Skin hyperpigmentation most commonly is caused by melasma, a cutaneous disorder associated with an overproduction of melanin by the tyrosinase enzyme. There currently are skin-lightening agents that are both effective and cytotoxic, or slightly effective and nontoxic. The agent most commonly prescribed for the treatment of hyperpigmentation is hydroquinone (HQ), a hydroxyphenolic compound that inhibits melanin production by inhibiting tyrosinase. In addition to topical agents, in-office aesthetic procedures such as chemical peeling, lasers, and dermabrasion are used for the treatment of hyperpigmentation. These nontopical treatment modalities carry unpredictable adverse reactions. Lumixyl, a novel synthetic oligopeptide-containing formulation that inhibits both mushroom and human tyrosinase enzymes, has been shown to have more efficacy than HQ at similar concentrations without cytotoxicity. In-use clinical safety studies have shown a low irritation profile with no visible signs of irritation or allergic reaction and good tolerability. Studies and results suggest Lumixyl can be a nonirritating and useful, physician-dispersed cosmetic alternative for the treatment of melasma.
hydroquinone (HQ), a hydroxyphenolic compound that inhibits the conversion of 3,4-dihydroxyphenyalalanine (DOPA) to melanin by inhibiting tyrosinase, the enzyme that begins the process of making melanin in skin.\textsuperscript{1,2} Hydroquinone preparations vary from 2% (over-the-counter) to 5% (prescription strength) with fluctuating positive and reversible results in 60% to 90% of patients treated with HQ.\textsuperscript{2} Adverse effects, such as erythema; stinging; irritant and allergic contact dermatitis; nail discoloration; post-inflammatory hyperpigmentation; hypopigmentation called “confetti-like”; and a chronic adverse effect, ochronosis, a permanent rippled sooty pigmentation, have been associated with HQ treatment.\textsuperscript{1,2} Due to possible adverse effects, such as toxicity to melanocytes, carcinogenicity, and exogenous ochronosis, the US Food and Drug Administration (FDA) has suggested that HQ be classified as a drug and regulated more stringently.\textsuperscript{4} Other forms of treatment for hyperpigmentation include kojic acid, a fungal metabolic product and potent antioxidant that inhibits catecholate activity of tyrosinase enzymes.\textsuperscript{1} Higher concentrations of kojic acid do not increase depigmentation and carry the adverse effect of allergic contact dermatitis.\textsuperscript{5} Azelaic acid is a dicarboxylic acid isolated from \textit{Pityrosporum ovale}, that is effective on hyperactive melanocytes.\textsuperscript{3} Azelaic acid causes slight irritation and has greater efficacy than HQ 2%, but efficacy has not been shown to be greater than HQ 4%.\textsuperscript{3} Topical tretinoin (retinoic acid) concentrations of 0.05% to 1% reduce pigmentation by dispersing pigment granules within keratinocytes and accelerating the turnover of epidermal cells, which helps to remove the dispersed pigment.\textsuperscript{2} Retinoids carry the adverse effects of erythema, peeling, burning, stinging, and postinflammatory hyperpigmentation and use of sunscreen is required during treatment with topical retinoids.\textsuperscript{2,5} Ascorbic acid (vitamin C) and tocopherol (vitamin E) are synergistic and usually formulated together. Ascorbic acid transforms melanin to leucomelanin (without color), changing melanin from jet black to light tan, though it is quickly oxidized in aqueous solutions.\textsuperscript{1,5} A novel synthetic oligopeptide (decapeptide 12) formulation, Lumixyl, has been shown to inhibit mushroom and human tyrosinase enzymes.\textsuperscript{3} A team of dermatologic researchers from Stanford University, California, formulated the novel synthetic oligopeptide, which is available as topical cosmetic cream and serum, with less adverse reactions and without toxicity to melanocytes that is available exclusively for distribution through physicians.\textsuperscript{3}

\section*{HYPERPIGMENTATION AND IRRITATION}
There are various at-home topical skin care treatments as well as in-office aesthetic procedures for the treatment of hyperpigmentation, including chemical peeling, laser treatments, and dermabrasion.

\section*{Chemical Peeling}
Chemical peeling of both superficial and medium depth involves removal of melanin, with varying success. Formulations of glycolic acid 50% to 80%, light Jessner solution, azelaic acid, and trichloroacetic acid 15% to 75% also are available for the treatment of hyperpigmentation.\textsuperscript{1,2} The results of chemical peeling can be unpredictable and reactions caused by chemical peels such as pigmentedary changes, hyperpigmentation, and hypopigmentation may occur, mostly in individuals with skin of color. Deep chemical peels can be complicated by keloid formation and hypertrophic scarring. Additional adverse effects of chemical peels are atrophy, bacterial and viral infections, milia, and telangiectasias.\textsuperscript{1} Trichloroacetic acid has possible severe adverse effects, including instantaneous epidermal necrosis, postinflammatory hyperpigmentation, and hypertrophic scarring. Glycolic acid at concentrations of 50% to 80% produces epidermolysis, which necessitates its use only in the in-office setting by physicians.\textsuperscript{2} Application of trichloroacetic acid can be accompanied by burning and possible pain. Patients with Fitzpatrick skin types I and II with a medical history of herpes simplex virus infection and/or without good compliance and tolerance should avoid treatments with trichloroacetic acid or can be given prophylactic antiviral medication.\textsuperscript{2}

\section*{Laser Treatment}
Laser treatment involves the disruption of melanin granules. Melasma and postinflammatory hyperpigmentation show only a moderate response to laser treatment. Treatment of facial and hand lentigines with Q-switched pigment-specific lasers has shown excellent response, while treatment of melasma with Q-switched lasers often results in initial clearance followed by recurrence or postinflammatory hyperpigmentation.\textsuperscript{2} Postinflammatory hyperpigmentation is a pathophysiologic response to cutaneous inflammation or trauma that can cause a melanocyte reaction of regular, increased, or decreased production of melanin.\textsuperscript{1} The inflammatory process stimulates hypertrophic melanocytes, which secrete more melanin. Postinflammatory hyperpigmentation is more obviously noted in brown or black-skinned individuals, has no gender or age predominance, and is found at the site of the preceding inflammation.\textsuperscript{6} Use of a resurfacing laser (pulsed/scanned CO\textsubscript{2}, erbium:YAG) for refractory dermaltypetype melasma has a more optimistic response. Resurfacing lasers ablate the superficial segments of the skin
including the abnormal melanocytes. One of the most common complications from the treatment of melasma with lasers, including Q-switched ruby lasers (694 nm), CO₂ lasers alone or in combination with Q-switched alexandrite lasers (755 nm), erbium:YAG lasers (2490 nm), and pigmented lesion dye lasers (500–520 nm) is postlaser hyperpigmentation, predominantly in individuals with darker complexions.\(^1\) Intense pulsed light (IPL) therapy has been used for hyperpigmentation treatment, as well as improvement of telangiectasias, fine lines and wrinkles, and erythema. Multiple treatment sessions with IPL have been shown to be necessary. Lighter complexioned individuals with epidermal melasma treated with 2 pulses of IPL therapy can obtain 76\% to 100\% clearance from baseline; however, after 4 sessions of treatment with IPL, mixed melasma and deep-pigmented lesions showed only fair or poor clearance (<50\%) based on physician experience scoring.\(^2\) Compliance can be compromised with treatment that requires multiple sessions. Combined treatment of IPL with topical therapies such as HQ or tretinoin can offer more effective response to melasma treatment.\(^3\) Treatment of melasma and postinflammatory hyperpigmentation in patients with Fitzpatrick skin type VI with topical tretinoin cream 0.1\% have had considerable lightening effects, though 50\% of these patients have experienced moderate dermatitis.\(^6\)

**Dermabrasion**

Dermabrasion has been used for hyperpigmentation and melasma treatment, but is not considered a standard treatment modality due to adverse reactions. Adverse reactions that have been associated with dermabrasion include keloids, milia, pruritus, and postinflammatory hyperpigmentation.\(^1\)

**Synthetic Oligopeptide Formulation**

Lumixyl is an oligopeptide-containing formulation that inhibits both mushroom and human tyrosinase enzymes and has shown to have more efficacy than HQ at similar concentrations without toxicity to melanocytes. Short-sequence oligopeptides P3 and P4 have been shown to have similar inhibitory activity against mushroom tyrosinase with higher potency with half-maximal inhibitory concentration (IC\(_{50}\)) values of 123 µM and 40 µM, respectively, compared with 680 µM for HQ.\(^6\) It has been shown that peptides P3 and P4 are more potent inhibitors of human tyrosinase activity than HQ at concentrations as low as 30 µM. At 100 µM, human tyrosinase activity was reduced by 35\% for P4 and 25\% for P3. When testing the effects of HQ and oligopeptides P3 and P4 at a concentration of 100 µM on the melanin content of melanocytes, P3 and P4 reduced melanin content by 27\% and 43\%, respectively (SD=2\%), while HQ was found to be 100\% cytotoxic.

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A participant with mild-to-moderate hyperpigmentation at baseline (A) and after 16 weeks of treatment (B) in a split-face, double-blind, randomized, placebo-controlled study of the novel synthetic oligopeptide-containing formulation, Lumixyl.
to melanocytes. Cytotoxic and proliferative effects of HQ, P3, and P4 on melanocytes were tested at various concentrations. It was shown that HQ is cytotoxic to melanocytes at concentrations of 100 µM or greater. Melanocyte proliferation rates for peptide P3 did not change at varying concentrations of 1 µM, 10 µM, or 100 µM.6

After retrieving this data, 5 healthy women between the ages of 32 and 42 with moderate recalcitrant melasma were selected to participate in a 16-week, split-face, double-blind, randomized, placebo-controlled study of the oligopeptide-containing formulation, Lumixyl.3 All 5 participants were women with Fitzpatrick skin types III through IV; 3 were of Hispanic decent and 2 were of Asian decent with moderate-to-severe recalcitrant melasma. All 5 participants had a history of failed improvement of melasma after 6 months of treatment with combination HQ 4%, retinoin 0.05%, and fluocinolone acetonide 0.01%. After a 16-week, split-face study, the side of the face treated with the oligopeptide formulation revealed greater than 40% improvement in melasma at 12 weeks and greater than 50% improvement at 16 weeks. General appearance of the side of the face treated with the Lumixyl oligopeptide formulation showed greater than 70% improvement. Global Assessment Scores were used to measure the degree of improvement. The Global Assessment Scores demonstrated good agreement between participants and physician graders. For the side of the face treated with placebo, participant and blinded physician examinations of digital photographs did not reveal any significant improvement in melasma at 16 weeks posttreatment compared to baseline (Figure). After completion of the study, volunteer satisfaction scores revealed 2 of the participants were very satisfied with the appearance of the side of the face treated with the oligopeptide-containing formulation and 3 were extremely satisfied.3

Efficacy
The oligopeptide formulation of Lumixyl has been shown to have a low irritation profile with the in-use clinical safety studies showing no visible signs of irritation or allergic reaction. Repeated insult patch testing of 50 participants, provided additional support to show that Lumixyl is nonirritating and did not cause allergic reaction. Supplementary repeated insult patch testing studies were performed to investigate irritation or allergic reaction and revealed that even with a higher concentration at 10 times the recommended dosage, an allergic reaction or irritation failed to be elicited.3 When comparing HQ to the oligopeptide formulation, they are both competitive inhibitors of mushroom and human tyrosinase enzymes; however, HQ is chemically formulated, an IC50 of at least 700 µM is needed to inhibit tyrosinase enzyme activity by 50% in the steady state, oxidizes easily in water, and oxidized by-products are cytotoxic to melanocytes.6 Treatment of hyperpigmentation with Lumixyl requires a lower IC50 of 40 µM to inhibit tyrosinase activity by 50% in the steady state compared to HQ, does not oxidize easily in water, contains no by-products, and biodegrades easily in the skin. Although skin-lightening treatment has been dominated by HQ since the 1950s, it is a known irritant and a recent proposal by the FDA seeks to classify HQ as a regulated drug due to the potential health risks associated with its use.7 There are only a few FDA–approved drug products that contain HQ. Patients with melasma being treated with HQ must discontinue use of HQ periodically due to potential risks that HQ carries. Skin lightening can be sustained safely during these break periods with the use of Lumixyl and eventually can be used over the long-term to sustain an even complexion after the HQ regimen has been completed.7

Combination formulations also may be used in conjunction with the synthetic oligopeptide formulation to optimize treatment results. Retinoids have been used in combination with Lumixyl and can be applied at night, with continued advisement of wearing sun protection with a minimum sun protection factor of 30 during the day. Because exfoliation helps to promote cell turnover and hastens results, it also can be used with cleansers that contain microbeads or with at-home skin exfoliating devices. Further combination treatment also may include laser and light therapies, with application of the oligopeptide formulation twice-daily for 2 weeks prior to the first in-office laser treatment.7

Comment
Studies suggest that the Lumixyl oligopeptide formulation may be a safe and effective modality for the treatment of melasma, including during pregnancy. Lumixyl has not shown to cause permanent loss of melanocytes and therefore will not lead to hypopigmented patches. Aggressive therapies for the treatment of hyperpigmentation, such as chemical peels or laser therapy, can pose difficulties with patient compliance and tolerance. The physical qualities of topical skin care regimens are of importance because negative traits such as bad odor, inelegant texturing, irritation, and quick oxidation cause decreased patient satisfaction. Lumixyl has no scent, does not oxidize, and has a silky texture in comparison to
Similarly effective alternatives, which makes it a well-tolerated product.

CONCLUSION
The oligopeptide-containing formulation, Lumixyl, is a nonirritating and useful physician-dispensed cosmetic alternative to more aggressive topical therapies, chemical peels, and laser treatments for the treatment of melasma and hyperpigmentation. It is proving to be a viable option in the management of melasma when used alone.

REFERENCES