 0.849 to 0.871 for round 2. Similarly, the ICC ranged from 0.853 to 0.876 for round 1 and 0.851 to 0.873 for round 2.

Clinical Relevance Determination

The absolute differences were calculated for scores assigned by 3 independent raters between pairs initially deemed *clinically different* vs *not clinically different* for photo pair selections (Table 4). The mean absolute difference in scores between 'clinically different' photo pairs was over 1 grade (Median [95% CI]; 1.49 [1.32, 1.65]), whereas the mean difference for 'not clinically different' photo pairs was close to half a grade (Median [95% CI]; 0.55 [0.43, 0.67]). The 95% CIs for *clinically different* vs *not clinically different* pairs do not overlap. These results suggest that the NLF scale facilitated accurate assessments when used by trained raters, and a 1-point difference on the NLF scale is clinically relevant.

The proportion of agreement of photo pair assessments revealed that raters often assigned the same assessments for the photo pairs compared with original assessments (ie, clinically different vs not clinically different). At least 2 out of 3 raters assigned the same assessments for 71.1% (64 of 90) of the total photo pairs, 85.7% (48 of 56) of the 'clinically different' pairs, and 47.1% (16 of 34) of the 'not clinically' different pairs. The high proportion

TABLE 2.

Demographics for Live-Participant Scale Validation	
Age (years)	
Mean (SD)	44.6 (15.1)
Median	45
Minimum, Maximum	18, 71
Height (cm)	
Mean (SD)	166.7 (8.7)
Median	165.1
Minimum, Maximum	150, 188
Weight (kg)	
Mean (SD)	69.1 (14.0)
Median	67.6
Minimum, Maximum	46, 104
Sex, n (%)	
Male	20 (27.4)
Female	53 (72.6)
Ethnicity, n (%)	
Hispanic or Latino	5 (6.9)
Not Hispanic or Latino	68 (93.2)
Race, n (%)	
American Indian or Alaska Native	1 (1.4)
Asian Indian	2 (2.7)
Black or African American	5 (6.9)
Chinese	1 (1.4)
Filipino	2 (2.7)
Korean	1 (1.4)
Vietnamese	1 (1.4)
Native Hawaiian or Other Pacific Islander	1 (1.4)
White	59 (80.8)
Fitzpatrick Skin Type, n (%)	
Type I	0 (0)
Type II	11 (15.1)
Type III	34 (46.6)
Type IV	23 (31.5)
Type V	1 (1.4)
Type VI	4 (5.5)

TABLE 3.

Intra-rater Reliability				
	Percentage Exact Agreement	Percentage Within 1 Grade	Weighted Kappa Coefficient (95% CI)	ICC (95% CI)
Right face				
Rater 1	58.9	97.3	0.855 (0.791, 0.918)	0.857 (0.540, 0.938)
Rater 2	75.3	98.6	0.902 (0.844, 0.959)	0.903 (0.850, 0.938)
Rater 3	71.2	100.0	0.921 (0.887, 0.956)	0.922 (0.879, 0.951)
Combined	--	--	0.893 (0.862, 0.923)	0.943 (0.894, 0.967)
Left face				
Rater 1	56.2	95.9	0.847 (0.782, 0.912)	0.849 (0.557, 0.932)
Rater 2	60.3	97.3	0.842 (0.773, 0.910)	0.843 (0.758, 0.900)
Rater 3	74.0	100.0	0.932 (0.901, 0.964)	0.933 (0.895, 0.957)
Combined	--	--	0.876 (0.844, 0.909)	0.934 (0.841, 0.967)

TABLE 4.

Evaluation of Clinical Relevance				
Original Assessments Used for Photo Pair Selections	Absolute Difference in Scores Between Paired Photos			
	n	Mean (SD)	Minimum, Maximum	95% CI of Mean
Clinically Different Pairs	168	1.49 (1.05)	0, 4	1.33, 1.65
Not Clinically Different Pairs	102	0.55 (0.62)	0, 2	0.43, 0.67

of agreement indicates that clinically relevant differences on the NLF Scale can be detected by raters when evaluating random side-by-side photographs with ≥1 grade difference.

DISCUSSION

The ongoing innovation and increasing popularity of nonsurgical aesthetic treatments have created an unmet need in clinical practice for evidence-based grading systems to objectively assess outcomes of aesthetic procedures, both as a part of validation and clinical study of new technologies for regulatory approval as well as for clinical use to evaluate provider performance, clinical outcomes, and aid patient education.[11,22] Without objective measurement tools, perceptions of success are subjective: the influence of physician and patient feelings affects reproducibility across a population of patients, and consistency in measurements necessitates an objective, validated measure.[8] Use of grading tools to objectively define starting points and treatment goals improves patient understanding and provides patients with realistic expectations of nonsurgical aesthetic procedures.[23]

The high reliability and clinical relevance of the presented NLF scale support its implementation in clinical practice and clinical research for pre-procedure assessment and evaluation of outcomes. Live validation of the NLF scale using trained board-certified plastic surgeons and dermatologists demonstrated a high test-retest reliability with almost perfect values for weighted kappa coefficients and ICC as measures of intra- and inter-rater reliability. The high reliability of the scale was observed for the right and left NLF when evaluated separately by raters. High intra-rater reliability indicates that the NLF scale can be used for dependable evaluation by the same rater multiple times, whereas high inter-rater reliability refers to consistency among various raters, thus ensuring utility for any trained rater. In addition to its precision suggested by the high reported reliability, the NLF scale facilitates accurate assessments when used by trained raters, demonstrating clinically relevant differences between grades through rater discernment of a 1-point difference.

Although several scales have been developed over the last 2 decades to assess wrinkle depth and NLF severity,[8–14] the NLF scale represented herein is unique in that it was developed and validated for the sole purpose of providing a scale with proven reliability for broad industry access. Additionally, it is unique in its vertical presentation of the facial images that display the same grade, facilitating assessment by allowing horizontal scanning across the scale to visualize increasing NLF severity. The presented NLF scale combines text descriptions and photographs, which has proved to increase NLF scale reliability, possibly by lessening the subjective interpretation inherent to observing photographs alone.[10] Of note, the scale includes images generated from photography of individual participants as well as a set of images morphed using AI-based methods, which creates an entirely objective differentiation between grades.

Live validation of the presented NLF scale was performed with a population representative of both sexes and a wide range of ages, self-reported races and ethnicities, and clinical-rater-assessed Fitzpatrick skin types. The NLF scale's reported high test-retest reliability may be attributed to its inclusion of multiple Fitzpatrick skin types of both sexes at each severity grade, giving

raters a broad representation of photographed participants to reference when making assessments. Illustrating each severity grade with 3 sets of vivid images framed as cropped right oblique and frontal, alongside corresponding detailed descriptions, effectively represents the NLF characteristics typical of each grade. Top-line photographs were morphed from a base image to satisfy descriptors representing each grade using data-based facial averaging, whereas the rest of the scale was populated with actual patient images selected for each grade of NLF severity. With this approach, the evaluator can isolate the NLF changes that occur with each progressing grade in the morphed image while simultaneously referencing multiple real-world images of patients representing each grade. Furthermore, the use of 'live' participants likely improves the accuracy of scale reliability by better reflecting patient assessment in clinical practice. In fact, data suggests that participant evaluation through 2-dimensional photography may decrease the visual analysis of defect depth, which is detectable in a 3-dimensional examination provided by live assessment.[12]

CONCLUSION

The proven clinical relevance, high reliability, user-friendly layout, and suitability for real-life populations of the NLF scale presented herein will likely benefit the facial rejuvenation field and prove useful for pre- and post-procedure assessment of NLF by providing a standardized grading system for objective evaluation. Furthermore, clear and vibrant photographs showcasing 2 views of the NLF in both morphed and actual patient images in combination with corresponding text descriptions enhance the scale's utility in clinical practice.

DISCLOSURES

Dr Lorenc is a Consultant for Allergan (Irvine, CA), Galderma (Fort Worth, TX), Merz (Raleigh, NC), Suneva Medical, Inc (San Diego, CA), and Thermi (Irving, TX), and received honorarium from Canfield Scientific (Parsippany, NJ) for scale development. Dr Smith is a consultant to Teoxane and has received honoraria from Canfield Scientific for scale development. Dr Bass is an Investigator for Cynosure, Merz and a Consultant for Allergan, Canfield, Cynosure, Endo, and Galderma. Dr Bank has received compensation and honorarium as a consultant and principal investigator for clinical trials/projects/scale validation with Allergan, Galderma, Merz, Croma Pharma, Endo Pharmaceuticals, Evolus, and Canfield Scientific. Dr Weiss received research funding from Canfield Scientific Inc. Parsippany, NJ. Doug Canfield is the Founder and President of Canfield Scientific. Brian D'Alessandro is an employee of Canfield Scientific. Lisa Cramer is an employee of Canfield Scientific. **Statement of Funding:** This research was provided by Canfield.

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ORIGINAL ARTICLE

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Quantifiable Changes in the Submental Area and Mandible Border After Dual-Modality Treatment With ATX-101 and VYC-20L for Overall Improvement in Jawline Contour

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ABSTRACT

Background: A phase 4, prospective, open-label, multicenter study showed that treatment with deoxycholic acid injections (ATX-10) followed by a hyaluronic acid filler (VYC-20L) is safe and effective for reducing submental fullness and improving jawline definition.

Objective: To quantify changes in the jawline and submental area using 3-dimensional (3D) photogrammetry and conduct an immunohistochemical analysis of submental tissue.

Methods: Participants received 1 to 6 ATX-101 treatments (8 weeks apart) followed by VYC-20L (optional touch-up after 14 days). Changes from baseline in jawline and submental volumes, submental major and minor strain events, submental skin displacement, and submental angles were quantified using photogrammetry. Submental skin biopsies (N=13) were excised for histologic analysis. Treatment-emergent adverse events (TEAEs) were monitored.

Results: Fifty-three participants were treated. From baseline to the final study visit, the mean volume increased for the jawline and decreased for the submental area. There was a larger percentage change from baseline in the minor versus major strain event, indicating greater skin surface compression than expansion within the submental area. Mean change from baseline in submental skin position indicated superior and posterior movement from a lateral perspective, while the mean submental angle decreased between baseline and exit. Collagen I and III expression significantly increased from baseline ($P<0.05$). All participants reported at least 1 TEAE; the majority were mild or moderate in severity.

Conclusions: Dual-modality treatment with ATX-101 and VYC-20L reduces submental fat and improves jawline definition with quantifiable changes in jawline volume, submental volume, strain, skin displacement, and angle, as well as collagen expression.

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INTRODUCTION

An excess of submental fat (SMF) can lead to an unappealing submental profile and poor jawline definition, thus affecting the overall appearance of the face.[1] As a result, individuals may seek aesthetic treatments for improving submental convexity and jawline contour.[1,2] ATX-101 (deoxycholic acid injections; Kybella® [US]/Belkyra™ [Canada, Australia, Europe, and South Korea]; Allergan Aesthetics, an AbbVie Company, Irvine, CA, USA) is a cytolytic agent that causes lysis of adipocytes and is indicated for improvement in the appearance of moderate to severe convexity or fullness associated with SMF.[3-7] In the ATX-101 phase 3 trials, skin laxity did not worsen and even showed improvements (ie, less wrinkling/lines, adherence to underlying structures) in the majority of participants despite reductions in SMF.[5,6,8] These results suggest that local inflammatory responses following ATX-101 treatment may induce neocollagenesis.[8,9]

A phase 4, prospective, open-label, multicenter, interventional study showed that sequential treatment using ATX-101 followed by VYC-20L (Juvéderm® Voluma™ with Lidocaine, Allergan Aesthetics), a hyaluronic acid (HA) filler used to restore facial volume in the midface[10,11] and structurally support the chin,[12,13] reduced SMF, and improved jawline definition.[14] Most of the participants (92.9%) achieved ≥1-point improvement from

baseline in the investigator-assessed Allergan Loss of Jawline Definition Scale (ALJDS) at the end of the study. Skin laxity, as measured by the Submental Skin Laxity Grade (SMSLG) scale, was also improved following a reduction in SMF. The current analyses report exploratory endpoints from the phase 4 study. The objectives were to evaluate changes from baseline in the jawline and submental area associated with sequential treatment of ATX-101 followed by VYC-20L using 3-dimensional (3D) photogrammetry and histologic changes from baseline after treatment with ATX-101 in biopsies taken from the submental area.

MATERIALS AND METHODS

Participants

The methods have been described elsewhere.[14] Briefly, adults aged 18 to 65 years were enrolled in the study based on the following inclusion criteria: grade ≥2 on the ALJDS on both sides of the face, grade 2 or 3 on the Clinician-Rated Submental Fat Rating Scale, stable body weight for ≥26 weeks prior to the study, and agreement to abstain from treatment/behavior that would affect the assessments of the submental area during the study. Key exclusion criteria included grade 4 on the SMSLG scale, grade 4 on the Allergan Jowl Fat Rating Scale, anatomic features that would affect assessments of the submental area (eg, body mass index [BMI] >35 kg/m^2, lower face asymmetry), or a history of filler or toxin injections, ablative procedures, skin resurfacing, plastic surgery, tissue grafting, implants in the face/neck area, systemic retinoid therapy, anticoagulation therapy, oral corticosteroid therapy, or oral surgery/dental procedures within 2 weeks prior to and after VYC-20L treatment.

Study Design

A phase 4, prospective, open-label, multicenter, interventional study was conducted at 3 centers in Australia from February 2018 to December 2019 (NCT03425253). The study was approved by a central ethics committee (Bellberry Human Research Ethics Committee, Eastwood, South Australia, Australia) and was conducted in compliance with the International Conference on Harmonisation guidelines on Good Clinical Practice. Participants provided written informed consent.

Participants received 1 ATX-101 treatment and up to 5 optional ATX-101 treatments, administered at least 8 weeks apart (Figure 1) until desired results were achieved. A single treatment consisted of up to 50 injections spaced 1 cm apart and 0.2 mL each. A maximum total volume of 10 mL was permitted per treatment visit (maximum of 60 mL over 6 visits).

Eight weeks after the last ATX-101 treatment, participants received a VYC-20L treatment along the mandibular border with an optional touch-up treatment 14 days later. A maximum total volume of 6 mL was allowed for initial and touch-up treatments combined (3 mL for each side of the face).

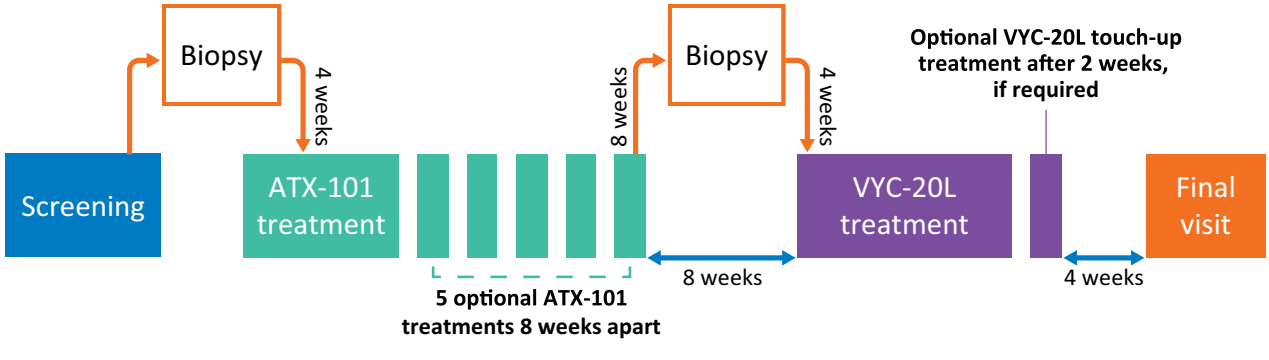
Assessments

Photographic Imaging Analyses

Images were taken using the VECTRA M3 Camera System (Canfield Scientific, Fairfield, NJ) to recreate a 3D depiction of participants' faces. Mean changes from baseline in volume and dimension of the jawline and submental area were measured by Canfield markerless tracking. Briefly, 3D photographs were used to build a mesh of corresponding points (markers) on the image. Comparisons of marker placement enabled measurable skin changes related to displacement and shape formation.

3D image analysis was used to measure left and right jawline volume, submental volume, submental strain, and submental skin displacement in the X, Y, and Z directions. Major and minor strain events were measured along a positive or negative axis, respectively. A change in the major strain (more positive values) indicates skin surface stretch or expansion, while a change in the minor strain (more negative values) indicates skin surface compression.[15] Two-dimensional (2D) images were used to measure the submental angle. Left and right jawline volumes were assessed at baseline, prior to VYC-20L treatment, and at the final study visit. Submental volume, strain, skin displacement, and angle were assessed at baseline, after each ATX-101 treatment, prior to VYC-20L treatment, and at the final study visit.

FIGURE 1. Study design.



Biopsy Analyses

A subset of participants consented to have optional biopsy samples (≈2 mm) excised from the submental area (≈1.5 cm from the submental crease and ≈1.5 cm left and right of the midline). Samples were collected at least 4 weeks prior to the first ATX-101 treatment (baseline) and at 8 weeks after the last ATX-101 treatment (≥4 weeks prior to VYC-20L treatment, or after the biopsy site healed). Biopsy samples were fixed in formalin and processed as formalin-fixed, paraffin-embedded tissue blocks.

Immunohistochemistry was conducted by blinded pathology scientists. Biopsy samples were sectioned, deparaffinized, subjected to antigen retrieval, and then incubated overnight at 4˚C with primary antibodies against procollagen I (cat# ab64409, Abcam, Cambridge, UK), collagen I (cat# ab138492, Abcam), collagen III (LS-B693, Lifespan Biosciences, Seattle, WA), or elastin (cat# ab77804, Abcam). Antibody binding was visualized with Alexa 568-conjugated secondary antibodies.

Whole-slide digital images acquired using the Hamamatsu NanoZoomer digital scanner (Hamamatsu Photonics, Japan) were analyzed to determine average immunofluorescence marker intensity for each antibody. Definiens Tissue Studio (Architect XD 64 version 2.7, Definiens, Munich, Bavaria) software was used for image analysis of the selected regions of interest (ROI; total area), which was defined as the dermis area, excluding the epidermis, glands, and blank space (ie, tears in the tissue). Procollagen I was calculated as the number of cells expressing the procollagen I marker normalized to the ROI (total number of cells expressing marker/ROI). Collagen I, collagen III, and elastin were assessed for expression levels using the average immunofluorescence marker intensity normalized to the total area of the ROI. The analysis for each marker was based on the average intensity across 5 sections (with a 100-µm interval) per biopsy sample.

Safety

Adverse events (AEs), serious AEs (SAEs), and treatment-emergent AEs (TEAEs) were monitored throughout the study. Injection site reactions (ISRs) during the VYC-20L treatment period were recorded in a 28-day diary.

Statistical Analysis and Analysis Populations

Statistical analyses were performed using SAS version 9.4 or higher (SAS Institute Inc., Cary, NC). Wilcoxon nonparametric paired comparisons between baseline and post-treatment biopsy samples (for the same participant) were performed. The full analysis set (FAS), which comprised participants who received at least 1 ATX-101 treatment and 1 post-treatment effectiveness assessment, was used for photographic imaging analysis. The safety population, which included participants who consented to participate in the study, was used for safety data analysis.

RESULTS

Participants

Of 58 enrollees, 53 participants met eligibility criteria and were treated (safety population). Most participants were female (83.0%) and most were White (96.2%); the mean age was 48.0 years (range, 24–64), and mean (SD) BMI was 28.0 (3.53) kg/m^2. The percentage of participants with baseline ALJDS grades (left side/right side) of 2, 3, and 4 were 37.7%/45.3%, 60.4%/54.7%, and 1.9%/0.0%, respectively. Of the 53 treated participants, 11 participants (20.7%) discontinued during the study due to withdrawal of consent (n=6), lost to follow-up (n=3), and AEs (n=2). Of the 6 participants who withdrew consent, 1 did so due to an AE and discontinued from the study.

Photographic Imaging Analysis

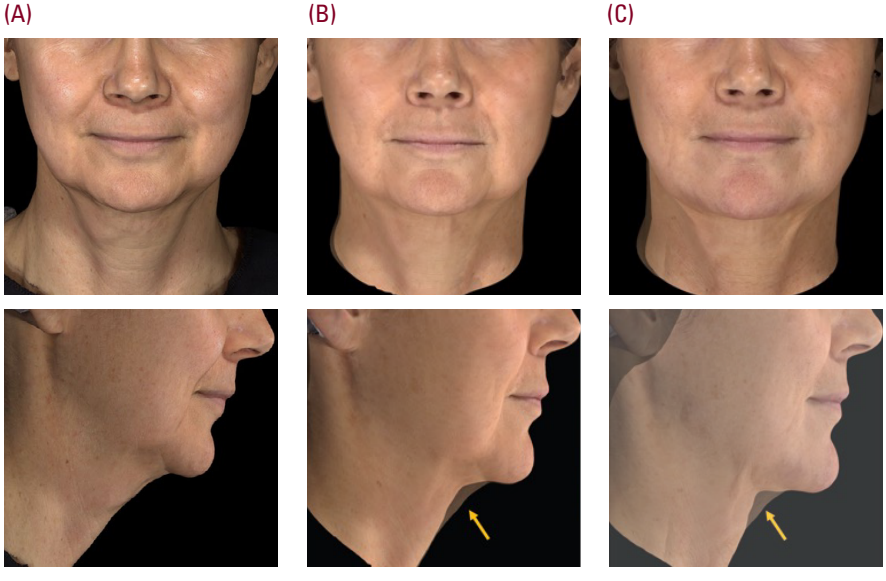
The photogrammetry results at the final study visit (4 weeks after the last VYC-20L treatment) are summarized in Table 1. Representative participant photographs are shown in Figure 2.

TABLE 1.

Summary of Photographic Imaging Analysis at Final Study Visit (Full Analysis Set)[a]	
Parameter (unit), n	**Mean (SD)**
Change from baseline in left jawline volume (cc), n=46	
Total volume change	0.9 (4.9)
Negative volume	–2.3 (2.6)
Positive volume	3.2 (2.9)
Change from baseline in right jawline volume (cc), n=46	
Total volume change	1.2 (5.0)
Negative volume	–2.3 (2.4)
Positive volume	3.5 (3.2)
Change from baseline in submental volume (cc), n=46	
Total volume change	–5.7 (5.5)
Negative volume	–6.3 (4.7)
Positive volume	0.6 (1.3)
Change from baseline in submental strain (%), n=44	
Major strain	3.6 (4.9)
Minor strain	–9.1 (3.9)
Change from baseline in submental skin position (mm), n=44	
X-directional movement	–0.1 (0.7)
Y-directional movement	3.2 (2.6)
Z-directional movement	–2.1 (3.4)
Submental angle (°), n=46	
Final study visit	60.8 (11.4)
Change from baseline	–15.8

[a]Although 53 participants initially received ATX-101, 4 participants discontinued the study prior to receiving VYC-20L. At the final study visit, there were 46 assessable participants for jawline volume, submental volume, and submental angle and 44 assessable participants for submental strain and submental skin position.

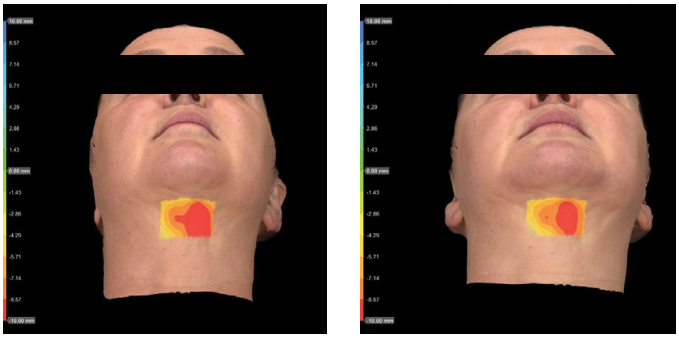
FIGURE 2. A 56-year-old female participant was taken at (A) baseline/prior to ATX-101 treatment, (B) 8 weeks after the last ATX-101 treatment/before VYC-20L treatment, and (C) at the final study visit/4 weeks after last VYC-20L treatment. The participant underwent 4 ATX-101 and 2 VYC-20L (initial + touch-up) treatments and achieved a 2-grade improvement on the ALJDS. The ghosted image (shaded area indicated by yellow arrow) represents the submental area at baseline/before ATX-101 treatment.



From baseline to the final study visit, the total mean volume for the left and right jawline (VYC-20L treatment area) increased by 0.9 and 1.2 cc, respectively, whereas the total mean volume for the submental area (ATX-101 treatment area) decreased by 5.7 cc. Figure 3 shows volume changes in the submental area of a representative participant.

For submental strain, the mean percentage change from baseline to the final study visit for the major strain event (stretch/expansion) was +3.6%, while the minor strain event (compression) mean percentage change was –9.1%. A larger change in the minor strain compared with the major strain event indicates greater skin surface compression than expansion within the submental area. Figure 4 shows major and minor strain events in the submental area of a representative participant.

FIGURE 3. A 52-year-old female participant showing change from baseline in submental volume (A) 8 weeks after the last ATX-101 treatment/before VYC-20L treatment (total mean volume change: –11.6 cc) and (B) at the final study visit/4 weeks after final VYC-20L treatment (total mean volume change: –10.4 cc). A color by distance map is shown (positive values/blue indicate an increase in height from the baseline surface, while negative values/red indicate a decrease in height from the baseline surface).



The mean changes from baseline to final study visit in submental skin position were –0.1 mm (X axis), +3.2 mm (Y axis), and –2.1 mm (Z axis). Skin movement in the Y and Z axes indicates superior and posterior skin surface movement from a lateral perspective. Figure 5 shows X-, Y-, and Z-directional skin movement in a representative participant.

For submental angles, the mean submental angle at the final study visit was 60.8°, a decrease of 15.8° from baseline (76.6°). Figure 6 shows changes in the submental angle of a representative participant.

Biopsy Analysis

Pre- and post-treatment submental skin biopsy samples were collected from all 13 participants who consented to the optional biopsy. The expression level of collagen I and III, as well as the ratio of collagen I to III, as measured by mean immunofluorescence intensity, was significantly increased compared with pretreatment levels at 8 weeks after the final ATX-101 treatment (P=0.0002, P=0.013, and P=0.003, respectively). The mean percentage changes from baseline in collagen I, collagen III, and collagen I/III immunofluorescence intensity are shown in Figure 7, and representative images

FIGURE 4. Major and minor strain events in a 56-year-old female participant (A) 8 weeks after the last ATX-101 treatment/before VYC-20L treatment (major strain: 4.1%, minor strain: –7.5%) and (B) at the final study visit/4 weeks after last VYC-20L treatment (major strain: 0.2%, minor strain: –8.2%). Major and minor strains indicate localized expansion and compression events, respectively. A larger minor strain event indicates localized compression of the skin surface within the given area of interest. A color by distance map is shown (positive values/blue indicate percentage increase from baseline in major strain, while negative values/red indicate percentage increase from baseline in minor strain).

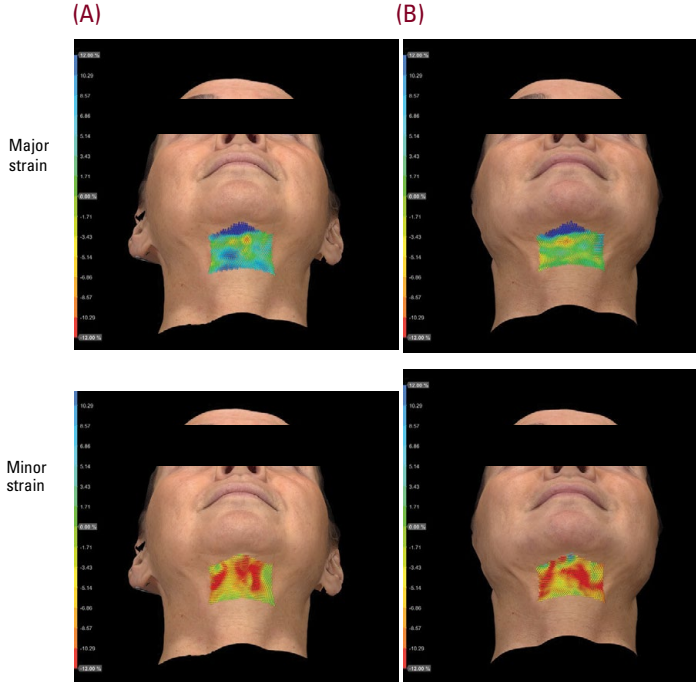


FIGURE 5. A 45-year-old female participant showed change from baseline in submental skin position at (A) baseline/prior to ATX-101 treatment, (B) 8 weeks after the last ATX-101 treatment/before VYC-20L treatment (X-directional movement: 1.0 mm, Y-directional movement: 6.7 mm, Z-directional movement: –3.9 mm), and (C) at the final study visit/4 weeks after last VYC-20L treatment (X-directional movement: –1.0 mm, Y-directional movement: 6.9 mm, Z-directional movement: –8.5 mm). Movement in the Y and Z axes corresponds with skin surface movement in the superior and posterior direction from a lateral perspective.

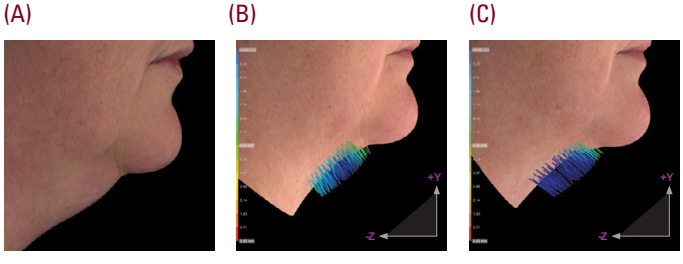


FIGURE 6. A 56-year-old female participant showing change from baseline in the submental angle. Representative photographs at (A) baseline, (B) 8 weeks after the last ATX-101 treatment/before VYC-20L treatment (change from baseline: –16.9°), and (C) at the final study visit/4 weeks after last VYC-20L treatment (change from baseline: –30.2°).

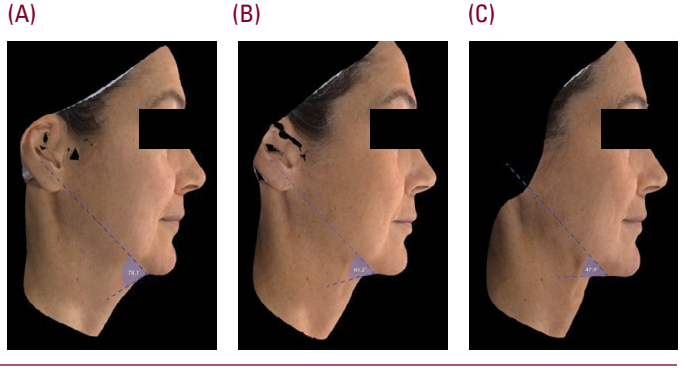


FIGURE 7. Biopsy analysis. Mean percent changes from baseline in average immunofluorescence intensity for collagen I, III, collagen I/III, and elastin 8 weeks after the last ATX-101 treatment. Percent change calculated as (Post-Pre)/Pre x 100.

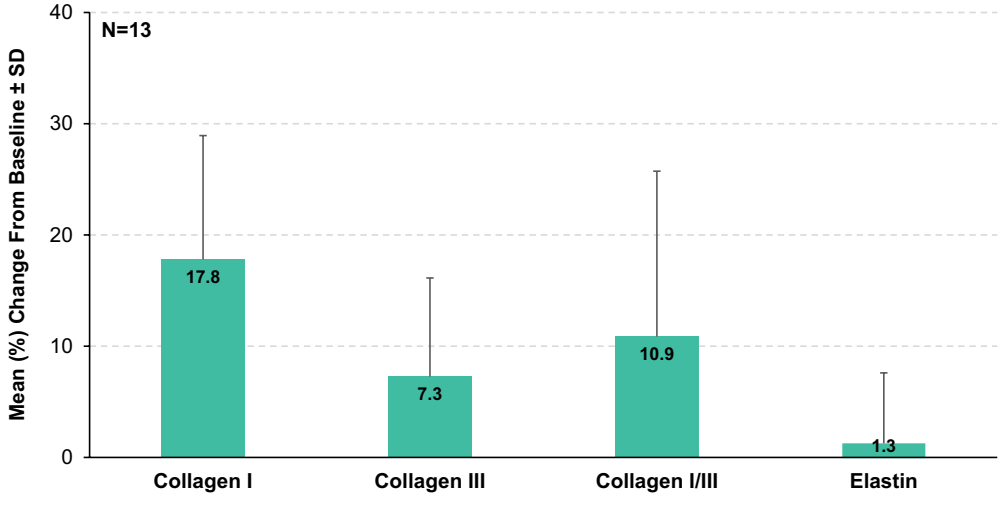
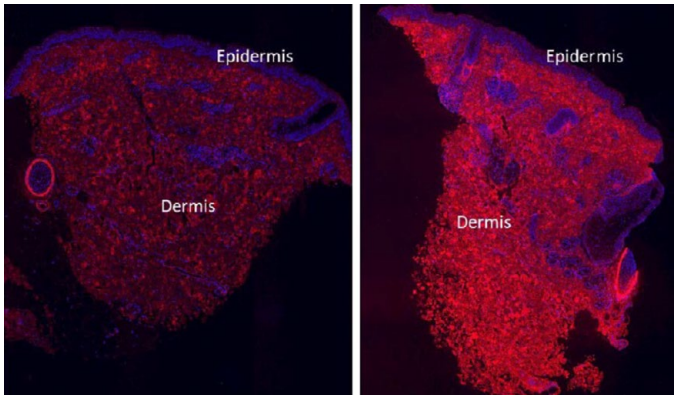


FIGURE 8. (A) Representative images of collagen I immunoreactivity before and (B) 8 weeks after the last ATX-101 treatment. Collagen I immunoreactivity was localized throughout the dermis of the submental skin. The expression level of collagen I increased after treatment. Collagen I (red), nuclear/structural stain (blue); image magnification: 4×.

(A) (B)



of collagen I are shown in Figure 8. No significant changes were detected for elastin (Figure 7) and procollagen I (mean percentage change in number of cells, +13.8%; data not shown).

Safety

All 53 participants reported at least 1 TEAE related to ATX-101, and 3 of 53 participants (5.7%) reported at least 1 TEAE related to VYC-20L. The majority of TEAEs related to ATX-101 and VYC-20L involved the injection site, including pain, swelling, and bruising, and were mild to moderate in severity (69.8%). Two participants (3.8%) experienced SAEs, which were unrelated to treatments or study procedures. Three participants (5.7%) discontinued the study due to ATX-101–related AEs, including pain, induration, discoloration, and rash at the injection site. Of these 3 participants, 1 withdrew consent from the study due to procedural pain. More detailed safety results are reported elsewhere.[14]

DISCUSSION

Age-related changes that contribute to loss of jawline definition include an increasing cervicomental angle (angle between the vertical portion of the neck and the transverse portion of the submandibular region), mandible recession, SMF accumulation, weakening of the mandible septum (which holds fat compartments in place), and skin laxity (which leads to sagging jowl fat).[1,16] An excess of SMF and its subsequent effect on the appearance of the jawline negatively impacts psychological well-being and behavior, thereby driving individuals to seek aesthetic treatments.[1,2]

The 3D photogrammetry and biopsy analyses reported here complement previously published clinical findings of a phase 4 open-label study[14] showing that sequential treatment with ATX-101 and VYC-20L reduced SMF and improved jawline definition. Volumetric changes in the jawline and submental area confirmed improvements in jawline contour and reductions in SMF, respectively, as measured by investigator- and patient-reported rating scales.[14] The changes in the major and minor strain events (greater compression vs stretch/expansion) were consistent with superior and posterior skin displacement in the submental area. Taken together, these results indicate that the skin is not sagging (ie, absence of "empty balloon" effect) despite reductions in SMF.

The observed improvements in skin laxity may result from neocollagenesis. The increased expression levels of collagen I and III, as well as collagen I/III, after ATX-101 treatment support previous observations suggesting that ATX-101 may induce neocollagenesis and remodeling of connective tissues.[9] The greater abundance of collagen I relative to collagen III is more desirable for skin rejuvenation because collagen I is softer, while collagen III is more rigid and associated with scarring.[17] The lack of significant changes in elastin levels indicates no apparent increase in elastogenesis at the sampled timepoint (8 weeks after last ATX-101 treatment). Although procollagen I did not show remarkable changes, the increased expression level of collagen I 8 weeks after ATX-101 treatment suggests that procollagen I may be increased at an earlier timepoint.

The current study supports previous ATX-101 studies reporting maintenance or improvement of skin laxity in participants.[2,6,8] Injection of ATX-101 results in adipocytolysis, which in turn elicits a mild, local inflammatory response.[9,18]

Following ATX-101–induced adipocytolysis and subsequent inflammation, histologic analysis of ATX-101–treated tissues demonstrated fibroblast recruitment and thickening of the fibrous septae, indicating collagen production.[9] Neocollagenesis may contribute to skin retraction/movement, thus resulting in unchanged or improved skin laxity despite reductions in SMF.[9] Future studies can examine the direction of fibers when new collagen is formed after ATX-101 treatment.

In the aesthetics field, 3D photogrammetry has become increasingly prevalent for objectively analyzing and documenting age-related facial changes and clinical outcomes.[19-21] Compared with traditional 2D photography, 3D photography enables quantification of depth, surface area, and volume of soft tissues.[20,22,23] Several studies have utilized 3D photography to quantify the reduction of SMF[22-24] and improvement in jawline.[25] Objective and standardized quantification of fat reduction, as well as volumetric and dimensional changes in the face and neck, may complement clinical rating scales and facilitate comparative effectiveness studies in the aesthetics field.[26]

The current study possessed some limitations. More timepoints may have provided better temporal resolution for observing changes in the expression levels of procollagen and elastin. A longer-term study may also be needed to provide a full assessment of the duration of effects.

CONCLUSION

In conclusion, sequential, dual-modality treatment with ATX-101 and VYC-20L reduced submental fullness and improved jawline definition with quantifiable changes in mandibular border volume, submental volume, major and minor strain in the submental area, and displacement of submental skin. Biopsy analysis showed an increase in collagen I, collagen III, and the ratio of collagen I to III, indicating neocollagenesis. Neocollagenesis may contribute to unchanged or improved skin laxity in the submental region after reducing SMF with ATX-101.

DISCLOSURES

Mark Ashton has no conflicts to disclose. Natasha Cook is an investigator and advisory board member for Allergan Aesthetics, an AbbVie Company. Greg J. Goodman is a consultant, speaker, and investigator for Allergan Aesthetics, an AbbVie Company. Stefania Roberts is a consultant for AbbVie. Rong Nie, Lucille Alker, and Michael Silberberg are employees of AbbVie.

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Data Sharing: AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent, scientific research, and will be provided following review and approval of a research proposal, Statistical Analysis Plan (SAP), and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the US and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html

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ORIGINAL ARTICLE

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Differentiation of NASHA and OBT Hyaluronic Acid Gels According to Strength, Flexibility, and Associated Clinical Significance

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ABSTRACT

Background: With a wide range of hyaluronic acid (HA) filler products available, knowledge of gel characteristics is a key part of tailoring treatments to each patient's aesthetic goals. This paper presents 2 main gel characteristics – strength/firmness and flexibility – for HA fillers produced using NASHA® and OBT™ and their clinical significance for tissue performance.

Methods: Three NASHA gels (Restylane®; Restylane Silk; Restylane Lyft) and 4 OBT gels (Restylane Refyne; Restylane Kysse; Restylane Volyme; Restylane Defyne) were studied in dynamic mode using a PP25 rheometric measuring system at 25˚C. Gel strength/firmness was measured using frequency sweep, with G prime evaluated at 0.1 Hz. Flexibility assessments used amplitude sweep measurements between 0.1% and 10,000% strain at 1 Hz, with xStrain being the strain value at the crossover point where G prime and G double prime have the same value.

Results: Restylane, Restylane Silk, and Restylane Lyft had G primes of 701, 416, and 799 Pa, respectively. OBT G primes for Restylane Refyne, Restylane Kysse, Restylane Volyme, and Restylane Defyne were 70, 160, 171, and 271 Pa, respectively. The xStrain values were 1,442% (Restylane Refyne), 908% (Restylane Kysse), 930% (Restylane Volyme), 761% (Restylane Defyne), 7% (Restylane), 19% (Restylane Silk), and 17% (Restylane Lyft).

Conclusions: OBT products had high flexibility (tolerance to deformation) and low to intermediate strength/firmness, which make them appropriate for dynamic facial areas. NASHA products showed greater strength/firmness, with the potential to create lift and projection. Altogether, NASHA and OBT HA gels covered a wide range of strength and flexibility.

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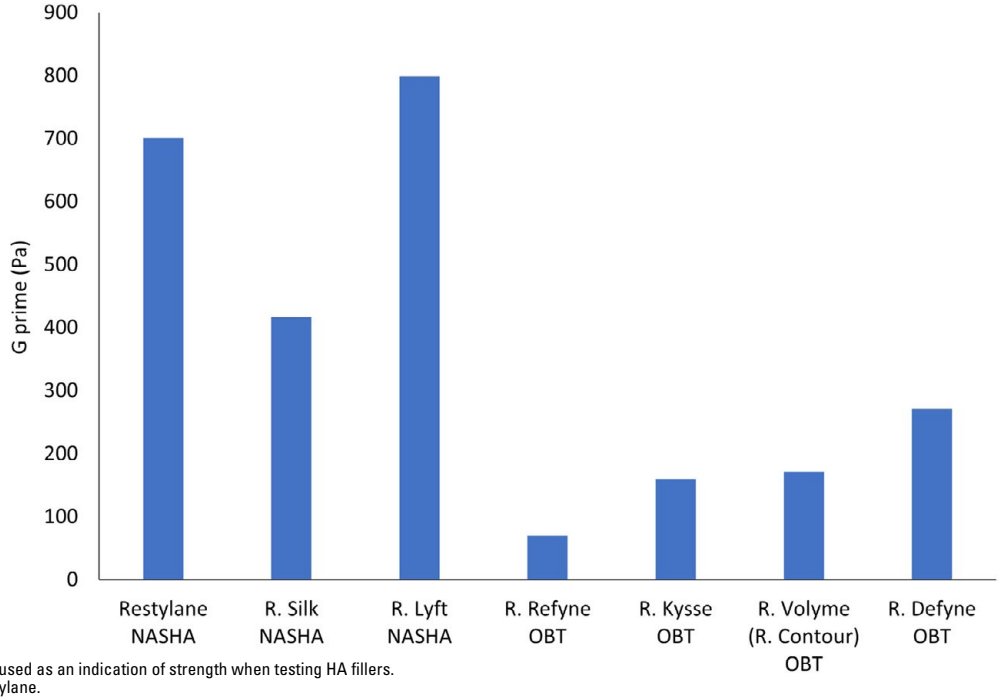
INTRODUCTION

The demand for minimally invasive aesthetic treatments, including hyaluronic acid (HA) fillers, has grown significantly in recent years, with the uptake of such procedures rising by more than 75% in the United States (US) over the past decade.[1,2] Clinician experience, expertise, and confidence in handling and administering these products have subsequently grown.[1,3] HA fillers provide a durable, yet non-permanent, non-surgical option to address facial volumetric changes associated with aging.[2,4-9] HA filler treatments in general aim to provide volume so that the face appears lifted while looking even and natural.[2,4-6]

HA gel strength/firmness is usually expressed as the elastic modulus, or G prime (G'), while flexibility can be defined by the xStrain (the strain value for the G prime/G double prime [G'']) crossover in the amplitude sweep).[2,10,11] The xStrain represents the furthest point at which the gel can recover following deformation.[2,11] Beyond this point, the gel begins to behave more like a liquid and will no longer be able to return to its original shape.[2,11] Because G prime and xStrain are two separate properties and not necessarily linked, products with similar G primes may exhibit different xStrains and vice versa.[12] Products with a higher G prime are stronger and more resistant to deformation than those with a lower G prime.[12] Products with higher xStrain are more flexible than those with lower xStrain values.[11,12]

The NASHA® technology, used for Restylane®, Restylane Silk (R. Silk), and Restylane Lyft (R. Lyft), allows for the preservation of the naturally long HA chains resulting in strong gels with high G primes. In addition, the NASHA technology uses minimal modification and controlled particle sizing.[11,13–17] HA fillers produced with NASHA exist both with and without lidocaine.[13,16,17] The OBT™ technology (referred to as XpresHAn in the US) produces flexible HA fillers where the strength/firmness (G prime) is varied by applying different degrees of crosslinking.[11,12,14,15,18–25] Fillers formulated using OBT include Restylane Refyne (R. Refyne), Restylane Kysse (R. Kysse), Restylane Defyne (R. Defyne), and Restylane Volyme (R. Volyme; Restylane Contour in the US).[19-22,25]

FIGURE 1. Elastic modulus (G prime) measurements for strength at 0.1 Hz for NASHA® and OBT™ formulations of Restylane hyaluronic acid fillers.



G prime measurements are used as an indication of strength when testing HA fillers.
HA, hyaluronic acid; R, Restylane.

Although measurement of flexibility is a well-established rheology method, xStrain as an indicator of flexibility for HA fillers was first applied to the OBT and NASHA gels.[11,26-28] Using the xStrain method, an amplitude sweep is conducted where the level of deformation (or % strain) is increased until the yield point at the end of the linear viscoelastic region (LVR) is reached, when the gel can no longer return to its original shape.[11] More flexible HA formulations can withstand high levels of strain before yielding.[11] The current study examined strength/firmness (G prime) and flexibility (xStrain) for the full range of NASHA and OBT HA fillers. In addition, this paper aimed to link these gel properties with clinical performance.

MATERIALS AND METHODS

G prime and xStrain

G prime (strength/firmness) and xStrain (flexibility) were measured for Restylane, R. Silk, and R. Lyft (NASHA gels) and R. Refyne, R. Kysse, R. Volyme, and R. Defyne (OBT gels) and performed in sequence, including a relaxation time of 30 minutes. A frequency sweep from 10 Hz to 0.1 Hz at 0.1% strain was followed by an amplitude sweep from 0.1% to 10,000% (0.001 to 100) strain at 1 Hz. The gap was 1 mm using a PP25 rheometric measuring system at 25°C. The frequency sweep was evaluated for G prime (G′), G double prime (G′′), G*, and tan delta (tan δ) at 0.1 Hz.

The amplitude sweep was first evaluated at 0.1% strain to verify that the applied frequency sweep strain was within the LVR. The strain was then evaluated at the crossover point of the amplitude sweep (where G prime and G double prime had the same value). This value denoted the xStrain.

RESULTS

HA fillers produced with NASHA technology demonstrated the highest G primes (strength/firmness). Restylane, R. Silk, and R. Lyft had G primes of 701, 416, and 799 Pa, respectively. Across the OBT formulations, G primes were 70 (R. Refyne),

TABLE 1.

Measures of Strength (G prime) and Flexibility (xStrain) for Restylane Hyaluronic Acid Fillers Formulated With Either NASHA or OBT

Product	G prime (Pa)	xStrain (%)
NASHA-based formulations		
Restylane	701	7
R. Silk	416	19
R. Lyft	799	17
OBT-based formulations		
R. Refyne	70	1442
R. Kysse	160	908
R. Volyme (R. Contour)	171	930
R. Defyne	271	761

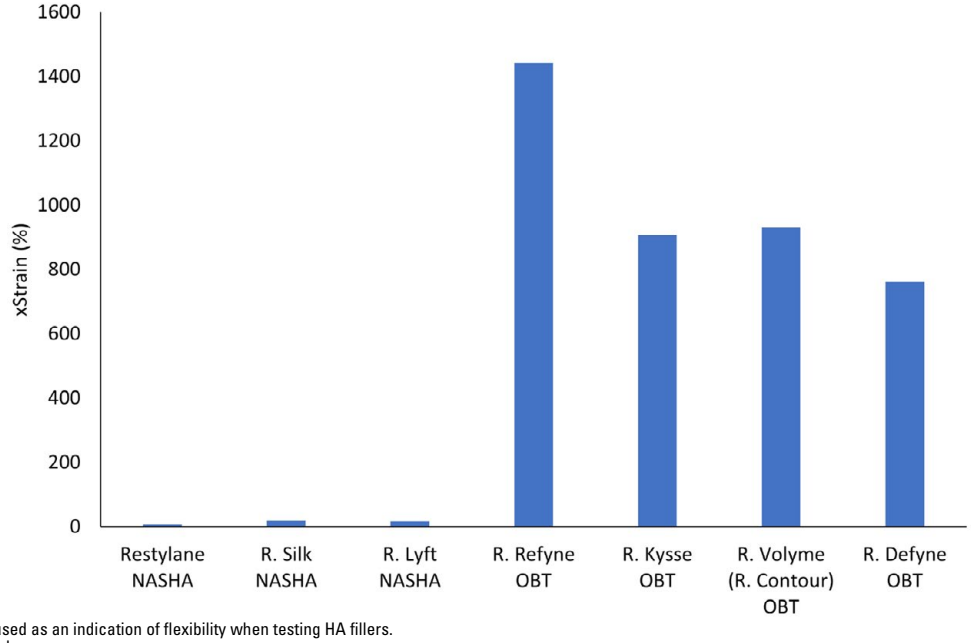
G prime measurements provide an indication of strength and xStrain measures flexibility when testing HA fillers. HA, hyaluronic acid; R, Restylane.

160 (R. Kysse), 171 (R. Volyme), and 271 (R. Defyne) Pa, respectively (Figure 1 and Table 1).

HA fillers produced with OBT technology demonstrated the highest xStrains (flexibility), comprising 1,442%, 908%, 930%, and 761% for R. Refyne, R. Kysse, R. Volyme, and R. Defyne, respectively. NASHA formulations showed xStrains of 7% (Restylane), 19% (R. Silk), and 17% (R. Lyft) (Figure 2 and Table 1).

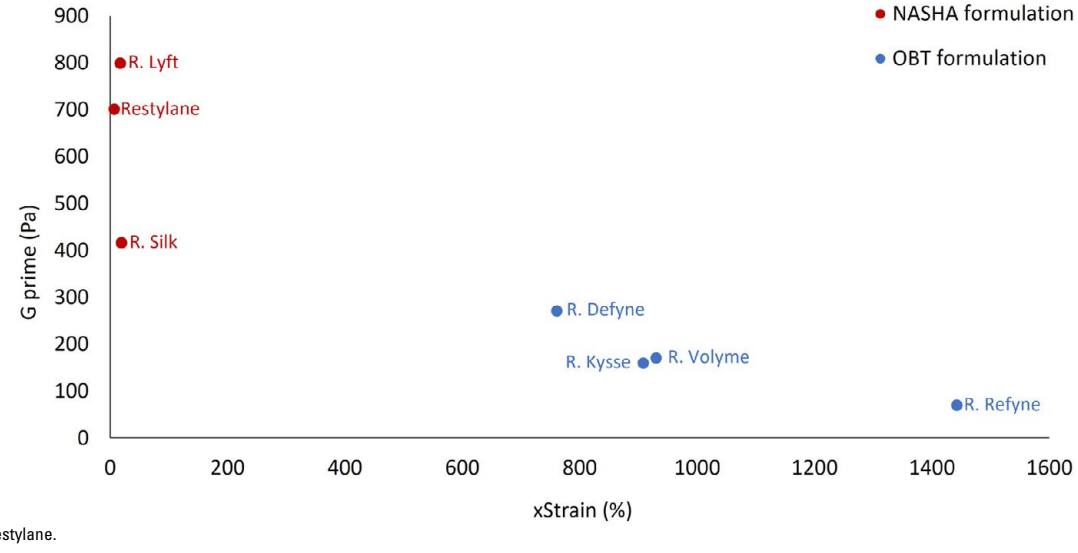
The combined characteristics of each HA filler in terms of strength/firmness (G′) and flexibility (xStrain) are plotted in Figure 3.

FIGURE 2. xStrain measurements for NASHA® and OBT™ formulations of Restylane hyaluronic acid fillers.



xStrain measurements are used as an indication of flexibility when testing HA fillers.
HA, hyaluronic acid; R, Restylane.

FIGURE 3. Strength (G prime) and flexibility (xStrain) balance for NASHA® and OBT™ formulations of Restylane hyaluronic acid fillers.



HA, hyaluronic acid; R, Restylane.

DISCUSSION

The data reported herein demonstrate a broad range in flexibility and strength/firmness for the HA fillers manufactured by the NASHA and OBT technologies. Among the variety of parameters used to differentiate HA fillers, both G prime and xStrain are based on accepted rheological measures, of which G prime may be the most widely used.[2,6,11] G primes for the Restylane fillers have previously been reported by, for example, Fagien et al (2019), Öhrlund et al (2018), and Lorenc et al (2017), and with similar results to what is reported herein.[6,11,29] However, G primes for two of the products produced by NASHA were slightly higher than previously reported.[6] In this study, respective G primes for Restylane and R. Lyft were 701 Pa and 799 Pa, compared with 544 Pa (Restylane) and 545 Pa (R. Lyft) reported by Fagien et al (2019).[6] A possible explanation may be slightly different instrumental settings as there is a lack of standard measurement guidance among different stakeholders.[29]

Access to a range of HA fillers with different physicochemical and rheological profiles provides the clinician with a toolbox of options that can be used to individualize and adapt aesthetic treatment according to personal requirements, facial structure, and desired outcome.[18,30,31] It is commonly suggested that clinicians must also have a good understanding of these properties to obtain optimum aesthetic results.[2,4,5,7–10,32,33] However, although there is a wide body of literature describing how physicochemical and rheological properties can be used to characterize different HA fillers, there are very few studies that correlate in vitro measurements with clinical performance.[6]

As reported in this study and previous studies, the NASHA technology typically produces strong/firm gels that are able to resist deformation.[6,12,33] Hence, these products are considered optimal for facial anatomical locations requiring precise projection, lift, or contouring. In a clinical setting, Di Gregorio et al (2022) demonstrated optimal aesthetic results with R. Lyft in the midface for subjects with thick tissue coverage and where the primary need for treatment was lifting or contouring.[18] Similarly, Jones et al (2020) showed improved aesthetic results for midface contouring with R. Lyft.[34] The high and precise projection capability of R. Lyft was demonstrated in a randomized and controlled clinical investigation showing R. Lyft to be effective in shaping the nasal dorsum and radix with aesthetic improvement maintained for up to 12 months.[35] Huang and Tsai (2020) also demonstrated long term aesthetic improvement and subject satisfaction (maintained over 24 months including one re-treatment) with both Restylane and R. Lyft used in multiple facial locations, including for example the midface, nose, and chin.[36]

As opposed to HA fillers based on the NASHA technology, HA fillers produced by the OBT technology are less strong/firm (softer, lower G prime) but highly flexible (high xStrain).[11] Softer gels may be less capable of resisting deformation compared with stronger/firmer gels, but greater flexibility allows them to tolerate deformation because they have the ability to return to their original shape once the strain is removed. Hence, a flexible gel is optimized for treating dynamic areas of the face (eg, nasolabial folds, marionette lines, and perioral regions including the lips) where an increased strain is applied during facial movements or expressions and removed when the face relaxes and returns to a static condition. Perceived naturalness of dynamic facial expression when the face was in motion was shown to be maintained or enhanced through 6 months following treatment of wrinkles and folds in the lower face, including nasolabial folds, marionette lines, and oral commissures, with R. Defyne or R. Refyne.[31,37] Percec et al (2020) used 3D digital imaging to show that R. Defyne and R. Refyne reduced the strain in most active facial expressions, and the changes in stretch and compression achieved resembled those of a more youthful face.[27] In addition, enhanced naturalness of the lower face when in motion was demonstrated after treatment with R. Defyne or R. Refyne in subjects with moderate to severe nasolabial folds and marionette lines.[26] Studies examining the use of R. Kysse in combination with R. Defyne and R. Refyne in the lips and perioral enhancement reported improved fulness, reduced wrinkle severity, and enhanced surface stretch, while natural movement and dynamic expression were maintained.[38-40]

CONCLUSION

Restylane HA fillers manufactured with NASHA and OBT Technologies displayed a wide range in both strength/firmness and flexibility. OBT products were highly flexible and lower in strength/firmness (with low to intermediate G prime), and have been shown to provide optimal clinical results in dynamic areas of the face such as nasolabial folds or lip region. By comparison, NASHA products were stronger (with higher G prime) but comparatively low in flexibility, conferring advantageous properties for targeted treatment to provide lift and projection in areas such as the nose and chin. These results provide a greater understanding of gel properties and how these properties translate to tissue performance to help guide clinicians in their selection of products for an optimal aesthetic outcome.

DISCLOSURES

Åke Öhrlund, Per Winlöf, Torun Bromée, and Inna Prygova are all employees at Galderma, Uppsala, Sweden.

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ORIGINAL ARTICLE

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International Consensus on Anti-Aging Dermocosmetics and Skin Care for Clinical Practice Using the RAND/UCLA Appropriateness Method

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ABSTRACT

Background: The objective was to provide international recommendations on anti-aging dermocosmetics for clinical practice starting with essential ingredients for protection and repair before working up to advanced products for specific concerns.

Methods: Seven international experts reviewed 8 hypothetical case scenarios covering different ages, skin issues (eg, sensitivity, acne, melasma), and exposure to exposome factors for both sexes and all Fitzpatrick skin types (FST). The RAND/UCLA appropriateness method was used to obtain consensus. Seventeen key ingredients were rated on a scale from 1 (totally inappropriate) to 9 (totally appropriate). Statistical analysis, 2 meetings, and email discussions refined the recommendations.

Results: High-factor broad-spectrum sunscreen (ie, protects against ultraviolet [UV] A and B rays), niacinamide, and other topical antioxidants were recommended for all scenarios. Further discussions were required for other ingredients. Tinted sunscreen/iron oxide were recommended for all FST, although compliance may be sub-optimal for darker skin phototypes (IV-VI), if not cosmetically acceptable. Combining a facial foundation with broad-spectrum sunscreen was recommended for darker phototypes to obtain visible light protection closely matching diverse color tones. Retinols were not recommended as a first-line treatment for sensitive skin, especially FST V and VI, due to the risk of irritation. After ablative laser treatment, alpha hydroxy acids should be avoided or used with caution in FST IV to VI due to the risk of post-inflammatory hyperpigmentation.

Conclusion: We describe a simple, practical tool for use in daily dermatology consultations for providing recommendations on anti-aging dermocosmetics to cover diverse and inclusive populations of patients, addressing all skin types and international needs.

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INTRODUCTION

Dermocosmetics are topical cosmetic products that penetrate the stratum corneum to provide medicinal or drug-like benefits.[1] Among the multitude of dermocosmetics available, consumers often seek professional guidance during dermatology visits for recommendations on the best options for their specific skin aging concerns, and it can be challenging for dermatologists to recommend the best products taking into account every patient's specificities.[2] Furthermore, there may be little scientific evidence on the effectiveness of some dermocosmetics (and the active ingredients) to guide the selection of products.[3]

The use of appropriate dermocosmetics to decrease visible signs of skin aging should be started early from around 20 years onwards. Multiple active ingredients may be required depending on the patient's specific concerns. The optimal skincare regimen for a given patient will depend on their age, gender, skin type, and skin conditions, as well as their exposure to exposome factors that influence skin aging: encompassing external environmental factors (sun exposure, pollution, temperature, microbiome alterations); lifestyle factors (lack of sleep, stress, poor nutrition, smoking); and internal factors (hormonal variations).[4,5]

The skin health and beauty pyramid concept was developed based on extensive scientific literature on ingredients, formulations, and technologies, and a robust understanding of the mechanisms of skin aging.[6,7] The pyramid simplifies product recommendations into 3 categories: pyramid base for protection and repair (photoprotection, antioxidants, DNA repair enzymes) against exposome factors, (eg, sun exposure, pollution, hormonal changes, lifestyle factors); pyramid middle for renewal by moisturization, exfoliation, and cell turnover (retinoids and alpha hydroxy acids [AHA]); and pyramid top for stimulation (peptides, bioidentical growth factors, stem cells, circadian rhythm modifiers).[6,7] Using this tool, dermatologists can start at the initial visit by recommending essential products for protection and repair and then work up in later visits to more advanced products that may be appropriate for specific concerns.

The objective of this study was to expand the pyramid concept to provide a scientifically validated practical tool to develop a rational approach to selecting the best antiaging dermocosmetic ingredients for diverse and inclusive patient populations, covering different ages, both sexes, Fitzpatrick skin types (FST), as well as skin issues (eg, sensitivity, acne, melasma) and exposure to exposome factors.

MATERIALS AND METHODS

Expert Panel Voting

A panel of 7 international dermatologists with experience in cosmeceuticals reviewed 8 hypothetical case scenarios as representative examples of the many diverse populations seen in dermatological consultations.

Method

The RAND/UCLA appropriateness method (RAM) was initially developed so that, even when robust randomized controlled trials are lacking, physicians can make decisions by combining evidence from scientific literature and collective expert opinion on the appropriateness of performing a procedure at the level of patient-specific symptoms, medical history, and test results.[8] The RAM is a modified Delphi method but differs by providing panelists the opportunity to discuss their judgments. This method was thus considered to be a good tool for reaching a consensus on the use of dermocosmetic products. The concept of appropriateness refers to the relative weight of the benefits and harms, where a dermocosmetic was considered appropriate and worth using (not considering cost) if the expected health benefit exceeded the expected negative consequences by a sufficiently wide margin.

TABLE 1.

Questionnaire to Evaluate Ingredients for Topical Dermocosmetics									
Topical Treatments	**Appropriateness Scale**								
Wide Spectrum SPF + UVAPF	1	2	3	4	5	6	7	8	9
Tinted Sunscreen / Iron Oxide	1	2	3	4	5	6	7	8	9
Niacinamide	1	2	3	4	5	6	7	8	9
Tranexamic Acid	1	2	3	4	5	6	7	8	9
Vitamin C	1	2	3	4	5	6	7	8	9
Vitamin E	1	2	3	4	5	6	7	8	9
Other Topical Aox	1	2	3	4	5	6	7	8	9
Hyaluronic Acid Low Molecular Weight	1	2	3	4	5	6	7	8	9
Hyaluronic Acid High Molecular Weight	1	2	3	4	5	6	7	8	9
Alpha Hydroxy Acid	1	2	3	4	5	6	7	8	9
Salicylic Acid	1	2	3	4	5	6	7	8	9
Glycolic Acid	1	2	3	4	5	6	7	8	9
Peptides	1	2	3	4	5	6	7	8	9
Retinol	1	2	3	4	5	6	7	8	9
Cassia Extract	1	2	3	4	5	6	7	8	9
Proxylane™ (C-Xyloside)	1	2	3	4	5	6	7	8	9
Omegas	1	2	3	4	5	6	7	8	9
Other Topical Treatments	1	2	3	4	5	6	7	8	9

Appropriateness scale from 1 (totally inappropriate: therapeutic never used) to 9 (totally appropriate: choice therapeutic)
Abbreviations: SPF, sun protection factor; UVA, ultraviolet A; Aox, antioxidant

A questionnaire was sent to the experts in October 2022. For each case scenario, the panel of experts rated the benefit-to-harm ratio of 17 ingredients for topical dermocosmetics (Table 1) on a scale from 1 (totally inappropriate: therapeutic never used; the expected harms greatly outweigh the expected benefits), through 5 (uncertain), to 9 (totally appropriate: choice therapeutic; the expected benefits greatly outweigh the expected harms).

Dermocosmetic ingredients for which a consensus had not been reached in the first round were discussed in a virtual meeting and further statistical analysis was performed. After consensus was reached, a second meeting and email discussions reviewed/validated the decisions.

Hypothetical Case Scenarios

Eight hypothetical case scenarios were prepared (by ZD and SLM) as representative examples of the many diverse populations seen in daily dermatological consultations:

Scenario 1

A 30-year-old female with FST IV has a 3-month-old son and recently noticed upper lip, bilateral jawline, and lateral forehead pigmentation. The presence of the dyspigmentation is emotionally distressing and is contributing to her post-partum depression. She has been avoiding public situations for the past months due to her appearance. She has tried several over-the-counter products without results. She is concerned that the melasma pigmentation continues to darken despite her avoidance of the outdoors and wonders why this is happening. She does not wear photoprotection as she is dissatisfied with the sunscreen appearance on her skin.

Scenario 2

A 25-year-old female with FST III is noticing the first signs of aging with fine lines around the eyes. She also has post-inflammatory hyperpigmentation (PIH) from acne scarring that is both recent and old. She uses only bar soap on her face and frequently goes to sleep without removing her cosmetics. She desires recommendations for a good acne prevention skin care regimen. She has been reading about the baby-botox trend and wonders if this is an option for wrinkle prevention; however, she is needle phobic and not sure she wants to put a toxin into her body.

Scenario 3

A 30-year-old FST II female with sensitive skin who works outdoors as a landscape architect desires to initiate anti-aging cosmetic solutions as she has lentigines on her face along with fine glabellar lines and facial dryness. She has a 6-month-old daughter and has noticed the difference between her skin texture and that of her daughter. She frequently gets fewer than 5 hours of sleep nightly, in between her work responsibilities and her daughter not sleeping through the night.

Scenario 4

A 35-year-old FST III male is recently divorced and wishes to renew his interest in dating. He has frequently consulted a dermatologist for treating his cystic acne. He completed a course of oral isotretinoin 3 months ago and is noticing a few isolated papules and pustules and xerosis. He wishes to resume sky diving but has not jumped for the past 6 months due to photosensitivity created by the oral retinoid. He also wants to both improve his appearance and prevent photoaging.

Scenario 5

A 40-year-old female with FST I has always used sunscreen and taken care of her health, but she works in a youth-oriented fashion environment and feels pressure to do more for her appearance. She has initiated botulinum toxin treatment for her glabellar lines and had hyaluronic acid injected into her nasolabial folds. She is satisfied with her anti-aging procedures but wants to improve her skincare regimen to address her suboptimal skin texture. She lives and works in New York City and is concerned about the effect of pollution on her skin.

Scenario 6

A 45-year-old perimenopausal female with FST II and pigmentation wishes to improve her skin performance. She has tried various dermocosmetics without the rapid results she desires; therefore, she elected to have a carbon dioxide laser resurfacing procedure and wants recommendations for both pre- and post-procedure skin care. She exercises infrequently and is about 40 pounds/18 kilos overweight but has recently started dietary counseling. Her goal is to re-enter the workforce with a revitalized appearance.

Scenario 7

A 45-year-old menopausal female with FST IV has just started a successful career as a live on-location television reporter. With the increased outdoor activities and sun exposure, she is noticing actinic pigmentation on her bilateral cheeks. She desires counseling on sunscreen selection that will not appear white and pasty on her skin, yet will provide excellent sun protection. Additionally, she has started noticing that, accompanying the occurrence of hot flashes, her skin aspect is changing, and she no longer tolerates her usual cosmetic routine. She is wondering if there is a problem with her skin and seeks advice on why this could be happening.

Scenario 8

A 60-year-old menopausal female with FST I desires suggestions to improve her appearance. Until her recent retirement, she was a heavy smoker (half a pack of cigarettes daily) due to the stress of her job. She notes upper lip and jawline dyspigmentation that has worsened considerably since she began estrogen replacement therapy.

RESULTS

Results of the consensus reached by the 7 international experts between November 2022 and April 2023 on the appropriate dermocosmetics for each scenario are shown in Figures 1 and 2. Broad-spectrum high sun protection factor (SPF) and high ultraviolet (UVA) photoprotection with PF at the base of the pyramid was universally considered appropriate for all scenarios, all FST, and both sexes. Topics that were discussed in more detail to reach a consensus concerned the use of tinted sunscreen with iron oxide particles with dark skin, the use of antioxidants, exfoliating ingredients and retinols with sensitive skin, dermocosmetics for men, and other antioxidants.

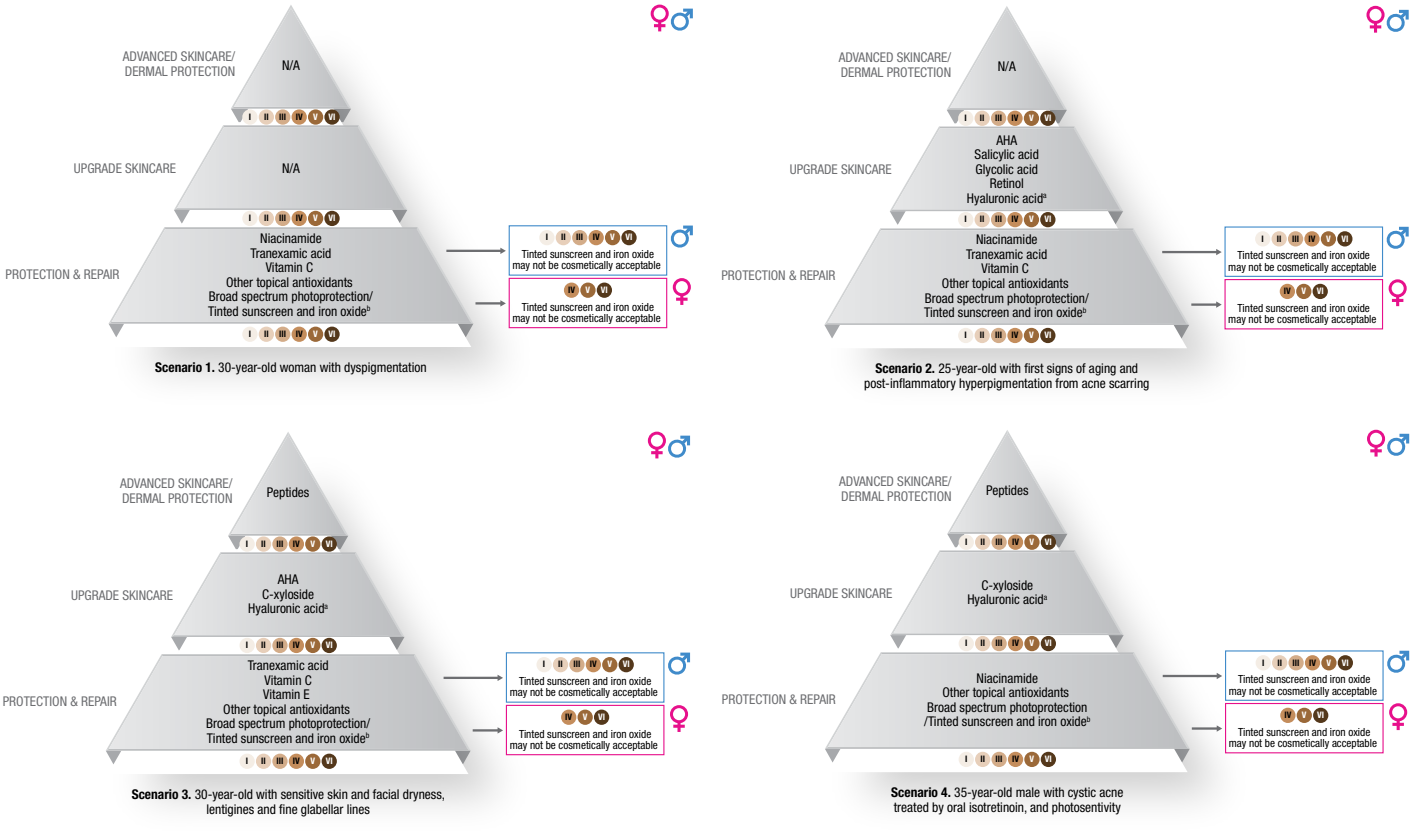
In scenario 1 with melasma, tinted sunscreen/iron oxide are recommended for lighter Fitzpatrick skin types I-III, especially for women. Protection against visible light (VL; specifically high-energy visible or blue light) is especially important for darker skin types (III-VI) as they are more sensitive to pigmentary disorders from blue light, therefore, tinted sunscreens/iron oxide are recommended if cosmetically acceptable. However, compliance may be sub-optimal for darker phototypes (FST IV-VI) as the range of colors of tinted sunscreens are limited and may not match the patient's constitutive skin tone, leaving a greyish/whitish aspect. The experts, therefore, recommend combining a facial foundation that perfectly matches the patient's skin tone with tinted broad-spectrum sunscreen containing iron oxides (UVA, UVB, VL) or non-tinted mineral sunscreen, as a solution to obtain VL protection for darker phototypes that closely color matches diverse color tones, including dark phototypes.

In scenario 1, antioxidants are recommended for all FST.

In cases of sensitive skin (scenario 3), retinols (present in numerous antiaging products) can be irritating for all phototypes, especially FST V and VI (risk of paradoxical worsening), so they should not be recommended as a first-line treatment. However, suitability will depend on the retinol formulation, concentration, and effectiveness. Additionally, retinoids should be avoided if breastfeeding.

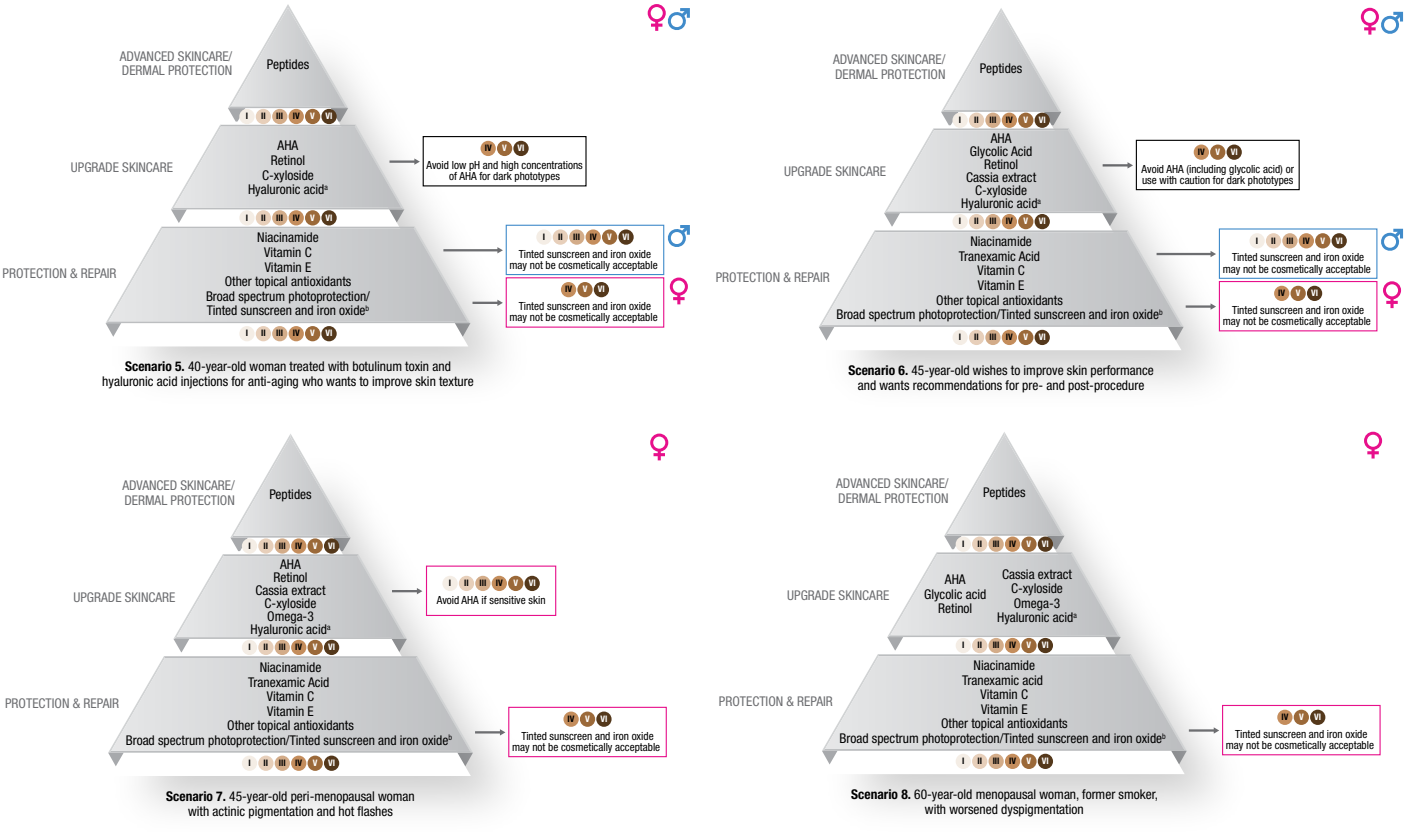
AHA including glycolic acid should also be avoided as they enhance photodamage by UV light.

FIGURE 1. Expert consensus results of appropriate dermocosmetics for clinical scenarios 1-4 illustrated using the skin health and beauty pyramid concept.



[a]Hyaluronic acid low/high molecular weight; [b]Tinted sunscreen/iron oxide/broad-spectrum photoprotection with high SPF and high UVA PF

FIGURE 2. Expert consensus results of appropriate dermocosmetics for clinical scenarios 5-8 illustrated using the skin health and beauty pyramid concept.



[a]Hyaluronic acid low/high molecular weight; [b]Tinted sunscreen/iron oxide/broad-spectrum photoprotection with high SPF and high UVA PF

In scenario 4, as men have more facial hair and are more prone to folliculitis, they are likely to find the appearance of tinted sunscreen/iron oxide inappropriate and not cosmetically acceptable. Antioxidants, C-xyloside, and peptides are all appropriate for men and women as both sexes need to protect and repair their skin from exposome factors and are affected by decreased synthesis of collagen and extracellular matrix compounds as they age.

In scenario 4, with the risk of sun exposure, vitamin C and tranexamic acid are not recommended as they make skin more photosensitive. AHA should also be avoided before sun exposure as it could cause stinging and burning, especially when receiving isotretinoin treatment as this makes the skin very dry.

In scenario 5, low pH and high concentrations (up to 5%) of AHA should be avoided for darker FST IV to VI in both sexes due to the risk of PIH. A progressive application starting at low concentrations, with moisturizers to reduce irritation, is advised for thick skin to improve the complexion.

In scenario 5, a daily cleanser is recommended after exposure to pollution during the day and other antioxidants may also be recommended to combat pollution.

For scenario 6, the experts did not reach a consensus after 2 rounds of discussions on whether AHA should be avoided for dark phototypes after ablative laser treatment. Glycolic acid has low molecular weight and can penetrate the dermis, causing irritation and risk of hyperpigmentation for phototypes IV to VI, in both men and women. Four out of 7 experts would avoid AHA (including glycolic acid) in FST IV to VI after ablative laser treatment due to the elevated risk of PIH. Two experts indicated that it would not be the most appropriate first option, but they would use it with caution, while one expert uses it regularly in FST IV to VI with caution, avoiding high concentrations and low pH. Salicylic acid, which is a beta hydroxy acid, has a larger molecular weight and may be less irritating as it does not penetrate the dermis, but was not considered to be appropriate after ablative laser treatment.

In scenario 7, AHA should be avoided at perimenopause when the skin has become more sensitive, especially if working outside.

In scenarios 7 and 8 for perimenopausal and menopausal women, botanical extracts with antioxidant effects may be recommended, but it will depend on the properties of the specific botanical extract. Cassia extract is an appropriate ingredient to combat the effects of the increase in cortisol in the skin at perimenopause.

DISCUSSION

As may be expected for young patients, such as in case scenarios 1 and 2, the pyramid base includes broad-spectrum sunscreen, antioxidants, and DNA repair, but no topical treatment for the top of the pyramid. In older patients, a consensus was rapidly reached that multiple ingredients are appropriate for perimenopausal and menopausal women, from protection and repair of the stratum corneum to epidermal correction and dermal protection advanced skin care. However, a consensus was not reached on whether AHA should be avoided after ablative laser treatment for dark phototypes at risk of PIH.

Photoprotection is fundamental for all scenarios and is the base of the pyramid. Broad-spectrum photoprotection with high SPF and high UVA PF are essential for all patients and should be adapted to skin phototypes and dermatoses, as previously described.[9] Protection against long UVA1 wavelengths is important as they penetrate more deeply and contribute to hyperpigmentation, photoimmunosuppression, photoaging, and photocancers.[10] Similarly, high-energy VL protection with tinted sunscreens containing iron oxides and/or pigmentary titanium dioxide is especially important for dark-skinned individuals as they are more sensitive to VL-induced pigmentary disorders.[11-13] Sunscreen technology differs by country with fewer sunscreen options in the US.[12] Generally, photoprotection is not always well adapted to darker phototypes as there is a large variation in constitutive skin tones between FST IV to VI, making it more difficult to find a good color match for tinted/iron oxide sunscreens to protect against VL. As an alternative for individuals (for example men) who find pigmented products cosmetically unacceptable, newer organic filters may offer some protection in the near visible region,[14] but tinted products containing pigments are still required to provide high protection against high energy VL to prevent pigmentary disorders.[13] Furthermore, although makeup has been found to offer no photoprotection,[15] a broad-spectrum sunscreen camouflage foundation containing a high concentration of iron oxides may offer high-energy VL protection.[16] For melasma, sunscreens should be broad-spectrum with high SPF, and provide high protection against UVA and VL. If the skin tone is not exactly matched, tinted pigmented sunscreens (containing iron oxides) in combination with camouflage foundation in a wider variety of colors can help match the skin tone of every patient while also masking pigmentary disorders and improving quality of life.[17]

Natural substances have been used in skin care for centuries and antioxidant botanical extracts are increasingly becoming alternatives to conventional, synthetic dermocosmetics.[18] Cassia extract is derived from a traditional medicinal plant and has antioxidant, antimicrobial, and anticancer effects.[19] Cassia extract has been reported to reduce the impact of cortisol, which increases in the skin at menopause, on collagen and hyaluronic acid synthesis to stimulate extracellular matrix synthesis.[19,20] C-xyloside is a cosmetic active ingredient derived from plants that has been shown to stimulate the synthesis of mucopolysaccharides in the dermis and epidermis to improve skin elasticity and tonicity.[21] As dermatologists are not always widely familiar with specific lesser-known extracts, there is a need for high-quality randomized controlled trials for dermocosmetics (and the active ingredients they contain) to make evidence-based recommendations.

Finally, a knowledge gap is the development of future recommendations on dermocosmetics as adjuncts for aesthetic procedures.

LIMITATIONS

The main limitation and bias of this study is the restricted panel size of international experts for the RAND/UCLA method. Other limitations of the method are the lack of ranking, resulting in variable scoring if a dermocosmetic was considered appropriate but not the first choice, or if appropriate but likely to be cosmetically unacceptable to the patient. Despite these limitations, the advantage of this simple approach is that it ensures only appropriate topicals are recommended for each specific patient type.

CONCLUSION

We describe a simple, practical tool for use in daily dermatology consultations that is adapted to specific patient needs, depending on age, sex, and skin phototype, and covers a diverse range of common skin issues. This work provides recommendations on anti-aging dermocosmetics with a worldwide consensus from experts to cover diverse and inclusive populations of patients, addressing all skin types and international needs. Appropriate dermocosmetics combined with complementary aesthetic procedures for each clinical scenario warrants further study to obtain optimal outcomes.

DISCLOSURES

ZD is a researcher and consultant for L' Oréal. LW, MS, BSFB, VV, MJ, and MK have received honoraria from L' Oréal. CD has no potential conflicts of interest to disclose. SLM is an employee of L'Oréal Group.

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ORIGINAL ARTICLE

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Revolutionizing Neck Rejuvenation: ABO Botulinum Toxin A Solution in Multipoint Technique and NASHA Gel Skinbooster

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ABSTRACT

Background: Neck rejuvenation is an increasingly sought-after cosmetic procedure that offers a versatile solution to address various aging-related concerns in the neck area. Because it is non-surgical, it is an appealing choice for both patients and practitioners. This protocol introduces a highly effective approach utilizing ABO Botulinum Toxin A solution and NASHA gel 12 mg/ml for neck rejuvenation, targeting patients with muscle hypertonicity and skin degeneration.

Materials and Methods: Patient selection is based on specific criteria. ABO Botulinum Toxin A solution is administered with tailored dosages and with a multipoint technique, followed by a structured NASHA gel skinbooster regimen. Precise injection techniques address muscle hypertonicity and improve skin quality. Follow-up appointments and personalized touch-up sessions maintain results.

Results: This is a minimally invasive, cost-effective approach with minimal downtime. ABO Botulinum Toxin A solution's precision and composition (efficacy) make it preferred. NASHA gel 12 mg/ml consistently enhances skin quality, providing tone, elasticity, hydration, and radiance. Gradual, long-lasting improvements boost patient satisfaction and confidence.

Conclusion: Physicians can expand their repertoire of treatment offerings with the combined use of ABO Botulinum Toxin A solution and NASHA gel 12 mg/ml for neck rejuvenation. This innovative approach aligns with ethical and environmental considerations, enhancing patient satisfaction and overall well-being. By learning and implementing this innovative protocol, aesthetic physicians can offer their patients a highly effective and sought-after (repetitioned) treatment option.

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BACKGROUND

Neck rejuvenation has consistently ranked among the most sought-after cosmetic treatments. This area of the body presents a confluence of aging-related concerns, including skin deterioration, weakened ligaments, displacement of adipose tissue, increased platysma tension, and alterations in the jawline due to bone changes. In instances where a more extensive surgical intervention becomes necessary to restore tissue positioning and address excess skin and fat, surgical procedures are typically recommended for critical cases. However, for individuals who either don't meet the criteria for surgery or opt against it, alternative approaches involving injection techniques offer the opportunity to target and address the various facets of the aging process in the neck region.

INTRODUCTION

Our protocol investigates neck rejuvenation using injectable treatments, namely ABO Botulinum Toxin A solution (Alluzience, Ipsen Ltd, Slough, UK/Galderma SA, Lausanne, Switzerland) and NASHA (non-animal hyaluronic acid) gel 12 mg/ml as a skin booster (Restylane® Skinboosters™, Vital Light lidocaine, QMED AB/ Galderma, Uppsala, Sweden). Cases characterized by significant skin laxity or pronounced subcutaneous fat accumulation in the submental region are deemed ineligible for this specific treatment approach.

This protocol is primarily intended for patients who exhibit concurrent skin degeneration and hypertonicity of the platysma and depressor muscles within the lower third of the face. Ideally, the most suitable candidates for this treatment are individuals for whom the predominant components of aging are muscle hypertonicity and skin degeneration.

The utilization of Abobotulinum Toxin A solution has gained prominence as a noteworthy therapeutic approach for its ability to interrupt muscle hypertonicity and modulate muscle contraction, obtaining an aesthetic improvement resulting from muscle relaxation. Each vial of the solution contains 125

Speywood units within a 0.625 ml solution, at a concentration of 200 u/ml. Significantly, the AboBoNT-A solution is characterized by its absence of excipients originating from either human or animal sources, instead incorporating a selection of meticulously chosen vegetable and synthetic excipients, preserving the toxin's activity while maintaining its liquid state. The composition of this formulation bears critical relevance to its clinical efficacy and safety profile.

Concurrently, NASHA gel has garnered considerable interest for its capacity to stimulate de novo collagen production within photodamaged skin, as substantiated by in vivo studies. When administered via injections, NASHA gel has demonstrated the potential to trigger collagen synthesis through a multifaceted array of mechanisms, encompassing the activation of growth factors, inhibition of collagen degradation, and mechanical stimulation of fibroblasts, wherein the latter mechanism holds particular significance.[1] The intrinsic capacity for endogenous synthesis of new extracellular matrix components presents a compelling avenue for influencing the magnitude and duration of clinical benefits conferred by dermal filler injections featuring crosslinked hyaluronic acid. Within this context, the sustained and progressive enhancements in skin quality, consistently documented within the medical literature following NASHA gel skin booster interventions, are plausibly attributable to the robust stimulation of collagen synthesis and the concurrent restoration of dermal matrix components.[2]

The efficacy of NASHA gel skin booster has been empirically validated when administered within a structured regimen of three sequential sessions, spaced at one-month intervals. This regimen has exhibited notable potential in enhancing skin elasticity, reducing cutaneous roughness, optimizing skin tone, augmenting skin hydration, mitigating fine lines, and ameliorating the appearance of atrophic scars. Such clinical findings have been recurrently upheld by an extensive body of scientific evidence.[1,3–8] These pivotal insights provide the fundamental basis for our comprehensive investigation into the integrated neck rejuvenation protocol presented, with a special focus on its clinical applications within the context of aesthetic medicine.

MATERIALS AND METHODS

Selecting the right patients is crucial as it greatly affects the success of the treatment. While the neck rejuvenation procedure could potentially apply to all patients, achieving optimal outcomes depended on carefully choosing patients based on specific criteria.

The treatment protocol follows a systematic, sequential approach. The initial step involves the administration of Abo Botulinum Toxin A solution (Alluzience, Ipsen Ltd, Slough, UK/ Galderma SA, Lausanne, Switzerland). The dosage of units administered should be tailored to individual indications. For patients exhibiting platysma hypertonicity, a basic treatment of 72 Speywood units is administered. In these cases involving (lateral and medial) hypertonic bands, a total of 36 units on each side is used. Additionally, for those with hypertonicity in the lower part of the neck, 24 units, 12 on each side, can be applied. Furthermore, patients with hypertonicity of the depressor anguli oris muscle and the mental muscle can be treated with 16 additional units, 8 units for each side, and 4 units for each muscle on each side. The dose ranges from 72 to 112 Speywood units. Patients are then scheduled for a follow-up appointment within a window of 15 to 30 days post-treatment. This initial session is subsequently repeated approximately every 6 months.

Upon completion of the Abobotulinum Toxin A sessions, patients are eligible to commence the neck rejuvenation protocol using NASHA gel 12 mg/ml as a skin booster. This phase consists of three sessions of NASHA gel, typically involving the use of 1 ml of NASHA gel as a skinbooster at a concentration of 12mg/ml (Restylane® Skinboosters™, Vital Light lidocaine, QMED AB/ Galderma, Uppsala Sweden) per session. Each session is repeated monthly for a total of three sessions. The administration of injections is facilitated by a specialized "smart click syringe," enabling precise delivery of 10 ul drops, typically totaling around 100 drops. Injections are carried out using a 29-gauge needle. In cases characterized by severe skin aging, a higher dosage of 2 ml per session can be considered.

To maintain the desired aesthetic outcomes, patients undergo touch-up sessions with NASHA gel 12 mg/ml as a skin booster every 4 to 6 months. NASHA gel has been shown in documented studies to have clinical effects such as improvement of skin elasticity, reduction in surface texture and roughness, improvement in skin firmness, hydration, reduction of fine wrinkles, and reduction in skin imperfections such as depressed acne.[9-15]

Hypertonicity typically becomes most apparent in specific facial and neck regions, primarily manifesting in the lower third of the face around the mandibular region and extending to the upper portion of the neck, including the sub-mandibular region. In these anatomical areas, excessive muscle contractions give rise to noticeable effects, such as a pronounced heaviness along the jawline, a dragging sensation of tissues downward, exacerbation of skin and tissue laxity, and deformation of the mandibular profile near the chin. Additionally, hypertonicity in these regions often corresponds with the emergence of platysmal bands on both the front and sides of the neck.

Conversely, skin degeneration tends to be more prevalent in the lower half of the neck, predominantly attributed to a combination of photoaging and chronological aging processes. The skin in this area undergoes gradual sagging, increased laxity, loss of tone

and elasticity, increased roughness, diminished radiance, and hydration, and the development of what are commonly referred to as "ring lines". This phenomenon is primarily attributable to prolonged sun exposure and the natural aging process.

Successful rejuvenation of the neck region with the administration of botulinum toxin requires a comprehensive understanding of patient selection, meticulous muscle identification, and precise execution of injection techniques.

Determining the appropriateness of patients is fundamental to the efficacy and safety of neck rejuvenation procedures with botulinum toxin. While the application of botulinum toxin holds promise for neck rejuvenation across a diverse patient population, ensuring that each patient aligns with specific criteria is paramount. This process involves a thorough assessment of individual characteristics, such as skin condition, muscle tone, and aesthetic goals, to ascertain suitability for the procedure.

In the lower third of the face, our focus is directed toward two pivotal muscles: the depressor of the angle of the mouth and the mentalis. These muscles, when hypertonic, can significantly contribute to aesthetic concerns. Additionally, within the neck region, heightened attention is placed on the platysma muscle, which often exhibits hypertonicity, therapy playing a central role in neck rejuvenation.

Achieving the desired outcomes while minimizing potential adverse effects necessitates a rigorous commitment to precision in the administration of botulinum toxin. This precision extends to both the prescribed doses and the designated injection points. Particular diligence is required when applying botulinum toxin in the sensitive areas of the lower third of the face and neck, making precise injection techniques even more imperative.

Effectively addressing the platysma muscle calls for a specialized technique that actively involves the patient. Patients are instructed to mimic an expression of disgust, a maneuver that aids in the identification of regions characterized by pronounced platysma muscle contraction. This contraction is particularly evident in the anterior and lateral platysmal bands, which play a pivotal role in neck aesthetics.

During muscle contraction, injections are initiated from the mandibular profile, proceeding in a top-to-bottom fashion according to the multipoint injection technique16 for the lower third of the face and the neck. Each intramuscular injection delivers 4 units of botulinum toxin and is strategically placed within the regions where the muscle contraction creates bulges near the mandibular ramus. These injections are thoughtfully aligned with the maximal emergence of the platysmal bands, both anteriorly and laterally.

During the phase when muscles contract, originating from the mandibular profile, a series of intramuscular injections, each delivering 4 units of botulinum toxin, is administered in a top-to-bottom manner. These injections are strategically positioned within the areas that bulge due to muscle contraction, closely situated to the mandibular ramus, and aligned precisely with the maximal emergence of the platysmal bands, both frontally and laterally.

The injection pattern follows a top-to-bottom approach. The number of injections varies based on the individual requirements of each patient. The guiding principle is to direct injections toward regions displaying the most pronounced muscle contraction, even when the asymmetry is observed between one side and the other.

For treating the depressor muscle at the corner of the mouth, patients are instructed to assume an expression conveying doubt or sadness. The injection is administered at the area of skin retraction, approximately 1 cm away from the labial corner (corner of the mouth) during contraction. Each side receives an intramuscular injection with a dosage of 4 units.

In the case of the mental muscle, patients are prompted to close their lips, resulting in the contraction of the mental muscle. The hypertonic areas in its medial portion are identified, and 1 to 2 intramuscular injections, each delivering 4 units are administered on each side.

Post-treatment precautions include avoiding exposure to heat sources for several days and scheduling a follow-up appointment between 15 and 30 days. During this visit, the neck rejuvenation protocol with Skinbooster can be initiated.

The NASHA gel as a skin booster is implanted using a "smart click syringe". The injection technique involves a retrograde approach in the deep dermis or superficial subdermis. Injections are carried out along the jawline and the horizontal lines of the neck. It is imperative to employ the correct injection technique to avoid injecting too superficially, which could lead to the formation of micro-bumps. After the treatment, no visible or palpable bumps should remain. Some minor bruising may occur but typically resolves within a few days. Sun exposure should be avoided for approximately one-week post-treatment. The treatment is repeated every month for a total of three sessions, with results improving progressively. Long-lasting results consolidate over time, and touch-up sessions are recommended every 4 to 6 months.

FIGURE 1. Patient treated with Abobotulinum toxin 125 solution US SPEYWOOD Nasha Skin Booster 12mg/ml in 3 sessions. *(Photos by Ivano Iozzo).*

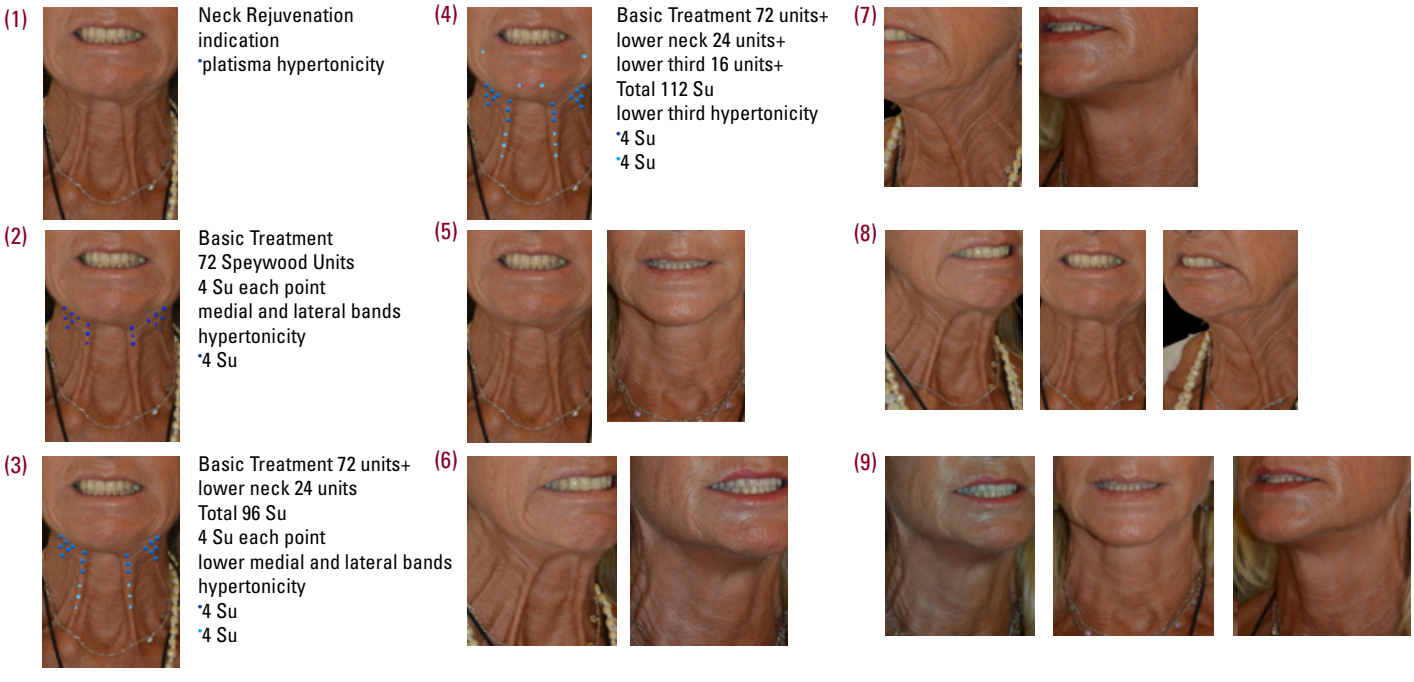


FIGURE 2. Abobotulinum toxin 125 solution US SPEYWOOD NASHA SKIN BOOSTER 12mg/ml in 3 sessions. (A) Before; (B) After 1 session 2 mL Nasha Skin Booster 12 mg/mL; (C) After 2nd session 2 ml Nasha Skin Booster 12 mg/ml; (D) After 3°rd session 2 ml Nasha Skin Booster 12 mg/ml.

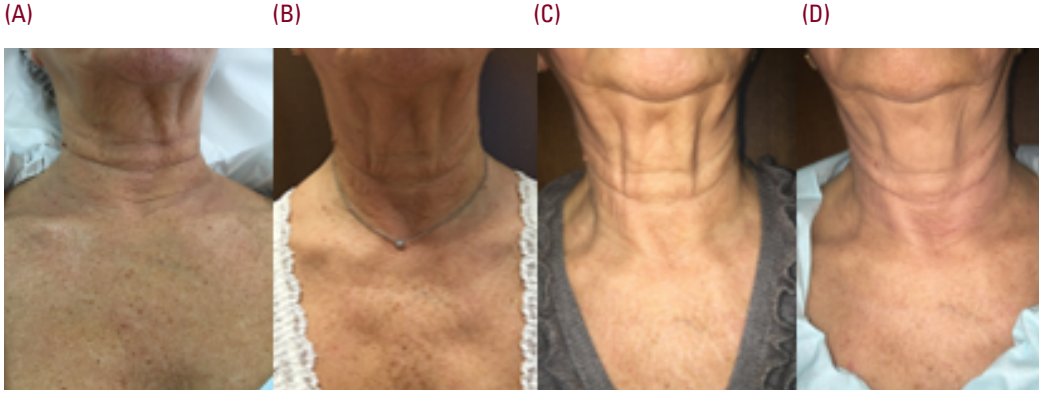
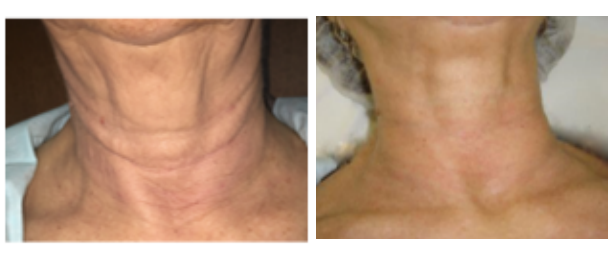


FIGURE 3. 125 US Speywood Abobotulinum toxin solution plus Nasha Skin Booster 12 mg/ml - 2 ml x 3 sessions (at 1 month). (A) Basic; (B) After complete protocol. (*Photos by Dr Magda Belmontesi*).



RESULTS

Neck rejuvenation through injectables offers a remarkable therapeutic approach that places a strong emphasis on patient well-being and satisfaction. It stands as a minimally invasive, swift, and virtually downtime-free procedure, delivering not only outstanding results but also a sense of convenience and ease to patients. This non-energy-based method is not only well-tolerated but also cost-effective. The enduring nature of the results, which progressively improve over time, is a significant benefit. Moreover, patients often report an enhancement in their psychological well-being, expressing increased happiness and self-assuredness.

The Abobotulinum Toxin A solution garners patient preference, not just for its precision and performance, but also for being free from any animal or human components. The fact that it is manufactured in an environmentally sustainable facility resonates with patients who value both the outcome and the ethical aspects of the formulation.

The use of NASHA gel 12 mg/ml as a skin booster serves as a powerful tool for elevating skin quality, restoring tone, enhancing elasticity, deepening hydration, and illuminating the skin with a radiant glow. Patients hold this treatment in high regard, recognizing it as an effective and transformative skin therapy, ultimately contributing to their overall well-being and satisfaction.

CONCLUSION

The combined approach of Abobotulinum Toxin A liquid and gel NASHA 12 mg/ml as a skin booster emerges as a powerful, patient-centered protocol for non-invasive neck rejuvenation. It is important to underscore that patient selection plays a pivotal role in this journey, ensuring that individual needs and aspirations are met to their utmost satisfaction.

DISCLOSURES

No funding or sponsorship was received for this study or publication of this article.

Dr. Ivano Iozzo, Dr Magda Belmontesi, Dr Carlo Digregorio, Dr Matteo Tretti Clementoni and Dr Valentina Angela Antonucci have no financial interests to disclose.

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ORIGINAL ARTICLE

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Optimized Patient Outcomes With the Novel Modality of Corrective Chemical Peel and Neurotoxin on Sameday Treatment

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ABSTRACT

Background: This study was conducted to improve standards of care in the cosmetic treatment of sun damage, fine lines, and wrinkles. Chemical Peels and Neurotoxins have been traditionally used cosmetically as monotherapies. This study aimed to confirm that the same day combination created no additional side effects while also improving outcomes.

Methods: The multi-generational study enrolled 30 patients with Fitzpatrick I-VI representation. The Roberts Skin Type Classification System was used to establish baseline patient information. Patients were treated with a VI Peel®, followed by Botox®. Objectively, photographic matching, Wrinkle Severity Scale, Uniformity of Pigment Scale, and Skin Tone Scales were used to evaluate skin improvement. Patient questionnaires were issued to assess satisfaction.

Results: Safety of the same day combination was established with no adverse events reported. Improvements on the Wrinkle Severity Scale showed an average rating dropping from 1.46 to 0.59 representing a 60% improvement. Improvements on the Uniformity of Pigment Scale showed an average rating dropping from 2.27 to 0.92 representing a 59% improvement. Improvements on the Skin Tone Scale showed an average rating dropping from 2.35 to 0.71 representing a 70% improvement. Questionnaires correlated with objective findings with high satisfaction.

Conclusion: This study confirmed the safety of the same day combination. Efficacy of VI Peel & Botox same day treatment was clinically proven by the improvements to Wrinkle Severity, Uniformity of Pigment, and Skin Tone via photographic matching. While perception studies indicated strong patient satisfaction with the combination.

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INTRODUCTION

The medical aesthetics industry is a high-growth industry slated to reach 18 billion by 2027. This growth is primarily driven by minimally invasive and non-invasive cosmetic procedures according to All the Research 2020 Report.[1]

The top 5 most performed minimally invasive therapies reported by the American Society of Plastic Surgeons include Botulinum Toxin Type A, Soft Tissue Fillers, Chemical Peels, Laser Skin Resurfacing, and Intense Pulsed Light treatments comprising over 13 million patient visits in 2020.[2] The diversity in the market continues to also evolve with not only a greater percentage of men receiving cosmetic treatments but also growth in familial aesthetics with grandparents, parents, and their adult children seeking both preventative and corrective care. As the aesthetic market continues to grow, advancements in optimal care have also evolved.

This study was conducted to improve standards of care in the cosmetic treatment of sun damage, fine lines, and wrinkles. Chemical Peels and Neurotoxins have been used cosmetically to improve patient concerns as monotherapies. This study aimed to confirm that the same day treatment combination creates no additional side effects, and that patient results and satisfaction are heightened as a result.

Collagen degradation and wrinkling of the skin are caused by multiple intrinsic and extrinsic factors. Addressing wrinkling in the skin is often accomplished by reducing muscle contractions with the aid of neurotoxins as well as the use of chemical peels to improve skin elasticity, stimulate collagen regeneration, and textural refinements.

Trials on chemical peels and botulinum toxin are vast, but research on the combination of the two therapies is minimal. One study published in 2006 by Marina Landau, MD, addressed the combination with the inclusion of both staggered and same day treatments.[3] The findings indicated safety of same day applications if only superficial and medium depth chemical peels were used in treatment.

OBJECTIVE

This study utilizes mechanisms of action of both products to simultaneously address fine lines and wrinkles. VI Peels contain a synergistic blend of acids that produce keratolytic and keratocoagulant qualities focused on desquamation and cellular renewal. The VI Peel blend contains Phenol, Trichloroacetic Acid, Salicylic Acid, Retinoic Acid, and Ascorbic Acid. Botox containing Botulinum toxin type A is a purified substance, derived from a bacterium that blocks muscular nerve signals temporarily preventing muscular contraction and subsequent wrinkle formation.

The expected benefit of this investigational combination includes improvements to Standards of Care in relation to the treatment of the cosmetic patient by establishing safety of the combination treatment, improving patient outcomes by simultaneously addressing photodamage, fine lines, and wrinkles through dual mechanisms and an overall improvement to patient satisfaction.

MATERIALS AND METHODS

Botox and VI Peel have been used successfully since 1989 and 2005 respectively with millions of visits annually for these treatments. VI Peels were selected due to consistency in outcomes but also because the blend of acids contains Phenol, Salicylic Acid, and Retinoic Acid. These acids possess antimicrobial qualities and a pH range of 1.0-2.0. In addition, Phenol's keratocoagulant and anesthetic qualities assist in preparing the skin for neurotoxin injections. Botox was selected as the neurotoxin due to its long-standing use in the industry. In this study, a maximum of 50u was allotted per patient and was injected per label indications to the glabella, frontalis, and/or orbicularis oculi. Discretion was given to the Principal Investigator on the number of units and locations required for each subject.

Studying these therapies as a same day treatment required defining the study population, delineating the treatment protocol, and producing clear outcome measurements.

Schedule of Events

The Schedule of Events listed in Table 1 below identifies the interaction points and identified data collection, intervention, and timeline of events. With uncertainty due to COVID, the researchers compressed informed consenting and day 1 visits into one visit. Subsequent visits allowed for ±3 day variance to allow for scheduling needs.

Study Population

The study enrolled 30 healthy subjects ranging in age from 30–70 years old. Four subjects' screens failed based on exclusion criteria. Of the 26 enrolled subjects, 24 completed the study in its entirety and two were lost to follow up. Enrolled subjects encompassed both men and women of varying race, ethnicity, and skin concern. While enrolled subjects were required to avoid soft tissue filler, medium to deep chemical peel, ablative laser, radio frequency treatment, ultrasound device treatment, and non-ablative laser treatment. The study duration upon completion of enrollment was 30 days.

Interventions

Visit 1 included a thorough investigator assessment via Case Report Form and included The Roberts Skin Type Classification System, Wrinkle Severity Scale, Uniformity of Pigment Scale, and Skin Tone Scale.

Subjects then completed a questionnaire via Survey Monkey. Baseline photographs taken forward facing, 45 degrees (Left and Right) and 90 degrees (Left and Right). The subject's face was cleansed and degreased with acetone. The VI Peel was applied according to protocol with an average of 5-6 layers applied at 1-minute intervals. Botox was then immediately administered according to label protocol. Subjects were monitored for 15

TABLE 1.

Schedule of Events				
Schedule of Events	Days from Baseline or Baseline Day 1	Baseline Day 1 Treatment	Day 7 ± 3 Days Follow Up	Day 30 ± 3 Days End of Study
Informed Consent	X	--	--	--
Inclusion / Exclusion Criteria	--	X	--	--
Demographics	--	X	--	--
Vital Signs	--	X	--	--
Medication Review	--	X	--	--
Facial Photos	--	X	X	X
Treatment VI Peel	--	X	--	--
Treatment Botox	--	X	--	--
Collect AEs	--	X	X	X
Questionnaire	--	X	X	X

FIGURE 1. 68-year-old female before (1A), after 7 days (1B), and after 30 days (1C).

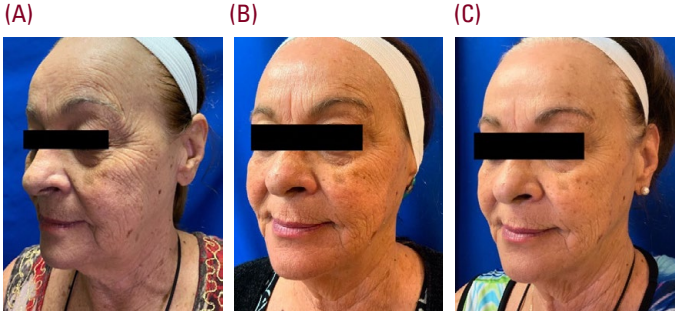


FIGURE 2. 53-year-old female before (2A), after 7 days (2B), and after 30 days (2C).

FIGURE 3. 46-year-old female before (3A), after 7 days (3B), and after 30 days (3C).

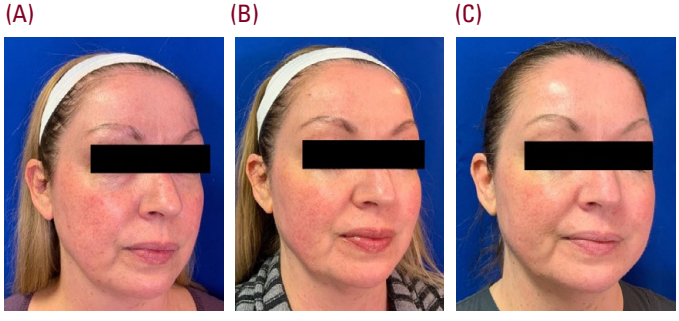
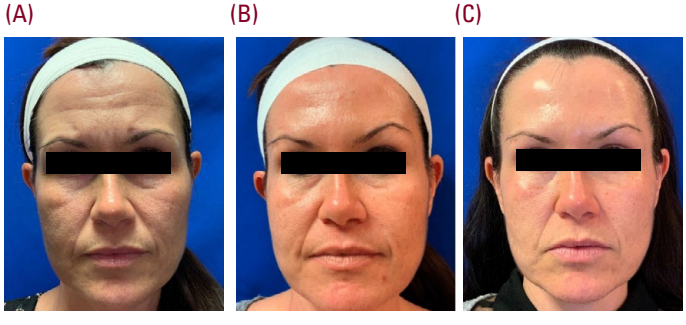


FIGURE 4. 38-year-old female before (4A), after 7 days (4B), and after 30 days (4C).



minutes after treatment to assure safety including allergic reactions. Subjects were given a take-home post peel kit along with verbal and written aftercare instructions.

Visit 2 (7 days) included an investigator reassessment of skin and skin response, completed Case Report Form, and completed 2nd set of photographs as stated above. Subject Perception Survey completed via Survey Monkey.

Visit 3 (30 days) followed the same flow as Visit 2.

Upon conclusion of the study, subjects were given a cleansing maintenance kit of 4 VI Derm topical skin care products.

Data

Data was analyzed based on subject demographics, investigator assessments, photographic matching, and subject questionnaires. Clinical data points in the results section will measure the rate and occurrence of side effects and/or adverse events as well as improvements to skin conditions. Antimicrobial ingredients in the VI Peel proved to be a proper antibacterial cleanse prior to botulinum toxin injection eliminating the need for additional alcohol, Puracyn, or Hibiclense.

Investigator baseline assessment was determined via The Roberts Skin Type Classification System. The four elements of the classification system include Fitzpatrick Skin Type (measures phototype), Roberts Hyperpigmentation Scale (propensity for pigmentation), Glogau Scale (defines photodamage), and Roberts Scarring Scale (describes scar morphology).[4] The four-part scale established baseline information on the study population as well as contributed to the demographic allocation of subjects.

Photographic Matching by Investigator includes data points from visits 1, 2, and 3 for Facial Wrinkle Severity Scale, Uniformity of Pigment Scale, and Skin Tone Scale. Photographs were taken with every visit encounter and included forward-facing, 45 degree left, 90 degree left, 45 degree right, and 90 degree right. Wrinkle Severity Scale: Grade 0= No Wrinkles, Grade 1 = Mild Wrinkles, Grade 2 = Moderate Wrinkles Grade 3 = Severe Wrinkles.

Uniformity of Pigment: Grade 0 = Uniform, Grade 1 = Mild, Grade 2 = Moderate, Grade 3 = Moderate to Severe, Grade 4 = Severely Ununiform.

Skin Tone: Grade 0 = Clear and Radiant, Grade 1 = Mild Irregularities, Grade 2 = Moderate Irregularities, Grade 3 = Moderate to Severe Irregularities, Grade 4 = Severe Irregularities. Subject Questionnaires were issued via Survey Monkey and included data points from Visits 1, 2, and 3. Surveys included

personal ratings of skin health as well as general satisfaction levels with the intervention. Subjects were provided QR codes to complete surveys at the start of each encounter. If the subject was unable to utilize the QR code, a paper form of the survey was provided.

RESULTS

Safety of the same day combination of VI Peel & Botox was established. There were no reports of adverse events or significant adverse events. Side effects reported were in-line with the rate of occurrence of each intervention as a stand-alone treatment. The most commonly reported side effect noted with the same-day combination was dryness in the perioral area from the VI Peel and bruising on the lateral canthal lines from the injection of Botox. Dryness after chemical peels is a common side effect that self-resolves.[5] Bruising after injection from Botox is the most commonly reported side effect that self resolves.[6] All reported side effects self-resolved within the 30-day study duration.

Improvement to the following scales was established via use of investigator subject assessment and photographic matching. Both assessments were completed after establishing the subject baseline status on day 7 and day 30 (Table 2).

Wrinkle Severity

On average, the subject baseline was 1.46 on the Wrinkle Severity Scale indicating Mild to Moderate wrinkles. On day 7, the average rating dropped to 0.92 indicating a 37% improvement and overall Mild Wrinkles. On day 30, the average rating continued declining to 0.59 indicating an additional improvement of 36% and overall grading of No Wrinkles. Overall scale improvement averages showed improvement at 60% and scale improvement from 1.46 to 0.59 over 30 days.

Uniformity of Pigment

On average, the subject baseline was 2.27 on the Uniformity of Pigment Scale indicating Moderate pigment irregularities. On day 7, the average rating dropped to 1.42 indicating a 37% improvement and overall Mild Pigment Irregularity was noted. On day 30, the average rating continued declining to 0.92 indicating an additional improvement of 35% and overall grading of Uniform Pigment. Overall scale improvement averages showed improvement at 59% and scale improvements from 2.27 to 0.92 over 30 days.

Skin Tone Scale

On average, the subject baseline was 2.35 on the Skin Tone Scale indicating Moderate to Severe Irregularities. On day 7, the average rating dropped to 1.04 indicating a 56% improvement and an overall drop to Clear and Radiant. On day 30, the average rating continued declining to 0.71 indicating an additional improvement of 32% and maintenance at the Clear and Radiant grade. Overall scale improvement averages showed improvement at 70% and scale improvements from 2.35 to 0.71 over 30 days.

Subjective Data Population Analysis: The study participants represented not only a 4-Decade span in age but also represented a broad range of races and ethnicities. Typically underrepresented in clinical studies, this study comprised of 69% Skin of Color and included men and women of varying ethnicities. 77% of respondents had never had a chemical peel, 58% of respondents had never had Botox before, and 100% had

TABLE 2.

Objective Data Results

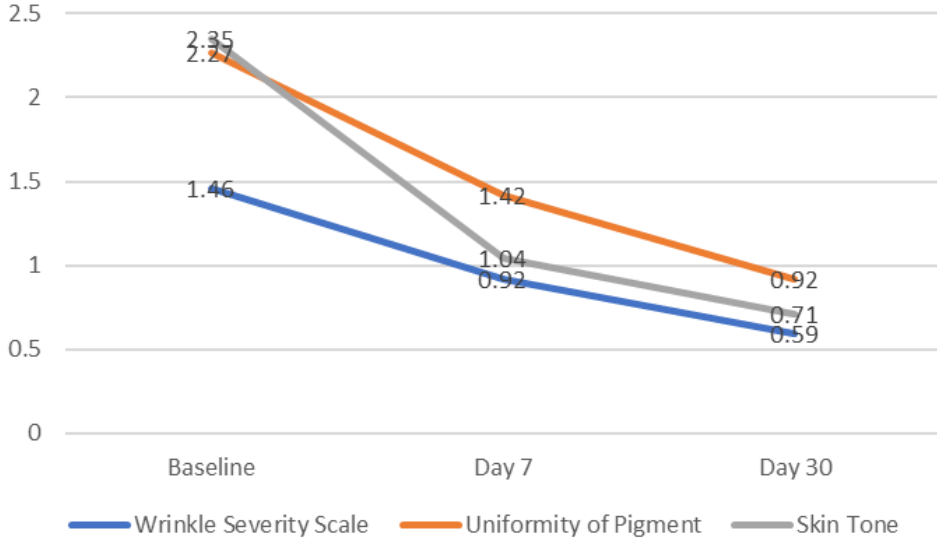
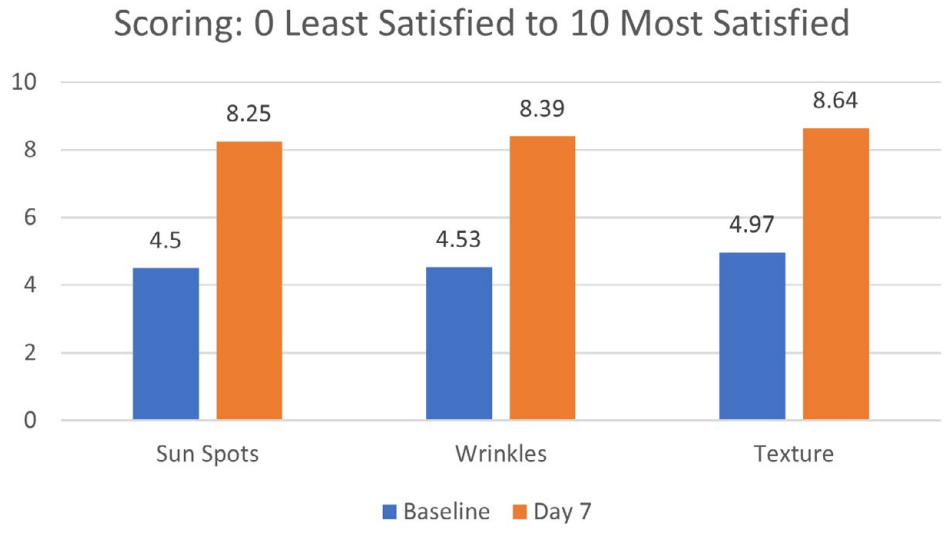


TABLE 3.

Subject Data Results



never had the VI Peel & Botox combination. Of the population 42% reported Dry Skin, 46% reported Combination Skin, 4% reported Normal Skin, 4% reported Oily Skin, and 4% reported Oily/Combination Skin.

Subjective Data & Perception Outcomes: Data obtained via subject surveys was analyzed both on individual survey responses and in comparison, with previous survey responses. Surveys were issued to subjects during their initial visit and on subsequent visits. Surveys focused on the subject's satisfaction with multiple aspects of their skin. A 10-point scale was used with 1 being least satisfied and 10 being most satisfied for the number of sunspots, number of fine lines & wrinkles as well as smoothness of texture. Table 3 provides results from subjects at baseline and day 7 with consistent increases on all 3 metrics. Satisfaction rating on number of sunspots increased by 83%. Similar results were seen with satisfaction with number of wrinkles increasing by 85% and texture increasing by 74%.

Upon the final survey, 96% of respondents were likely to repeat the treatment and 100% of respondents felt their skin looked better after having the combination of VI Peel and Botox.

DISCUSSION

Upon conclusion of the study, several unique findings and applications of this combination emerged. The objectives of the study were met in that safety of the same day combination was met along with significant improvements to photodamage, fine lines, and wrinkles but additional applications and findings grew with the analysis of the data.

Generational Diversity

According to ASPS, the 40-54-year-old bracket is the largest group receiving minimally-invasive procedures at 5.4 million.[2] By adding in the next younger (30–39-year-old) and the next older (55–69-year-old) age bracket, the number of minimally-invasive treatments in this group nearly doubles this total with another 5.0 million treatments. Regarding generational appeal, the study found significant improvements not only for those over fifty but also for those in their 30s and 40s. The future patients in aesthetics are the sons and daughters of the current generation. Providing a safe and effective treatment that offers generational appeal allows practitioners the ability to offer universally appropriate interventions for their growing patient base. The novel combination also reduces the "aging out" of viable cosmetic intervention offerings with a simple but impactful treatment.

Skin of Color

Remarkably, the study participants were predominantly Skin of Color with safety being of utmost concern. Patients of color carry a greater risk of hyperpigmentation from chemical peeling as well as many other aesthetic interventions. The results of the study clearly showed the safety of not only the VI Peel but also the same day combination with Botox. This population of patients is growing within the United States and by 2050 over half of the population will be Skin of Color expanding safe treatment methodologies for this group.[7] Outside of clinical risk factors associated with this demographic, the study engaged and allowed for adequate representation of varying races and ethnicities which are often underrepresented even in direct-to-consumer communications.[8-9]

Practice Efficiencies

Non-Invasive interventions comprise 53% of all cosmetic treatments provided in 2020 according to the latest report from Global Medical Aesthetics Markets.[10] As previously mentioned, botulinum toxin and chemical peels remain respectively the top first and third non-invasive treatments. The intervention of VI Peel & Botox occupied less than 30 minutes of clinician time and produced a clinically significant impact on patient outcomes. For the aesthetic patient, the combination falls under a minimal financial investment with a maximum service value. While for the practice, the combination addresses the aesthetic patient's needs with little impact on provider time thereby increasing provider access, efficiency, and a service that can now safely be delegated.

CONCLUSION

Achieving outcomes for the aesthetic patient interested in Anti-Aging and beautification begins with establishing safe care practices throughout aesthetics and dermatology. This study solidified the safety of the same day combination of VI Peel & Botox as there were no adverse events or significant adverse events and side effects were minimal and consistent with incidence rates of the individual treatment as a stand-alone intervention. VI Peel prepped the skin and provided the antiseptic cleanse needed before the botulinum toxin injections. Although this study focused on Botox, the same protocol can be used with other FDA-approved botulinum toxins.

Additionally, this study engaged subjects ranging in race and ethnicity with over 69% of subjects identifying as Skin of Color and at a higher risk of developing Post-Inflammatory Hyperpigmentation of which there was no incidence.

With safety established, the outcome for the consumer is highly evidenced by the photographic matching of before and after on day 7 and again on day 30. Further established clinically by the improvements in Wrinkle Severity at 60% overall improvement, Uniformity of Pigment at 59% improvement, and Skin Tone at 70% improvement. Addressing photodamage and wrinkles with the novel combination achieves outcomes for both primary and secondary conditions simultaneously. Of particular use for those in the Sunbelt states of California, Arizona, Texas, and Florida with inherent year-round sun exposure can lead to the development of photodamage and wrinkle formation.

The clinical significance of this combination will appeal multi-generationally to patients where anti-aging and skin health remain at the forefront of their buying habits. The perception studies indicated strong satisfaction with the combination with 100% of respondents agreeing that their skin looks better after the combination of VI Peel & Botox.

Introducing novel standardized treatments in the aesthetic space not only allows for safer more effective treatments but engages consumers with results that continue weeks beyond the initial intervention.

DISCLOSURES

Wendy Roberts has no conflicts of interest to declare. Nancy Miller is also employed by the Vitality Institute study sponsor. Statement from Nancy Miller: "I had full access to all of the data in this study and I take complete responsibility for the integrity of the data and the accuracy of the data analysis."

Sponsor: Vitality Institute Medical Products

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CASE REPORT

Journal of Drugs in Dermatology

Post-Hyaluronic Acid Filler Reaction Treated With Abrocitinib: A Case Report

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ABSTRACT

Post-hyaluronic acid filler nodules are an uncommon, unpredictable complication that presents a challenge to clinical therapy. We report a case of a female in her fifties who developed edema and nodules 6 weeks after hyaluronic acid (HA) filler injection. After minimal improvement with oral steroids and intralesional hyaluronidase, a trial of oral abrocitinib was initiated, which yielded significant clinical improvement. Thus, abrocitinib may be a novel therapeutic option for delayed onset nodules following injection of hyaluronic acid.

J Drugs Dermatol. 2024;23(1):1355-1356. doi:10.36849/JDD.7271

INTRODUCTION

The use of soft tissue fillers is an increasingly popular means of rejuvenation; it was the second most common minimally invasive cosmetic procedure worldwide in 2020.[1] Although fillers have a favorable safety profile,[2] adverse events may still occur. One such event is the occurrence of delayed onset nodules. Although more common with permanent fillers such as polymethylmethacrylate or silicone, nodules have also been reported with non-permanent hyaluronic acid fillers.[3-4]

Historically, the risk of delayed onset nodules in the hands of a well-trained injector is low[2,4–6] with the incidence for granulomatous reactions ranging from 0.02%–0.4%.[7] However, there is a reported increase in nodule formation with the use of newer fillers with proprietary cross-linking technology.[8–11]

Recent publications suggest that targeting the Janus kinase (JAK) and signal transducer and activator of transcription (STAT) pathway decreases inflammation, leading to disease improvement in granulomatous diseases. One such medication is abrocitinib, a JAK inhibitor approved in the US for the treatment of refractory, moderate to severe atopic dermatitis in adults.[12] In this case report, we document clinical improvement of delayed onset nodules from filler with the use of oral abrocitinib.

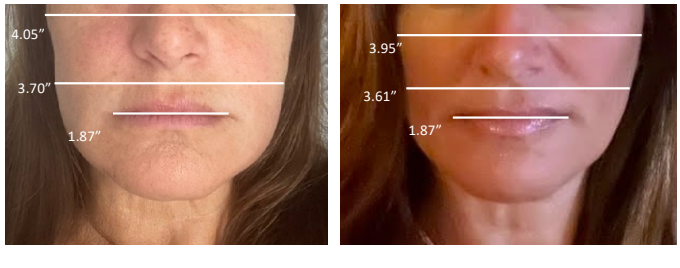
CASE REPORT

A 55-year-old woman presented with a chief complaint of swelling over her cheeks and jawline 6 weeks after hyaluronic acid filler injections (Juvederm Voluma®) to her zygomatic arches. The patient reported previous hyaluronic acid filler injections without complications. Past medical history included atopic dermatitis particularly affecting her face, as well as Hashimoto's thyroiditis. Prior to consulting dermatology, the patient underwent three courses of oral antibiotics (cephalexin, amoxicillin clavulanate, and clarithromycin) as well as two separate week-long courses of a methylprednisolone taper. She reported rapid improvement during steroid therapy but with rebound swelling upon completion of each taper. Concomitantly, five courses of hyaluronidase injections were also attempted, which softened and decreased the size of some but not all of the nodules. Oral antihistamines were of no benefit.

On physical examination, the patient had erythematous patches on bilateral eyelids and malar cheeks, mild swelling of the zygomatic arches and lower cheeks, and multiple firm, palpable nodules of varying sizes over the upper, mid, and lower cheeks. The patient also had dermographism at the time of her visit, and eyelid swelling.

After baseline examinations to rule out active infection, the patient was started on abrocitinib 100 mg/tab daily, fexofenadine (Allegra) 180 mg/tab twice daily, and fluticasone 0.0005% ointment for pruritus. The patient reported marked

FIGURE 1. 55-year-old female develops swelling and palpable nodules in zygomatic arches and submalar cheeks subsequent to Juvéderm® Injectable Filler. (A) Before Cibinqo treatment, 2.17 and 1.98 ratios of mouth to width of the face at zygomatic arches and submalar cheek, respectively. (B) After 2 months on Cibinqo, 2.11 and 1.93 ratios of mouth to width of the face at zygomatic arches and submalar cheek, respectively.



improvement in itch and reduction in swelling within 14 days of starting the abrocitinib. At the 2-month follow-up, the edema had resolved with further improvement in some of the nodules as well as pruritus (Figure 1). There was visible reduction in the width of the patient's face and swelling at both the zygomatic arches and in the submalar regions of her face (Figure 1).

DISCUSSION

Late onset nodules post-filler injections are an uncommon and unpredictable complication. The pathophysiology for this phenomenon remains unclear – multiple mechanisms have been implicated including protein impurities left over from the bacterial fermentation process[9] and biofilm formation.[7,13] Recently, it has been proposed that the breakdown of the cross-linking components used to stabilize the filler may lead to an immunologic reaction and subsequent granuloma formation.[8,10,11,14]

Although nodules may resolve over time without intervention, the typical standard of care for persistent nodules includes oral and intralesional steroids, antibiotic therapy, and hyaluronidase injections. Other novel measures to manage nodules include the use of lasers[15] as well as energy based devices.[16] Definitive management of recalcitrant nodules includes surgical removal or incision and drainage.[2,7]

Abrocitinib reversibly inhibits the Janus kinase 1 (JAK1) enzyme by blocking the adenosine triphosphate binding site.[12] JAK inhibitors have been shown in recent reports to reduce inflammation and granuloma formation.[17,18] In an open-label clinical trial (n=15), 10 patients with cutaneous sarcoidosis demonstrated marked improvement in their skin, and even complete response (n=6), after 6 months of tofacitinib 5 mg twice daily.[19] Similarly, significant improvement was seen in 5 patients on tofacitinib for severe, recalcitrant granuloma annulare.[20] Tofacinitib is also a therapeutic option for ulcerative colitis, gaining FDA approval in 2018. Other considerations included the patient's desire for medical management as well as ease of oral intake. Abrocitinib has a low incidence of adverse effects, including hematologic toxicity and dose-dependent lipid abnormalities.

CONCLUSION

JAK inhibitors offer a promising targeted treatment for granulomatous disorders. However, to our knowledge, the use of JAK inhibitors for reactions to fillers has not been documented in the literature; thus, our case offers unique insight and the potential to expand our therapeutic armamentarium. Its oral route and short half-life make JAK-1 inhibitors an appealing novel therapeutic option. The study of its use in granulomatous diseases can progress our understanding of its therapeutic potential.

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DISCLOSURES

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BRIEF COMMUNICATION

Journal of Drugs in Dermatology

The 200-Year Timeline on Botulinum Toxin: From Biologic Poison to Wonder Drug

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ABSTRACT

The history of botulinum toxin dates back to the late 1700s, when food preparation, storage, and later canning practices led to outbreaks of botulism across Europe and the United States. It is from these initial incidents that the remarkable discovery of botulinum toxin was eventually made, sparking over 200 years of further scientific inquiry and medical innovation. To date, 6 botulinum toxin products have been commercialized in North America with numerous indications across the specialties of ophthalmology, neurology, urology, dermatology, plastic surgery, and otolaryngology. This article traces the key moments and important players in the remarkable journey of this biologic poison and wonder drug.

J Drugs Dermatol. 2024;23(1):1357-1359. doi:10.36849/JDD.7288

INTRODUCTION

The global medical botulinum toxin market is currently valued at 5.8 billion USD and is expected to rise to 15 billion USD by the year 2030.[1] From its beginnings as a deadly food-borne toxin, botulinum toxin (BoNT) has had a revolutionary journey to its current powerful and versatile iteration, with indications for numerous cosmetic and medical applications.[2-4] As future strides are made in novel uses and approvals for BoNT,[5-7] it is worth remembering the historical foundation on which we stand, from the isolation of the toxin to the remarkable experiments that ultimately led to its pervasive medical use, summarized in Table 1.

Commentary

The history of BoNT can be viewed as four distinct transformational stages:

1) Outbreaks of food poisoning led to the seminal discovery and isolation of the toxin (1793 – 1920s)

From the late 1700s to the early 1900s, multiple food-associated epidemics occurred across Europe and the United States of yet unknown cause, with numerous fatalities. Through experiments on animals and himself, Dr Justinius Kerner of Germany was the first to surmise the ultimate source of a sausage-poisoning epidemic was a biologic toxin acting on nerve signals to cause multi-organ and respiratory failure.[8] Later on, Emile Pierre-Marie van Ermengem in Belgium identified Clostridium botulinum as the bacteria producing the exotoxin, and Dr Hermann Sommer of the US isolated the first crude form of botulinum toxin type A (BoNT-A).[9]

2) Threat of BoNT use in biological warfare (1940s–1970s)

After the bombing of Pearl Harbor by the Japanese in World War II, the US government placed increased attention on the covert study of wartime threats for offensive and defensive reasons, including the study of lethal toxins and biological agents, due to fears that the Germans were weaponizing such toxins and agents against Americans. A team of scientists including Carl Lamanna, Arthur Guyton, and Edward Schantz worked jointly at the U.S Biological Warfare Center to culture the first purified stores of BoNT-A and further study its physiologic effects in humans. When fears of the Germans using weaponized botulinum toxin were proven to be unfounded, the Americans abandoned the study of the use of the toxin for warfare.[10-11] At the end of World War II in 1945 when the covert toxin experimentation concluded at Camp Detrick, Dr Schantz became the custodian for the remaining stores of purified BoNT-A. Starting in the 1950s and throughout his career after leaving Camp Detrick in 1972, he shared the toxin with qualified physicians and scientists for research purposes, sparking the next stage in the history of botulinum toxin.[9] Dr Arnold Burgen in the UK, Dr Vernon Brooks in Canada, and Dr Daniel Drachman in the US performed separate experiments to collectively elucidate the effect of BoNT on neuronal synaptic terminals and its ultimate denervation of muscles through the neuromuscular junction.[12-15]

3) Animal and human clinical trials spearheaded by ophthalmologist Dr Alan Scott (1972 – 1989)

Dr Alan Scott, an ophthalmologist and researcher at the Smith-Kettlewell Eye Research Institute in San Francisco who had been working since the 1960s to find a novel surgery-sparing therapeutic to treat strabismus, learned of the effect of botulinum toxin on muscles and requested samples of BoNT-A from Dr Schantz.[9] After successful results in Rhesus monkeys, Dr Scott published his breakthrough primate research in 1973.[16] This research ultimately led to Food and Drug Administration (FDA) approval of the first human clinical trial of BoNT. In 1978, Dr Scott became the first to inject medicinal botulinum toxin

TABLE 1.

Key Moments in the History of Botulinum Toxin From 1793 – 2021	
Factor	**Score**
1793	Outbreak in Wildbad, Germany. Six people die from botulism poisoning associated with blood sausage.
1822	Justinius Kerner, a physician in Germany, performs animal experiments and deduces that botulinum toxin acts by interrupting nerve signal transmission.
1895	Three musicians die from botulism in Ellezelles, Belgium after eating raw ham.
1895-1897	Professor Emile Pierre-Marie Van Ermengem from University of Ghent identifies Clostridium botulinum in ham.
1919-1920	Food poisoning deaths from California-produced black olives occurring in Ohio, Montana, Michigan, Tennessee, and New York.
1926	Dr Hermann Sommer isolates a crude form of botulinum toxin.
1943	US chemical warfare research facility established at Camp Detrick in Frederick, Maryland.
1943-1946	Carl Lamanna purifies botulinum toxin A at Camp Detrick.
1943-1946	Arthur Guyton develops evidence of how botulinum toxin affects acetylcholine at the neuromuscular junction.
1947	Dr Schantz prepares and maintains a pure culture of botulinum A toxin.
1950	Dr Schantz begins sharing toxins for research and food safety purposes. This continues until 1994 when the supply was exhausted. Dr Schantz would provide botulinum toxin A to 150 researchers worldwide.
1950s-1960s	Drs Arnold Burgen, Vernon Brooks, Dan Drachman separately carry out experiments to describe the effect of botulism on muscle.
1961	Dr Alan Scott, a young ophthalmologist at the Smith-Kettlewell Eye Research Institute in San Francisco, California, begins studying the extraocular muscle in humans and animal models.
1971	Dr Schantz retires as Chief of Fort Detrick Lab. He takes botulinum A culture with him to his new post at the Food Research Institute at the University of Wisconsin-Madison and continues as the custodian of the toxin.
1972	Dr Scott contacts Dr Drachman and upon his advice, receives botulinum toxin A culture from Dr Schantz and injects the extraocular muscle of Rhesus monkeys.
1973	Dr Alan Scott reports on his use of botulinum toxin at annual meeting of the Association for Research in Vision and Ophthalmology and publishes his groundbreaking work.
1977	New drug approval (IND) status for botulinum toxin A granted to Dr Scott.
1978	FDA clinical trials begin in humans. Dr Scott injects the lateral rectus muscle of a 26-year-old man with strabismus after retinal detachment surgery. He is the first person to receive medicinal botulinum toxin A.
1981	Dr Scott's seminal paper on the results of his human clinical trial of botulinum toxin is published after treating 147 patients.[18]
1981-1983	Dr Scott names botulinum toxin A, "Oculinum", and forms a corporation of the same name to keep up with testing and manufacturing operations and facilitate FDA approval to meet demand of clinical trial.
1982	Dr Scott expands clinical research team with voluntary contributions from researchers to grow the clinical trial.
1982	Dr Jean Carruthers, a Canadian ophthalmologist, spends several months studying with Dr. Alan Scott in San Francisco. She observes Dr. Scott's clinical trial patients who were treated for strabismus, dystonia, and muscle spasms. Dr Scott invites Dr Carruthers to join this clinical trial.
1989	First FDA drug approval for botulinum toxin A for treatment of blepharospasm and strabismus in patients 12 years and older, following the results of Dr Scott's pivotal trial.
1989	Allergan forms distribution agreement with Oculinum, Inc.
1991	Oculinum is acquired by Allergan for $9M. Dr. Scott estimated total cost of the drug development from 1971 to 1990 to be $4M. Allergan changes name of Oculinum to Botox.
1991	Dr Carruthers presents on cosmetic use of botulinum toxin at Annual Meeting of American Society for Dermatologic Surgery.
1994	Allergan develops new botulinum culture as Dr Schantz's original toxin culture runs out. Allergan production plant is in Westport, Ireland.
2000	Botox and Myobloc are approved for treatment of cervical dystonia
2001	Botox is approved for cosmetic use in Canada.
2002	Botox becomes first botulinum toxin approved for cosmetic use in USA. First cosmetic approval is for glabellar lines.
2004	Botox is approved for treatment of primary axillary hyperhidrosis.
2009	Dysport is approved for treatment of cervical dystonia. Dysport receives first cosmetic approval for treatment of glabellar lines.
2010	Botox is approved for treatment of chronic migraine and upper limb spasticity in adults. Xeomin is approved for treatment of cervical dystonia and blepharospasm.
2011	Botox is approved for treatment of urinary incontinence due to neurologic conditions. Xeomin receives first cosmetic approval for treatment of glabellar lines.
2013	Botox is approved for treatment of overactive bladder. Botox receives second cosmetic approval for treatment of lateral canthal lines.
2015	Dysport and Xeomin is approved for treatment of upper limb spasticity in adults.
2016	Botox is approved for treatment of lower limb spasticity in adults. Dysport is approved for treatment of lower limb spasticity in pediatrics.
2017	Dysport is approved for treatment of lower limb spasticity in adults. Botox is approved for cosmetic treatment of forehead lines.
2018	Xeomin is approved for treatment of chronic sialorrhea in adults.
2019	Botox is approved for treatment of upper and lower limb spasticity in pediatrics. Myobloc is approved for treatment of chronic sialorrhea.
2019	Jeuveau receives first cosmetic approval for treatment of glabellar lines.
2019	Abbott Laboratories purchases Allergan for $63 billion, and spins off subsidiary Abbvie as pharmaceutical arm, overseeing Botox. Abbvie retains the brand name of Allergan for marketing purposes.
2020	Xeomin is approved for treatment of chronic sialorrhea in pediatrics.
2021	Botox is approved for treatment of destrusor overactivity associated with a neurologic condition in pediatrics.
2021	Dr Alan Scott dies.

FIGURE 1. Timeline of FDA approvals of medical indications for botulinum toxin, 1989 – 2021.

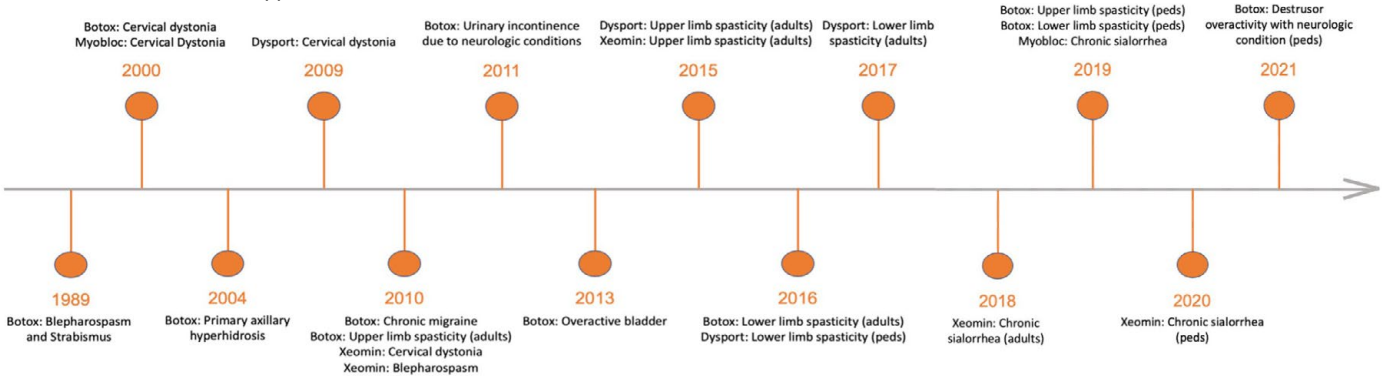
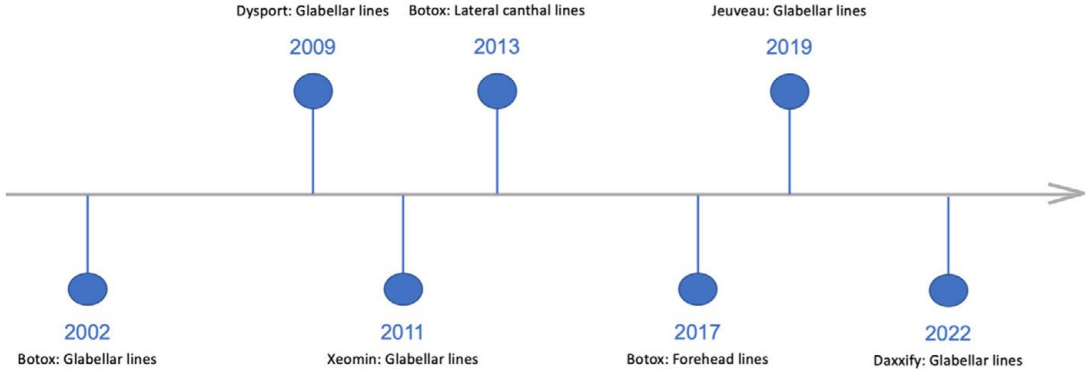


FIGURE 2. Timeline of FDA approvals of cosmetic indications for botulinum toxin, 2002 – 2022.



into human subjects, with safe and effective results. In 1981, he published his seminal clinical trial results.[17] After this initial success, more physicians joined Dr Scott's strabismus clinical trials as clinical investigators, including Dr Jean Carruthers, a Canadian ophthalmologist, who would go on to collaborate with her dermatologist husband, Dr Alistair Carruthers, in studying and popularizing the use of BoNT in cosmetic dermatology. Though aware of the aesthetic potential of BoNT for facial muscles and rhytides, Dr Scott expressed no interest in pursuing this indication himself.

4) BoNT as a wonder drug: FDA approvals (1989 – Present)

In 1989, the FDA issued the first landmark approval of BoNT-A for blepharospasm and strabismus associated with dystonia in patients twelve years and older. Numerous other medical and cosmetic indications followed in the coming decades. By the time of Dr Alan Scott's passing in 2021, 5 different commercial products of BoNT (Botox® (onabotulinumtoxin-A, Abbvie/Allergan Aesthetics), Dysport® (abobotulinumtoxin-A, Galderma), Xeomin® (abobotulinumtoxin-A, Merz Pharmaceuticals), Jeuveau® (prabotulinumtoxin-A, Evolus), and Myobloc® (rimabotulinumtoxin-B, Solstice Neurosciences)) would be FDA approved in the US with a combined 28 different indications across the specialties of ophthalmology, neurology, urology, dermatology, and otolaryngology (Figure 1 and 2). Most recently at the time of this writing, a 6th product, Daxxify® (daxibotulinumtoxinA-lanm, Revance), has been approved by the FDA for cosmetic indication.

DISCLOSURE

The authors have no conflicts of interest to declare.

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BRIEF COMMUNICATION

Journal of Drugs in Dermatology

Objective Facial Assessment With Artificial Intelligence: Introducing the Facial Aesthetic Index and Facial Youthfulness Index

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INTRODUCTION

Facial appearance has a substantial impact on psychosocial wellbeing, which may be considered an essential aspect of overall health. Cosmetic rejuvenation using a multimodal approach has been demonstrated to restore a sense of wellness for many patients, with improvements in mental health and self-confidence. Optimal care and treatment outcomes in many fields of medicine rely on objective evaluation metrics rooted in science, and clinicians are increasingly turning to digital health tools to aid in diagnosis and patient management. In aesthetic medicine, assessment is largely subjective and carries a high risk of bias, and dermatology-specific uses account for only a small fraction of available digital tools. A new application using artificial intelligence (AI) has been developed to standardize facial landmarks and characteristics for consistent, unbiased assessment in aesthetic medicine. A detailed analysis of large data sets across gender, age, and ethnicity groups validated by digital images and live assessments contributed to the development of the Facial Aesthetic Index (FAI) and Facial Youthfulness Index (FYI), AI-based algorithms that can identify and prioritize potential interventions for individualized treatment recommendations and provide users with a visible history of treatments and results. As both a diagnostic aid and consultation assistant, the FAI and FYI reflect a holistic impression of facial attractiveness using mathematically selected predictors and have the potential to set a new standard of care in aesthetic rejuvenation.

Demand for Objective Measurements in Aesthetic Medicine

According to the World Health Organization (WHO), health is not merely the absence of disease or infirmity but is defined as a state of complete physical, mental, and social well-being.[1] Facial attractiveness has a demonstrated effect on perceived biological health, mental health, and socioeconomic dimensions.[2,3] The abrupt shift to video conferencing during the pandemic has led to increased self-scrutiny and subsequent increase in demand for both surgical and non-surgical aesthetic procedures.[4] Research has demonstrated that a multimodal approach to full facial rejuvenation not only improves self-perception of age but also may significantly improve psychological well-being and self-confidence.[5] Optimal patient care and satisfaction relies on an objective understanding of aesthetics and beauty, but therein lies the difficulty: there is a lack of objective pre- and post-assessment tools for comprehensive treatment in the largely subjective field of aesthetic medicine.[6]

Many medical specialties rely on objective diagnostic criteria and outcome assessment based on scientific evidence and measurable treatment response. In aesthetic medicine, there is a lack of standardized, impartial evaluation metrics for assessment and treatment. There are validated scales[7,8] that assess the appearance of certain features, such as jowls, nasolabial folds, lateral canthal lines, or infraorbital hollows, but they still require a subjective assignment of severity or grading and fail to provide a complete picture of the aging face. There is no universally accepted definition of beauty and attractiveness.[9] Ratios and equations can be used to assess symmetry and proportions for a mathematical appreciation of beauty, but the perception of attractiveness is multidimensional and easily influenced by other factors, such as an individual's self-esteem, apparel, and confidence.[10-12]

Clinicians carry inherent biases informed by cultural background, geographic location, familiarity, individual visual environment, social media, peers, and patient population which have an effect on the ability to appreciate "normal" in a patient population and set exact parameters of beauty and attractiveness.[9] This may lead to vastly different aesthetic ideals across providers, subjective perceptions about beauty,

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treatment priorities, and outcomes, and a high risk of inherent bias in the determination of attractiveness and related facial landmarks before and after aesthetic procedures. Without objective metrics, facial rejuvenation relies on an instinctive and deeply personal assessment of beauty married with an in-depth knowledge of anatomy and the aging process. The lack of standardized facial measurements and clear definitions of aesthetic outcomes and beauty are still major obstacles preventing real change in the consultation dynamics to help better serve patients' expectations and subsequently improve satisfaction.[6]

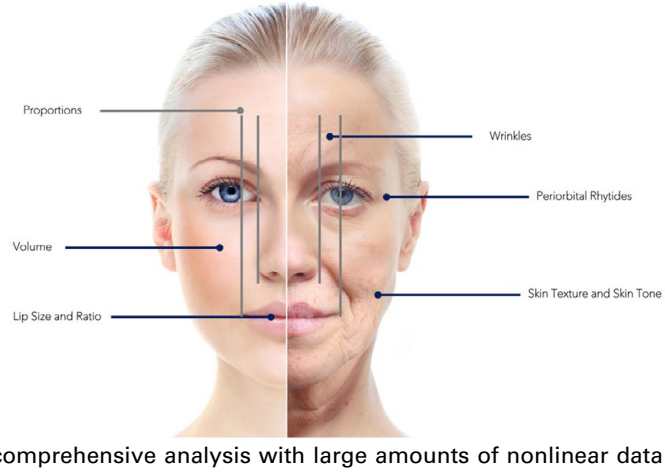
In other fields of medicine, clinicians are increasingly turning to digital health tools to aid in diagnosis and patient management. Innovation in digital health tools brings new approaches to the management of health conditions and holds great promise for improving human health.[13] Now an established part of the digital health landscape, the number of health-related mobile applications topped 350,000 in 2021, and there are rising efforts to fit digital health into clinical practice, as evidenced by the increasing inclusion of digital health tools in clinical trials and treatment guidelines. When broken down by therapeutic area, mental health, diabetes, and cardiovascular disease–related apps dominate, while dermatology accounts for only a small fraction of available disease-specific apps.[13] This may be surprising but also temporary; the rapid rise of teledermatology in recent years will likely lead to further development of patient-directed technology and artificial intelligence (AI) as an adjunct to care.[14]

Harnessing Artificial Intelligence in Facial Aesthetics

Artificial intelligence is the development of technology that simulates human cognitive functions.[15] In healthcare, the most promising application of AI involves machine learning, which consists of computer-based algorithms that use historical data to extract knowledge and interpret meaning—in other words, to learn.[16] The dominant AI technology for analyzing high-dimensional complex data, such as images, is deep learning, a subset of machine learning.[17] Deep learning harnesses mountains of data using a sophisticated artificial neural network, a collection of algorithms designed to process raw data (such as images) and produce an output (eg, diagnosis) with the least amount of error and without being told to do so. Arranged in multiple layers, these neurons, represented by algorithms, learn to recognize patterns and intricate structures in large data sets and adapt their connections in response, much like the human brain.[18,19]

In dermatology and dermatologic surgery, where visual analysis is the cornerstone of diagnosis, AI has the potential to improve patient care, and there is an upward trend in its use as a diagnostic aid for automatic detection of skin lesions, such as melanoma and non-melanocytic skin cancers, psoriasis, acne, dermatitis, and onychomycosis.[18,20] Its ability to perform

FIGURE 1. Individualized analysis provided by the FAI.



comprehensive analysis with large amounts of nonlinear data makes it a favorable aid for medical decision-making[20]; as such, it has been used successfully in various aspects for the ongoing dermatologic management of certain autoimmune disease[21] and in surgical settings, such as biopsy[22,23] and laser hair removal[24] and restoration.[25] Of particular interest for facial rejuvenation is the discovery that AI can accurately estimate a patient's true age before plastic surgery and predict age reduction postoperatively.[16,26]

Standardized Assessment: The Facial Aesthetic Index and Facial Youthfulness Index

A new digital health tool aims to provide a computer-based analysis of images for an objective evaluation of facial parameters while reducing the risk of subjective bias in aesthetic patients. The Facial Aesthetic Index (FAI; Caarisma®, ICA Aesthetic Navigation GmbH, Frankfurt, Germany) is an AI-based algorithm based on the detailed analysis and subsequent validation of over 200 original and derived facial variables in more than 15 facial regions to identify and summarize common landmarks of clinical facial features. Using a series of 4 photographs representing 4 different facial expressions, the FAI analyzes and compares a patient's unique characteristics

FIGURE 2. The FAI analyzes individual characteristics of a patient's face to assign a rating of attractiveness on a scale of 1 to 7 at baseline and generate the FYI. These algorithms can then forecast which facial features have the greatest potential for improvement and track treatment outcomes along the aesthetic journey of a patient.

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such as skin texture and tone, proportions, symmetry, volume, and lip size and ratio, as well as the presence and severity of wrinkles (Figure 1) with the average of all recordings in large datasets across gender, age, and ethnicity groups and provides a 7-point FAI rating score that reflects a holistic impression of overall attractiveness using mathematically selected predictors. The facial analysis also generates a Facial Youthfulness Index (FYI), a validated measurement of the user's face in terms of apparent youthfulness that is displayed alongside the FAI. The algorithms can forecast which facial features have the greatest potential for improvement and prioritize key drivers that reflect primary treatment options offering the most benefit for each patient. Facial improvements over time can be observed visually and mathematically, offering visible confirmation of treatment outcomes (Figure 2). The tracking of long-term treatment outcomes with visuals and data may motivate patients to remain compliant with treatment recommendations and provides practitioners with complete documentation and improved quality assurance. In addition, this technology may serve as powerful education and communication tool that may strengthen trust between patients and physicians.

CONCLUSIONS

The WHO Constitution states that enjoyment of the highest attainable standard of health—complete physical, mental, and social well-being—is a fundamental right of every individual.[1] With its unbiased assessment of individual improvement potential and mathematically validated treatment recommendations, the FAI has the potential to contribute to an improvement in overall health and set new standards of care in facial rejuvenation. Aesthetic medicine is long overdue impartial evaluation metrics for assessment and ongoing treatment to provide optimal care and management. Tracking facial improvements over time using data, with demonstrated improvements in the FAI and FYI scores, as well as in visible appearance, represents an important leap in assessment capabilities. The FAI should be incorporated as a reliable measurement tool in clinical research and a standard pre- and post-assessment tool and enhanced consultation assistant in aesthetic clinics to detect primary treatment areas, identify how each would contribute to optimizing individual scores, track treatment history, and demonstrate improvement over time.

DISCLOSURES

Sonja Sattler is KOL and paid consultant or performs research for MERZ Aesthetics, Crown Aesthetics, Allergan (AbbVie), Evolus, Ipsen, LG Chem, Advanced Aesthetic and Technologies and Hallura. Konstantin Frank is a paid consultant, speaker or performs research for Allergan (AbbVie), Croma Pharma GmbH, Merz Aesthetics, Evolus, BTL, Galderma Inc. and AestheFill. Tatjana Pavicic is Consultant and speaker for Merz Aesthetics, Advanced Aesthetic Technologies (AAT), and investigator for Merz Aesthetics, AbbVie, AAT, LG & Croma. Peter Peng is consultant for Allergan, Cynosure, Candela, Sofwave, Lumenis, skinceutical. Rainer Pooth is consultant for Aptos, Croma Pharma, Dialectica, HaematoPharm, Secerna.

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LETTERS TO THE EDITOR

Journal of Drugs in Dermatology

The Potential Impact of Off-Label Medication Use on Patient Access: A Cross Sectional Survey of Minoxidil Availability

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To the Editor:

Early and effective treatment for Androgenetic Alopecia (AGA) is crucial to prevent long-term dermatologic and psychosocial consequences.[1,2,3] With the release of and attention to the *New York Times* (NYT) article 'An Old Medicine Remedies Hair Loss for Pennies a Day' on August 18th, 2022, low dose oral minoxidil (LDOM) drew heightened patient interest for management of AGA, with 71% of nationwide Dermatologists surveyed nationwide in one study claiming a sudden rise in medication inquiry, and prescription numbers surpassing 85% total increases since the aforementioned NYT article was published.[3,4] Given the increased demand for this off label use, a potential for LDOM 2.5 mg shortages in recent months is plausible and could impact continuity of care. We sought to evaluate current inventories of varied dosages of oral minoxidil at mainstream pharmacies in surrounding neighborhoods of Washington DC, Maryland, and Northern Virginia.

Four retail chain pharmacies with approximately even distribution among suburban, urban, and rural towns in the DMV (District of Columbia, Maryland, and Virginia) (Table 1) were selected including CVS, Giant, Walgreens, and Harris Teeter. During the first week of October 2023, a total of 277 pharmacies were contacted by telephone using standardized scripts to assess the availability and quantity of oral minoxidil in stock both for 2.5 mg tablets and 10 mg tablets, with specific inquiry for a 30-day supply and thirty tablets of each dosing. Charting, calculations, and analysis of results were performed using prism.

Twenty-three percent (33/143) of all Northern Virginia pharmacies confirmed availability of both oral minoxidil 2.5 mg and 10 mg tablets, with adequate inventories for thirty-day supplies. Similar findings with limited reserves for both dosages were reported when calling Washington DC (17.9%, 12/67) and Maryland (14.9%, 10/67) pharmacies. Only 40.1% (111/277) of all contacted pharmacies in the DMV reported availability of LDOM 2.5 mg tablets for a thirty-day supply; 29.6% (82/277) of the very same DMV pharmacies reported having oral minoxidil 10 mg tablets to cover the same time frame. When stratified geographically, Maryland showed the greatest deficit in oral minoxidil availability: 28.3% (19/67) of the state's pharmacies confirmed thirty-day supplies of LDOM 2.5 mg tablets in stock and 22.3% (15/67) of the pharmacies noted having thirty-day supplies of oral minoxidil 10mg tablets. Northern Virginia and Washington DC pharmacies demonstrated similar inventory distributions of LDOM 2.5 mg tablets, with 44% (63/143), and 43.2% (29/67) respectively, having availability. Volume of oral minoxidil 10 mg tablets also lagged, with 32.2% (46/143) of Northern Virginia pharmacies confirming sufficient supply for a thirty-day prescription fill, and 26.8% (18/67) of Washington DC pharmacies with analogous counts (Figure 1).

These data reveal a significant care gap resulting from oral minoxidil 2.5 mg and 10 mg shortages within the DMV, which could potentially translate to the national level. Such paucities pose a challenge both for Dermatologists managing AGA but also primary care physicians utilizing this medication on label. This study underscores the need and opportunity for approaches

FIGURE 1. Evaluating current inventories of oral minoxidil in the DMV.

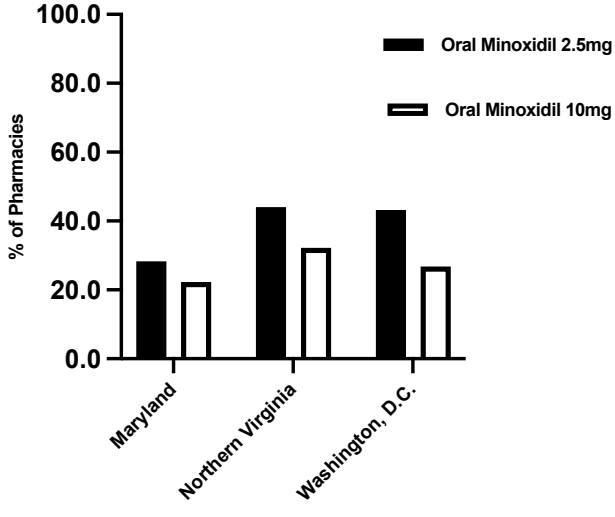

TABLE 1.

2020 Census Total Population of All Contacted Neighborhoods Within the DMV[5,6]	
Maryland	
Bethesda	68,056
Rockville	67,117
Potomac	47,018
Gaithersburg	69,657
Germantown	91,249
Silver Spring	81,015
Oxon Hill	18,791
Northern Virginia	
Alexandria	159,467
Fairfax	24,146
Vienna	16,473
Tysons	26,374
McLean	50,773
Oakton	36,372
Reston	63,226
Herndon	24,532
Ashburn	46,511
Fairfax Station	14,030
Falls Church	14,658
Arlington	234,000
Annandale	42,240
Springfield	32,960
Washington, DC	
Dupont Circle	15,099
Foggy Bottom	14,642
Georgetown	701,974
West End	13,037
Chevy Chase	10,176
Tenley Town	1,806
Navy Yard	2,794
Anacostia	54,812
Downtown DC	8,449
Shaw	10,004
Columbia Heights	30,400
Palisades	2,390
Foxhall	4,900
Capitol Hill	29,120
Northeast DC	148,886
Wharf	2,914

to both disseminate information regarding potential shortages and ascertain how to best access or share finite resources in times of low inventories. Given AGA management is chronic and abrupt cessation of therapy can have detrimental effects on treatment course, there must be a consensus on how to address supply scarcities to prevent interruptions of patient care.

DISCLOSURES

The authors have no conflicts of interest to declare.

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Factors Impacting New Drug Adoption in the Clinical Setting: A Survey of Dermatologists

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INTRODUCTION

Dermatology has seen a significant influx of new Food and Drug Administration (FDA) medication approvals in recent years. In the last decade alone, 39 new drugs for dermatologic indications have been approved.[1] The advent of biologics and Janus kinase inhibitors has dramatically improved the management of several chronic and often difficult to treat conditions, including psoriasis, atopic dermatitis, alopecia areata, and vitiligo.[2] Despite some of these new therapies demonstrating clinical superiority over existing treatments, the majority of practicing dermatologists still do not prescribe them.[3] Limited studies in other specialties have analyzed new drug adoption parameters.[4,5] To our knowledge this is the first study to quantitate the factors influencing a dermatologist's decision to adopt new medications.

This study was granted IRB exempt status. An anonymous online survey that included 10 considerations when starting a new drug was distributed to dermatologists at a national conference in October 2022. Each factor was scored by respondents using a scale from 0 (not at all important) to 100 (extremely important). The mean scores for each factor and subgroup analyses based on practice setting and years in practice were calculated using SPSS version 28.0.1.1.

Three hundred and fifty seven dermatologists responded to the survey (71% response rate). The top five factors influencing new drug adoption were reported efficacy (92.6), insurance coverage (87.1), reported side effects (86.1), the difficulty of treating the disease targeted by the drug (84.5), and data-driven publications in peer-reviewed journals (80.8). The bottom five factors were drug price (78.9), podium presentations (70.4), colleagues adopting drug usage (59.2), presentations by pharmaceutical reps (50.7), and poster presentations (45.8) (Table 1).

The subgroup analyses demonstrated that dermatologists practicing for at least 21 years placed a significantly greater value on pharmaceutical rep presentations than those in practice for 0 to 5 years or 11 to 20 years (57.1 vs 41.7, P=0.004 and 57.1 vs 47.7, P=0.04). Dermatologists in solo private practices also placed greater value on pharmaceutical rep presentations than those at academic centers (60.0 vs 37.7, P<0.001).

The top three factors that dermatologists considered for new drug adoption were efficacy, insurance coverage, and side effect profile. Even if a drug is efficacious and safe, it likely will not be readily adopted by dermatologists if their patients cannot afford it. This highlights the importance of accessibility for new drugs to be integrated into practice. Additionally, for conditions such as atopic dermatitis and psoriasis, many insurance companies require that a patient trial older medications that are typically less effective before covering a newer therapy. This can delay treatment success and lead to significant morbidity.

TABLE 1.

Factors Impacting Drug Adoption. Relative importance of each factor for dermatologists adopting usage of a new drug in the clinical setting on a scale from 0 (not at all important) to 100 (extremely important).

Factor	Score
The reported efficacy of the drug	92.6
Whether the drug is covered by insurance	87.1
The reported side effects of the drug	86.1
The difficulty of treating the specific disease state with current medications	84.5
Publications in peer-reviewed journals presenting the drug's data	80.8
The price of the drug	78.9
Podium presentations of the drug's data at regional and national Dermatologic conferences	70.4
Colleagues in the community adopting drug usage	59.2
Pharmaceutical reps presenting the drug's data to you in your clinical setting	50.7
Posters at regional and national conferences presenting the results of clinical trials using the drug	45.8

The direct correlation noted between practice years and greater value assigned to pharmaceutical rep presentations may be explained by more experienced clinicians building relationships and trust with their reps over time. Recent graduates may not have had as much exposure to these presentations due to the COVID-19 pandemic. Furthermore, the finding that dermatologists working in private practices assigned greater value to pharmaceutical rep interactions than those at academic centers could be due to significantly greater access to reps in those practice settings.

Limitations of this study include potential selection bias as respondents were limited to conference attendees. However, demographic data showed that the survey participants included dermatologists in a variety of practice settings and stages of their career. Another limitation is that the factors analyzed may not have been all-inclusive. In addition, each individual drug could have specific considerations that hinder usage, such as black box warnings[6] or prescribing overhead.

With the recent approval of several dermatologic therapies (some of which are more effective than prior options) and more coming, it is important to understand why dermatologists may or may not choose to integrate these drugs into practice. This study identified the relative impact that factors associated with drug adoption have and demonstrated that dermatologists with varying years of experience and across different practice settings are relatively consistent. Future studies will be helpful to further elucidate the challenges associated with clinical integration of new drugs.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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LETTERS TO THE EDITOR

Journal of Drugs in Dermatology

Oral Minoxidil Media Coverage: The Impact on Patient Perceptions and Practitioner Approaches to Androgenetic Alopecia

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INTRODUCTION

Androgenetic alopecia (AGA) has an estimated global prevalence of up to 80% in men and 42% in women that results from the effect of dihydrotestosterone miniaturizing scalp follicles.[1,2] The diagnosis often provokes significant emotional distress and psychological burden to patients, leading to increased demand for effective treatments.

Mainstream news outlets in recent years have attracted heightened participation among healthcare professionals to use such mediums to disseminate medical information for disease awareness and prevention, as it represents an unprecedented opportunity to improve health literacy, self-efficacy, and treatment adherence among populations.[1] While proving useful, these channels have also opened the door for spread of misinformation with potential implications including encouragement of unproven treatments without adequate disclosures or discussion of risks.[1,3] With the release of and attention to the *New York Times* (NYT) article 'An Old Medicine Remedies Hair Loss for Pennies a Day' in August 2022, low dose oral minoxidil (LDOM) gained a surge in popularity with rising public curiosity toward AGA management. Although recognized as an off-label approach when compared to its topical analogue, we sought to elucidate the influence of this publication on consumer interest by surveying dermatologists on their perceived change in patient interest and resulting volumes as well as assessing communal interest trends on AGA and LDOM using Google Analytics.

MATERIALS

An IRB approved (#NCR224464) thirty-question survey was sent using the *ODAC* conference email listserv. Respondents were predominantly dermatologists, a minority (estimated ~14%) were other dermatology providers including physician assistants and nurse practitioners. A total of 201 surveys were completed and anonymously compiled for further analysis. Concurrently, public interest trends on AGA were examined using Google Analytics and correlated with health-related news over matching time intervals. Weekly relative search volumes (RSV) over a one-year period from February 2022 to February 2023 pertaining to AGA-associated internet search terms, 'low-dose oral minoxidil' (LDOM), 'pattern hair loss' (PHL), and 'androgenetic alopecia' (AGA), were identified and scaled from 0 to 100- in proportion to the time at which a given term's popularity is maximal, represented by an RSV of 100.

FIGURE 1. Relative search volumes [RSV] for the terms 'low dose oral minoxidil', 'pattern hair loss', and 'androgenetic alopecia' on Google from February 2022 to February 2023 with climax peaks observed during the week of August 14th- 20th, 2022 corresponding to popular culture news and the release of the NYT article.

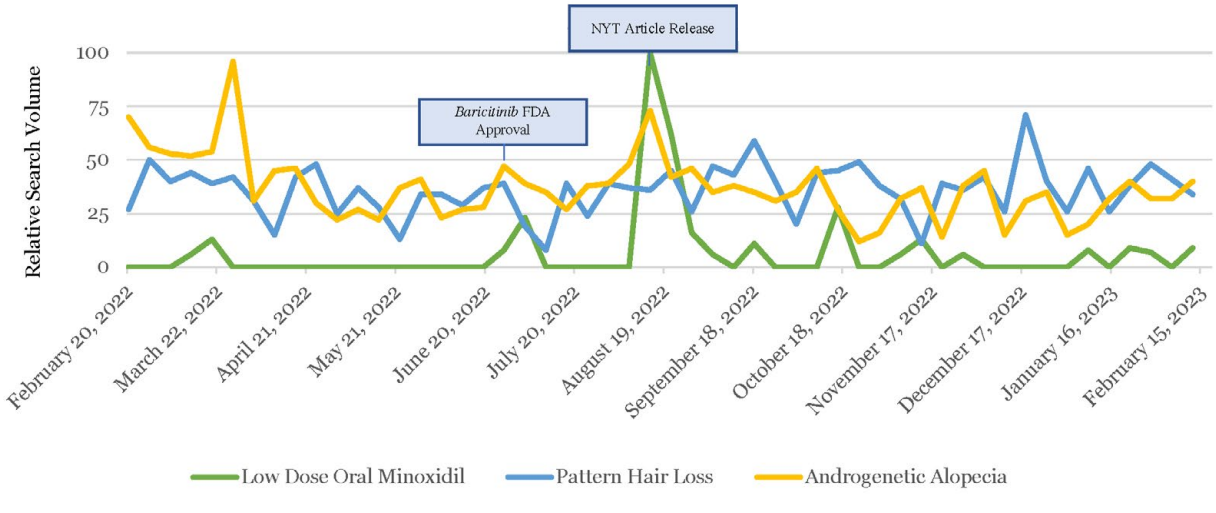

TABLE 1.

Oral Minoxidil Media Coverage: The Impact on Patient Perceptions and Practitioner Approaches to Androgenetic Alopecia		
Have you appreciated an increase in patient visits, NEW or RETURN, specifically to discuss/prescribe OM?	Total Responders = 142	
	Yes	101/142: 71.1%
	No	41/142: 28.9%
Approximately how many NEW patients per week are you seeing coming in with this specific request?	Total Responders = 97	
	0 -to- 5	81/97: 83.5%
	5 -to- 10	13/97: 13.4%
	10 -to- 15	3/97: 3.1%
Approximately how many RETURN patients per week are re-visiting specifically inquiring about OM?	Total Responders = 97	
	0 -to- 5	73/97: 75.3%
	5 -to- 10	22/97: 22.7%
	10 -to- 15	2/97: 2.1%
Of the patients for whom you've prescribed OM, have any encountered any of the below issues related to access?	Total Responders = 96	
	Failure of insurance coverage	6/96: 6.25%
	Increased out-of-pocket expense	6/96: 6.25%
	Low stock/inventory at local retail Rx	5/96: 5.21%
	Having to resort to special compounding Rx	9/96: 9.38%
	None of the above and/or OTHER	79/96: 82.3%
Have these patients raised any of the following claims?	Total Responders = 95	
	It is helpful for ALL forms of hair loss	15/95: 15.8%
	OM is more effective than 5-a-reductase inhibitors for AGA	15/95: 15.8%
	OM will promote thicker hair regrowth w/i 10M	12/95: 12.6%
	OM will prompt unwanted bodily hair growth	36/95: 37.9%
	OM is linked with sexual dysfunction	2/95: 2.1%
	Off-label use of OM is not safe	3/95: 3.2%
	Hair will begin to thin and fall-out after stopping OM	50/95: 52.6%
	None of the above and/or OTHER	33/95: 34.7%
Do you find yourself prescribing more OM since the release of the NYT article?	Total Responders = 97	
	Yes	83/97: 85.6%
	No	7/97: 7.2%
	Uncertain	7/97: 7.2%

RESULTS

Respondents, stratified by professional healthcare titles, number of years in practice, care center type, and U.S. regions, were asked how the release of the *NYT* article influenced their dermatology practice. A specific focus was placed on whether they had appreciated an increase in patient visits to discuss and/or prescribe LDOM, and if they ultimately found themselves prescribing it at a greater frequency than prior to the *NYT* article (Table 1). 71% of surveyed respondents reported a surge in LDOM inquiry, with Board Certified Dermatologists (68.4%) and Dermatology Residents (62.5%) seeing the greatest spikes, irrespective of their number of years in practice. 76.9% of the 13 respondents working in Community Hospitals/ Multispecialty Clinics reported increases in LDOM interest, followed by Private Practices (48, n= 71) and Academic Institutions/VA (20, n= 31) closely tying the list at 67.6% and 64.5%, respectively. 83.5% reported seeing 0-to-5 and 13.4% 5-to-10 new patients per week, combined with 75.3% seeing 0-to-5 and 22.7% 5-to-10 returning patients per week with the above medication request. Most notably, a total of 85.6% respondents accounting for all U.S. demographic regions reported significant increases in LDOM prescriptions.

Furthermore, weekly RSV values for selected health-related terms LDOM and PHL exhibited trivial fluctuations six-months prior to August 2022, averaging at RSV < 25 and RSV < 50, accordingly. AGA RSV values demonstrated greater variability; web searches peaked at 97 during the week of March 27th-April 2nd, 2022, plummeted to 23 during the first week of May 2022, and again ascended to 47 during the week of June 26th-July 2nd, 2022-coinciding with the same dates *baricitinib* received FDA approval for alopecia areata. Google Analytics following the release of the *NYT* article on August 18th, 2022, showed notable peaks in LDOM, PHL, and AGA RSV values at 100, 37, and 73, respectively, during the week of August 14th-20th, 2022 corresponding to popular culture news. Nonetheless, those numbers returned to their baseline RSV values within four weeks and have continued to demonstrate minimal oscillations as of September 18th, 2022.

DISCUSSION

We demonstrated that patient interest in LDOM has increased substantially, with 71% of nationwide Dermatologist respondents claiming upsurges in medication inquiry and prescription numbers surpassing 85% total increases since August 18th, 2022.

While authors of the *NYT* publication were strong proponents of LDOM attesting that it restored hair growth amidst several patients, no information was offered about its ideal dosing, treatment duration, adverse effects, and if efficacy was achieved with monotherapy or in combination with other medications. In reviewing recent literature, studies suggest that optimal safe doses of LDOM range between 0.625 mg and 5 mg daily, with the expectation to be used lifelong. 1.25 mg and 2.5 mg tablets are the most commonly prescribed dosages though are often adjusted in congruence with patient AGA severity.[1,4] Furthermore, six meta-regression analyses from other studies assessing LDOM efficacy demonstrated there exists a positive dose-dependent relationship that contributes significantly and results are best observed at 24 weeks following treatment initiation. For example, increasing an LDOM dose by 1mg/day was associated with sex-adjusted increases in total hair density (mean difference = 47.1 hairs/cm^2, P=0.007), terminal hair density (mean difference = 9.1hairs/cm^2, P=0.001), and hair diameter (mean difference = 1.4 um, P= 0.01).[4] However, investigators also witnessed dose-dependent risks of hypertrichosis, pedal edema, and cardiovascular events.[4] Fortunately, Dermatologists are comfortable using LDOM as an adjunctive treatment with other 5-a reductase inhibitors-including finasteride and dutasteride, to elicit maximal effects and improve long-term patient adherence.[2,5]

Together, these data highlight the impact media can have on patient education and care seeking behaviors and resulting practice trends. It is of the utmost importance that a collaborative and evidence-based approach be taken between journalists and health care practitioners to ensure that the widely disseminated information is realistic and evidence based.

DISCLOSURES

The authors have no conflicts of interest to declare.

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Natural Weight Loss or "Ozempic Face": Demystifying A Social Media Phenomenon

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ABSTRACT

New patients turning to semaglutide (Ozempic® and Wegovy®), a glucagon-like-peptide 1 (GLP-1) agonist, for weight loss, have captivated social media platforms. Wegovy® carries a United States (US) Food and Drug Administration (FDA) approval for chronic weight management in patients who have a body mass index (BMI) ≥ 27 kg/m^2 and at least one weight-related condition (eg, hypertension, type 2 diabetes, cholesterol) or in patients with a ≥ 30 kg/m^2 BMI. Although other semaglutide formulations are not FDA approved for weight loss, the term "Ozempic face" has consumed the media with the medication's rising popularity. This term is a new purported side effect, used to describe the rapid facial weight loss leaving a distorted facial appearance. This challenges the healthcare team to discern whether a new adverse effect is a novel or a natural consequence of rapid weight loss. Dermatologists are well positioned to counsel patients receiving or discontinuing GLP-1 agonists and recommend appropriate countermeasures, as appropriate.

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INTRODUCTION

As diabetes mellitus medications with weight loss benefits become increasingly popular, non-diabetic patients turn to medications like Ozempic® and Wegovy® (generic semaglutide) for a similar intervention. Only Wegovy® has been approved by the United States (US) Food and Drug Administration (FDA) for chronic weight management in patients who have a body mass index (BMI) ≥ 27 kg/m^2 and at least one weight-related condition (eg, hypertension, type 2 diabetes, cholesterol) or in patients with a ≥ 30 kg/m^2 BMI.[1]

Increasing use of these medications has generated the emergence of the term "Ozempic face" across social media platforms as diabetic and non-diabetic patients experience adverse effects. The term describes the extreme weight loss in the face leaving distorted contours of facial anatomy and skin sagging.[2] Semaglutide, a glucagon-like-peptide 1 (GLP-1) agonist, is indicated for type 2 diabetes mellitus and may be preferred in patients with comorbidities such as atherosclerotic cardiovascular disease (Ozempic®).[3] Side effects of GLP-1 agonists include nausea, gastrointestinal upset, pancreatitis, and weight loss.[4] Although known to cause weight loss, the relationship between the GLP-1 agonist mechanism of action and facial weight loss is not characterized and may be unrelated. Our review of normal physiological responses to weight loss aims to demystify the "Ozempic face."

Known GLP-1 Agonists and Weight Loss

GLP-1 agonists increase glucose-dependent insulin release, decrease glucagon secretion, and reduce gastric emptying, promoting an increase in patients' satiety.[5] Evidence of GLP-1 agonists favoring adipose catabolism of the face, as opposed to other body regions, is lacking.[3,5,6] In addition to lifestyle modification, GLP-1 agonist use for the treatment of type 2 diabetes mellitus may yield an average of 17.6% weight loss versus 2% weight loss with lifestyle modification alone for 68 weeks.[3]

Adipose and Facial Contour

Elastin, a main component of the dermal skin layer, allows skin to stretch and recoil.[2] Over time, elastin turnover decreases and can be damaged by various factors including ultraviolet (UV) radiation.[2,6] When patients receive a GLP-1 agonist known to increase weight loss, concurrently with a natural decline in elastin turnover, the lack of recoil and loss of subcutaneous fat can produce wrinkling and sagging; this effect may have gone undetected until the addition of GLP-1 agonist. There is no evidence that subcutaneous adipose tissue is more likely to be catabolized compared to other adipose stores.

A Dermatologist's Role

Dermatologists must ask about concomitant medication use when consulting patients requesting facial fillers. Given the ongoing social media phenomenon, physicians must consider recent weight loss with GLP-1 agonists as patients attempt to combat the wrinkling and sagging effects caused by rapid weight loss. According to the American Academy of Dermatology, facial fillers provide immediate results to replace and combat skin elasticity and can last between two months to indefinitely.[7] Dermatologists must anticipate an emerging patient population seeking fillers after GLP-1 agonist use and explain realistic expectations with medication use, weight loss,

and fillers. This includes hypothetically dissolving fillers after GLP-1 agonist cessation as they regain natural adipose tissue around the face to prevent compounded fullness of facial features. This is an important consideration for patients electing for a more permanent facial filler. Dermatologists should take a comprehensive patient history to ensure patients taking GLP-1 agonists (both on- and off-label) are aware that cessation will lead to weight regain[8] and to counsel patients appropriately.

DISCUSSION

Physicians must counsel patients about expected medication outcomes. Dermatologists are instrumental in discussing the potential side effects of facial fillers with concurrent GLP-1 agonist intake. Increasing focus across social media platforms demonstrates GLP-1 agonist popularity among non-diabetic patients seeking rapid weight loss. Despite this phenomenon, this adverse effect is explained by any variation of rapid weight loss in combination with slow elastin turnover and is not solely medication derived.

CONCLUSION

Available evidence confirms the effectiveness of GLP-1 agonist weight loss in patients with and without type 2 diabetes mellitus. As consumers turn to social media as a source of medical information, misinformation occurs. Currently, there is no evidence to suggest GLP-1 agonists directly catabolize adipocytes within the face. As the usage of semaglutide increases, it is critical that a dermatologist obtains an accurate history from a patient and counsels them on the compounded effect of facial filler and GLP-1 agonist cessation.

DISCLOSURES

The authors have no conflicts of interest to declare.

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FEATURED CONTENT

Journal of Drugs in Dermatology

NEWS, VIEWS, & REVIEWS

Applications of Bioactive Peptides in Dermatology

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INTRODUCTION

Most physiological processes in the body are regulated by the interaction of specific amino acid sequences, functioning either as peptides or fragments of proteins. Peptides are compounds containing two or more amino acids linked by an amide bond that transmit biochemical signals.[1] Synthetic engineering of bioactive peptides allows for the targeted promotion of physiological processes while minimizing associated side effects (Table 1). By substituting amino acids, diverse peptide analogs are created to regulate the potency, solubility, toxicity, and cost of potential therapies.[2] The ability to modify and control peptide compounds with ease is unique, as many other biological molecules are chemically challenging to alter. Consequently, bioactive peptides offer not only a broad array of potential active ingredients, but also can be developed and tailored to be made suitable for specific indications and demographics.[3]

Table 1. Advantages and Limitations of Engineered Bioactive Peptides

Advantages	Limitations
High specificity	Limited skin penetration
Limited side effects	Short half-life
Easy to modify	Low stability

Peptide Delivery

Although many advancements in peptide synthesis and therapeutic use have been made in recent decades, delivery to target sites is still a challenge. Peptides are often administered parenterally since they are unstable when administered orally due to first-pass degradation/metabolism. Yet, the typically short half-life of peptides requires frequent injections, thus alternative routes of delivery are being actively researched. Transdermal delivery is a promising alternative as this route encounters less enzymatic degradation; however, the greatest impediment is the actual target - the formidable skin barrier.[4]

Peptides require active methods of delivery through the skin given they are typically large molecular weight (>500 Da), polar and hydrophilic molecules. One approach to improve active diffusion is with the use of physical or chemical permeation enhancers.[4-6] Encapsulation within polymeric particulate delivery systems, such as phospholipid-based liposomes, which are known to penetrate the skin more easily, can improve topical delivery. Moreover, chemical modification of peptides through the addition of lipophilic derivatives is a strategy to increase encapsulation efficiency. Physical penetration enhancers include application of energy to drive delivery of peptides (iontophoresis, electroporation, or sonophoresis), minimally invasive disruption of the stratum corneum (microneedles, jet injectors), and ablation of the stratum corneum (lasers, radiofrequency, suction blister, thermal poration). Innovative technologies continue to be researched for transdermal delivery of peptides, particularly novel combinations of enhancement techniques which show promise in delivery optimization by leveraging synergistic mechanisms.[4]

Dermatologic Applications

Skin Aging

In the current era, significant efforts and research are driving the development of peptides targeting skin aging, generating a robust market in the cosmeceutical industry for peptide innovation. Ex vivo and translational studies have demonstrated that bioactive peptides increase fibroblast production of collagen, decrease collagen breakdown, and increase extracellular matrix protein expression, maintaining the skin's structural integrity and combating the natural aging process.[7-9] Additionally, peptides promote anti-aging by scavenging free radicals, chelating pro-oxidative transition metals, decreasing hydroperoxides, and enzymatically eliminating certain oxidants.[10] Currently, there are four categories of anti-ageing peptides with varying primary mechanistic processes: signal peptides, neurotransmitter-affecting peptides, carrier peptides, and antioxidants (Table 2).[10]

Table 2. Bioactive Peptide Categories and Mechanisms of Action

Peptide Categories	Primary Mechanism of Action
Signal peptides	Promote collagen synthesis by stimulating fibroblasts
Neurotransmitter-affecting peptides	Enhance botulinum toxin function to reduce facial muscle contraction thus decreasing sagging and wrinkling
Carrier peptides	Stabilize and provide essential trace elements for enzymatic processes involved in skin rejuvenation
Antioxidants	Scavenge damaging free radicals

Acne

Oral antibiotics are commonly employed in the treatment of moderate to severe inflammatory acne, however long-term

use beyond clinical guidelines can result in the emergence of antimicrobial resistance. Synthetic antimicrobial peptides (AMPs), engineered analogs of naturally occurring AMPs, have been evaluated as antibiotic alternatives. Granulysin-derived peptides are bactericidal against *Cutibacterium acnes* and possess anti-inflammatory properties.[11] The added value of these peptides has been evaluated in conjunction with isotretinoin, with data suggesting that granulysin-derived peptides improve the efficacy of isotretinoin.[12]

Wound Healing

Bioactive peptides can enhance the skin reparation and renewal processes after injury by promoting collagen and elastin production, cellular proliferation, inflammation, and angiogenesis.[10] Specifically, AMPs have been shown to promote wound healing through immunomodulation and cytokine production.[13] AMPS are effective against multidrug-resistant organisms in wound infections and may be advantageous during prolonged treatment considering the challenges associated with antibiotic resistance.[14] Only a handful of AMPs have obtained FDA approval for bacterial skin infections or wounds, including gramicidin D, daptomycin, oritavancin, telavancin and dalbavancin.[15,16]

Pigmentation

Synthetic α-MSH analogs have been evaluated for their ability to enhance melanin synthesis, imparting photoprotection. Pharmacological modifications to tetrapeptides derived from α-MSH have increase their stability and efficacy on melanocyte α-MSH receptors, reducing DNA damage from UV radiation.[3] Ongoing research on these oligopeptides may lead to topical agents that replenish or boost melanin density in the skin, potentially reducing the incidence of skin cancer and imparting protection for those with photosensitive disorders.

Conversely, inhibiting melanin synthesis is important for regulating hyperpigmentation disorders. PTPD-12, a synthetic peptide derivative, was found to induce depigmentation via an autophagy pathway when topically applied to human skin explants.[17] Decapeptide-12, a relatively new peptide, has been found to be safer than hydroquinone in reducing melanin content, with efficacy of more than 50% after 16 weeks of twice-daily treatment.[18] Building upon this promising profile, a topical formulation containing decapeptide-12 was evaluated in a randomized, split-face, placebo-controlled study and was found to significantly improve the appearance of recalcitrant melasma.[19]

CONCLUSION

The utilization of bioactive peptides in dermatology is advancing, presenting advantages difficult to achieve with conventional therapies. Nevertheless, ongoing optimization to address the two major drawbacks of peptide development in dermatology, limited skin permeability and poor in vivo stability, is necessary.[20] Additionally, continued evaluation of efficacy, dose optimization, and safety with clinical and product-specific studies is crucial.

Disclosure

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