

Clinical Evaluation of a 4% Hydroquinone + 1% Retinol Treatment Regimen for Improving Melasma and Photodamage in Fitzpatrick Skin Types III-VI

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ABSTRACT

The benefits of monotherapy with hydroquinone for melasma and retinoids for photodamaged skin is well established. Here we report results of a hydroquinone skincare regimen designed for melasma treatment combined with a cosmetic retinol cream on subjects presenting with both melasma and facial photodamage in a 24-week study. Improvement in melasma and photodamage efficacy parameters of melasma pigmentation intensity and melasma area and severity index (MASI), as well as overall photodamage and mottled hyperpigmentation were found by week 4, the first post-baseline time point. By week 8 significant improvements were also found in melasma disease severity assessment, tactile roughness, fine wrinkles, crepiness, actinic lentigines, and laxity. By week 18 significant reduction in coarse wrinkles was evident. Benefits persisted through the study end on the panel of 31 subjects, with over ¾ of participants demonstrating improvements in 10 of the 11 graded attributes. For the remaining attribute, coarse wrinkling, approximately 50% of the panel showed improvement. The regimen produced an average of “marked improvement” in melasma severity (51-75% improvement). Results of tolerance evaluations documented overall treatment mildness for a majority of the study participants. Subject questionnaires concur with high ratings of the study regimen for tolerability, efficacy perception, product aesthetics and overall treatment satisfaction in subjects of Fitzpatrick Skin Type III-VI classification with melasma and photodamage in mild-to-moderate severity.

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INTRODUCTION

Hyperpigmentation disorders, including melasma, are common, particularly in women,¹⁻³ among people with darker complexions (Fitzpatrick skin types IV-VI), and especially those living in areas of intense ultraviolet (UV) radiation such as Hispanics (especially of Caribbean origin), Asians and African Americans.⁴⁻⁹

Melasma is not uncommon in the United States (US). In a study of 2000 dermatology patients of black origin in Washington, pigmentary problems other than vitiligo were the third most commonly-cited skin disorder.¹⁰ Among a Latino population in Dallas, prevalence of melasma was 8.8%, and 4.0% of respondents reported a previous occurrence.¹¹ A questionnaire sent to an Arab population resident in Detroit identified a 14.5% incidence of melasma and 56.4% complained primarily of alterations in skin tone.¹² It has been estimated that 50% to 70% of pregnant women in the US develop melasma.¹³ Melasma can also lead to decreased socializing, diminished self-esteem and lower productivity, due to its psychosocial impact.¹⁴⁻¹⁶ Treatment can have a positive impact on quality of life.¹⁷

It is not uncommon for patients with melasma to exhibit symptoms of facial photodamage such as mottled hyperpigmentation,

lentigines, fine and coarse wrinkling, tactile roughness and elastosis, and it would be advantageous to provide a skin care system that addresses both.¹⁸⁻²¹

Monotherapy with hydroquinone (HQ) has been used to treat hyperpigmentation for more than 50 years. HQ is considered the gold standard. While controversy exists regarding the long-term safety of HQ, its efficacy in treating melasma, both alone and in combination with other agents is well established.²² Pigment lightening by HQ becomes evident after 5–7 weeks of treatment and common adverse events (AEs) include erythema and burning.²³

Topical retinoids have also been shown to be effective in melasma treatment,^{24,25} and as well as reducing many of the clinical manifestations of photodamaged skin.²⁶ Treatment related AEs include retinoid dermatitis characterized by burning or stinging, erythema, scaling and dry skin.

Unfortunately, monotherapy, whether HQ or retinoid, can require significant treatment duration before meaningful results are evident.²⁷ As a result, coupled with various AEs when high concentrations are applied, combination therapies have become popular.

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It is well known that the combined use of HQ and tretinoin improves both facial photodamage and melasma. Clinically, HQ therapy combined with retinoids such as tretinoin and/or corticosteroids has been found to be more effective in treating melasma than HQ monotherapy.²⁸⁻³¹ In addition, a combination of 4% HQ and 0.3% retinol cream was shown to be more effective than tretinoin 0.05% emollient cream in improving collective signs of photodamage in terms of dyspigmentation, fine wrinkles, and tactile roughness in 16 weeks.³²

An easy-to-follow skin care system is available that incorporates a 4% formulation of HQ into a comprehensive skin care regimen providing cleansing, toning, exfoliation, and photo-protection. The objectives of our study were to evaluate treating epidermal melasma and photodamage with this skin care system in conjunction with retinol 1.0% cream for up to 24 weeks.

METHODS

Study Design

Single-center, investigator-blinded study. The IntegReview Institutional Review Board (IRB) in Austin TX approved the protocol, and the study was conducted according to the principles of the 2004 version of the Declaration of Helsinki. All patients signed informed consent.

Inclusion Criteria

Patients were eligible for study enrollment if they were healthy females aged 35 to 65 years with mild-to-moderate epidermal melasma (score of 2-5 on the Investigator Melasma Disease Severity Assessment), mild-to-marked melasma pigmentation (score of 1-7 on the Investigator Pigmentation Intensity Assessment), mild-to-moderate facial photodamage (score of 2-5 on the overall Facial Photodamage Scale), and a Fitzpatrick skin type of III to VI. Their cutaneous melanosis was required to have remained stable for the last three months.

Treatment Regimen

Patients were treated with the 4% HQ skin care system (Obagi Nu-Derm®, Obagi Medical Products Inc., Irvine, CA) and 1.0% retinol and moisturizer for 24 weeks. The hydroquinone skin care system involved applying the following proprietary products: foaming gel cleanser (twice daily), toner (twice daily), 4% hydroquinone (twice daily), exfoliant containing alpha hydroxy acids (each morning), and sunscreen (SPF 50) containing micronized zinc oxide and octinoxate (each morning). Retinol 1.0% cream was applied each evening mixed 1:1 with 4% hydroquinone. Subjects performed the first test material application under supervision in the clinic.

Outcome Measures

Investigators evaluated melasma disease severity, melasma pigmentation intensity, melasma improvement assessment, photodamage improvement and local cutaneous tolerability

(erythema, dryness, peeling) based on the criteria in Table 1-3. Patients evaluated any burning or stinging (Table 3), and completed questionnaires regarding their skin condition, regimen performance, product aesthetics and tolerance.

In addition, overall melasma severity was assessed using the Melasma Area Severity Index (MASI).²⁴ The melasma severity in each of the four facial regions (forehead [F], right malar region [MR], left malar region [ML], and chin [C]) was assessed based on three variables: percentage of the total area involved (A), pigment intensity (PI), and homogeneity (H), see Table 4, and MASI calculated using the following equation:

$$\text{MASI} = 0.3 (\text{PI}_F + \text{H}_F) A_F + 0.3 (\text{PI}_{MR} + \text{H}_{MR}) A_{MR} + 0.3 (\text{PI}_{ML} + \text{H}_{ML}) A_{ML} + 0.1 (\text{PI}_C + \text{H}_C) A_C$$

Values 0.3, 0.3, 0.3, and 0.1 before each bracket represent the respective percentages of the total facial area. The maximum MASI score is 48.

TABLE 1.

Investigator Assessment of Melasma Disease Severity and Pigmentation Intensity (attributes graded separately)

Severity	Score	Melasma Coverage of Face	Facial Pigmentation Intensity
None	0	No noticeable lesion area	
Minimal/Trace	1	1%-10%	Localized
	2	11%-25%	Mild, diffuse
3			
Moderate	4	26%-40%	Moderate, diffuse
	5		
Marked	6	41%-50%	Marked, dense
	7		
Severe	8	>50%	Severe, dense

TABLE 2.

Melasma Improvement Assessment

Score	Change from Baseline
0	Worse
1	Unchanged - No detectable improvement from baseline evaluation
2	Slight improvement (1%-10%)
3	Mild improvement (11%-25%)
4	Moderate improvement (26%-50%)
5	Marked improvement (51%-75%)
6	Almost complete clearing (76%-90% improvement)
7	Complete clearing, no signs of hyperpigmentation

TABLE 3.**Tolerability Evaluations - Objective Irritation (clinically graded): Erythema, Dryness and Peeling; Subjective Irritation (assessed by subjects): Burning and Stinging**

Score	Erythema	Dryness	Peeling	Burning	Stinging
0=None	No erythema present	No dryness present	No peeling present	No burning present	No stinging present
1=Mild	Slight but definite redness	Slight but definite dryness	Slight but definite peeling	Slight burning sensation	Slight stinging sensation
2=Moderate	Definite redness	Definite dryness	Definite peeling	Definite warm, burning, somewhat bothersome	Definite stinging, somewhat bothersome
3=Severe	Marked redness	Marked dryness	Marked peeling	Hot burning sensation may interrupt daily activities or sleep	Marked stinging sensation may interrupt daily activities or sleep

Facial photodamage was assessed using an overall integrated score (range 0-6, where 0=none and 6=severe). Individual photodamage characteristics were reported, including lentiginos, tactile roughness, laxity, mottled hyperpigmentation, fine wrinkling, coarse wrinkling, and crepiness (range, 0-5, where 0=none and 5=very severe).

Full-face images were taken of each prospective subject using the VISIA CR (Canfield Imaging Systems, Fairfield, NJ).

The above-mentioned outcome measures were evaluated at baseline and weeks 4, 8, 12, 18, and 24; except the melasma improvement assessment (which was not evaluated at baseline). Adverse events (AEs) were recorded, if applicable throughout the study.

Statistical Analyses

Changes from baseline in efficacy parameters of melasma disease severity, melasma pigmentation intensity, MASI, overall integrated photodamage, individual photodamage attributes of lentiginos, tactile roughness, laxity, mottled hyperpigmentation, fine wrinkling, coarse wrinkling, and crepiness were evaluated using paired t-tests. An α of ≤ 0.05 was considered statistically significant.

TABLE 4.**Assessment of Pigment Intensity, Lesion Size, and Homogeneity**

Score	Pigment Intensity (Darkness) [PI]	Lesion Size (Area) [A]	Homogeneity [H]
0	Absent	No involvement	Absent
1	Slight	>10%	Slight
2	Mild	10%-29%	Mild
3	Marked	30%-49%	Marked
4	Severe	50%-69%	Maximum
5		70%-89%	
6		90%-100%	

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RESULTS

The study was conducted between November 2014 and June 2015.

Patients

Overall 38 patients were enrolled in the study and 31 (81.6%) completed the study. Three subjects requested withdrawal, two were discontinued due to noncompliance and two were lost to follow-up but included in the Intent-to-Treat [ITT] Population. Patients had a mean age of 50.8 years old with 33.3% Asian (11/33), 27.3% Hispanic or Latino (9/33), 24.2% (8/33) Black or African American, 12.1% (4/33) Caucasian, and 3.0% (1/33) Pacific Islander. They had Fitzpatrick skin types of III (51.5%), IV (21.2%), V (24.2%), or VI (3.0%).

No patient discontinued the study due to lack of efficacy or adverse event.

At baseline, mean melasma disease severity and pigmentation intensity scores were moderate [4.27 (± 0.94) and 4.88 (± 1.39), respectively]. The MASI was 15.32 (± 6.87) and overall integrated facial photodamage score was mild-to-moderate

TABLE 5.**Baseline Efficacy Parameters**

Parameter	Mean Score (\pm SD)
Melasma Disease Severity	4.27 \pm 0.94
Melasma Pigmentation Intensity	4.88 \pm 1.39
MASI	15.32 \pm 6.87
Overall Integrated Facial Photodamage	3.76 \pm 0.79
Lentiginos	2.03 \pm 1.10
Tactile Roughness	2.58 \pm 0.75
Laxity	2.67 \pm 0.69
Mottled Hyperpigmentation	3.33 \pm 0.69
Fine Wrinkling	2.79 \pm 0.55
Coarse Wrinkling	2.24 \pm 0.87
Crepiness	2.39 \pm 0.83

TABLE 6.

Self-Assessment of Baseline Skin Condition (N=33)

Parameter	Very Much	A Lot	A Little	Not at All
How embarrassed or self conscious have you been because of your skin?	11 (33.3%)	11 (33.3%)	9 (27.3%)	2 (6.1%)
How much have people focused on your skin discoloration rather than on what you are saying or doing?	2 (6.1%)	12 (36.4%)	11 (33.3%)	8 (24.2%)
How much has your skin discoloration made you feel unattractive to others?	12 (36.4%)	13 (39.4%)	6 (18.2%)	2 (6.1%)
How much effort have you put into hiding your skin discoloration from others?	14 (42.4%)	9 (27.3%)	8 (24.2%)	2 (6.1%)
How much has your skin affected any of your social or leisure activities?	3 (9.1%)	9 (27.3%)	11 (33.3%)	10 (30.3%)

(3.76 \pm 0.79); Table 5. Baseline scores for individual facial photodamage parameters were for lentigines 2.03 (\pm 1.10), tactile roughness 2.58 (\pm 0.75), laxity 2.67 (\pm 0.69), mottled hyperpigmentation 3.33 (\pm 0.69), fine wrinkling 2.79 (\pm 0.55), coarse wrinkling 2.24 (\pm 0.87), and crepiness 2.39 (\pm 0.83); Table 5.

Baseline patient self-assessment of skin condition is summarized in Table 6. Almost everyone (93.9%) was embarrassed or self-conscious about their skin discoloration to some extent. Most bothersome were feelings of being unattractive (“very much” or “a lot” in 75.8% of patients) or having to hide skin discoloration from others (“very much” or “a lot” in 69.7% of patients).

Efficacy

The 4% HQ system plus retinol 1.0% regimen was associated with a significant reduction in baseline melasma disease severity and pigmentation intensity from week 8 and week 4, respectively (P <.001, Figures 1 and 2). In addition, there were significant reductions in MASI and overall integrated facial photodamage from week 4 (P =.003 and P =.044, respectively).

By week 24, investigators reported a 37.1% mean improvement in melasma disease severity [from 4.27 (\pm 0.94) to 2.68 (\pm 1.17), P <.001], a 47.7% mean improvement in melasma pigmentation intensity

[from 4.88 (\pm 1.39) to 2.58 (\pm 1.15), P <.001], and a 64.1% reduction in MASI [from 15.32 (\pm 6.87) to 5.58 (\pm 4.24), P <.001; Figure 3].

The MASI improved in 96.8% of patients, with improvements in melasma disease severity and pigmentation intensity in 83.9% and 93.5% of patients, respectively.

Investigators also reported a 42.4% mean change in overall integrated facial photodamage [from 3.76 (\pm 0.79) to 2.19 (\pm 0.79), P <.001; Figure 3]. Improvements were noted in 96.8% of patients. Changes in specific aspects of photodamage were significant from week 4 (mottled hyperpigmentation, P <.001), week 8 (lentigines, tactile roughness, laxity, fine wrinkling [all P <.001], and crepiness [P =.006]), or week 18 (coarse wrinkling, P =.002; Figure 4).

At week 24, 90.4% of patients considered their study treatment was “more effective” or “much more effective” than other treatments; 93.6% percent were “very satisfied” or “satisfied” with the overall effectiveness; and 67.8% considered the study treatment “easy” or “very easy” to apply. Skin felt “smoother” or “much smoother” to 96.8% of patients.

The majority of patients reported improvements in other skin characteristics. A “good”, “very good”, or “excellent” improvement in skin texture (roughness) was reported at weeks 12 and

FIGURE 1. Investigator melasma disease severity assessment scores (baseline to week 24, ITT Population, N=33).

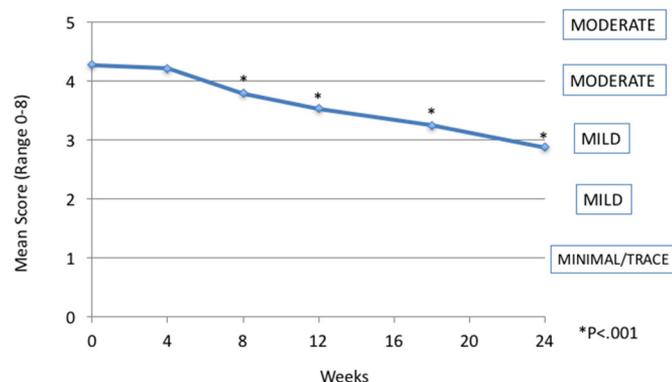


FIGURE 2. Investigator melasma pigmentation intensity assessment scores (baseline to week 24, ITT Population, N=33).

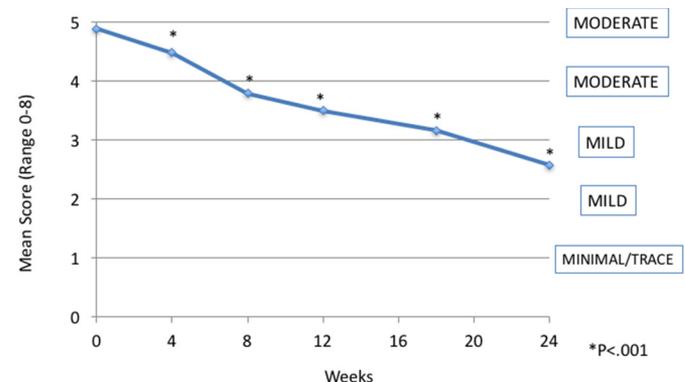
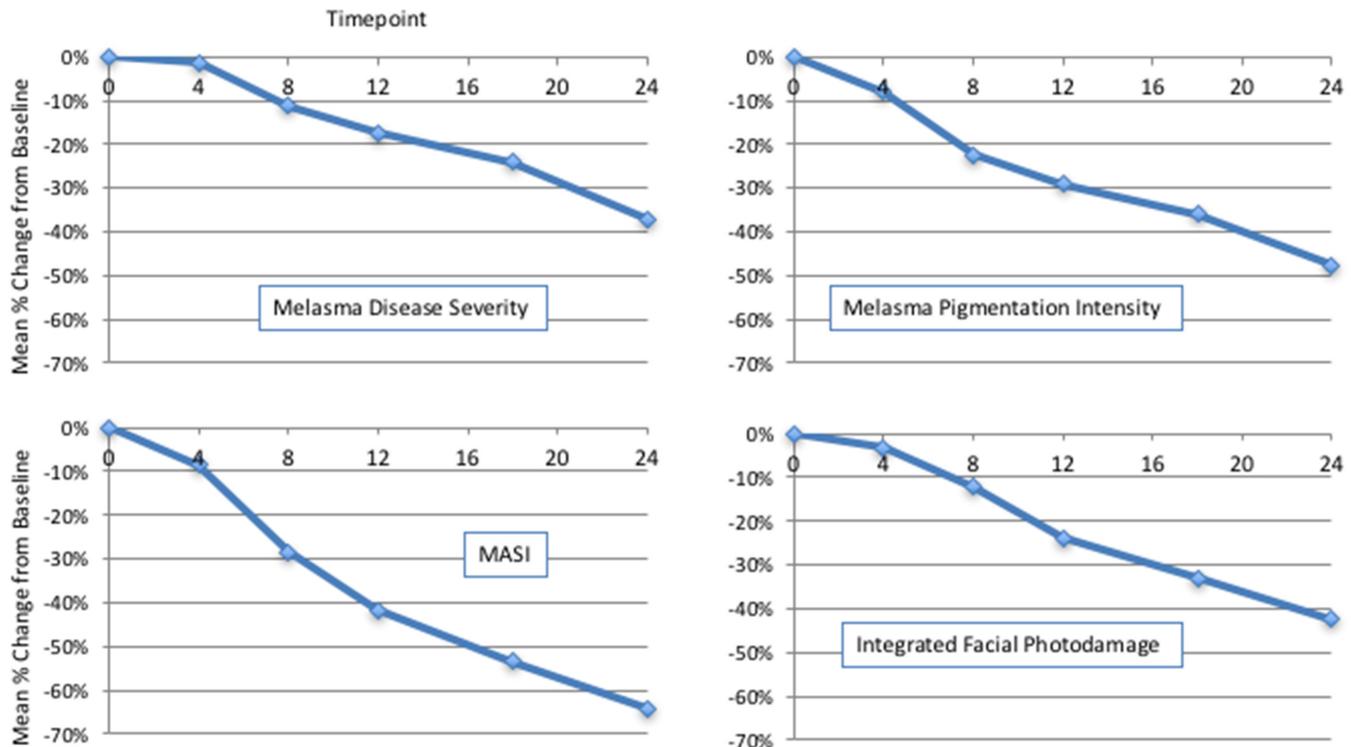


FIGURE 3. Mean percent change in efficacy parameters from baseline (ITT population, N=33).

24 in 75.0% and 74.2% of patients, respectively, in 75.0% and 84.0% of patients for skin firmness (laxity/looseness), in 81.2% and 87.1% of patients for brown spots/dyschromia, and in 53.1% and 64.5% of patients for fine lines and wrinkles.

Representative patient example photographs show improvement in melasma severity, pigmentation intensity and signs of photodamage at week 18 and at study end (Figure 5).

Tolerability

None of the subjects using the test material received a score greater than 2 (moderate) for the tolerability parameters of erythema, burning, and stinging at any time point. One (2.8%) subject received a score of 3 (severe) for dryness and peeling at week 4 and week 8.

There were a total of 27 AEs (dry skin, erythema, pruritus, skin exfoliation), with 21 considered to be probable related to the test materials and one considered to be possibly related to the test materials.

DISCUSSION

This study demonstrated that treatment of epidermal melasma with a 4% HQ skin care system plus retinol 1.0% cream achieves significant reductions in melasma severity and pigmentation intensity from week 4 onward. In addition, the combination treatment led to a significant and early improvement

in photodamage. Patient satisfaction was high and the study treatment was associated with improvement in skin condition. Treatment was generally well tolerated with only one patient reporting severe cutaneous intolerance (dryness and peeling) early in the treatment schedule (week 4 and 8). Many of the objective and subject reactions observed or reported are typical for topical products that contain retinol or HQ.

The results from this study are consistent with those reported treating melasma using the 4% HQ skin care system in conjunction with tretinoin (0.025%,³³ 0.05%³⁴, 0.1%,³⁵ or 0.2%³⁶). Only

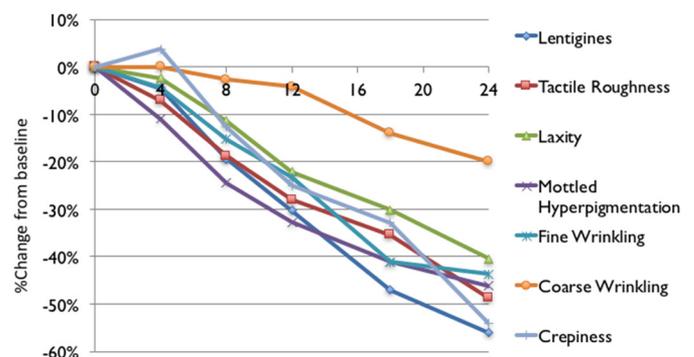
FIGURE 4. Mean percent change in individual photodamage parameters from baseline (ITT population week 4-24, N=33).

FIGURE 5. Representative patient examples showing improvements in melasma severity and photodamage from baseline to week 18 and 24.

those studies utilizing lower concentrations (of 0.025% and 0.02% tretinoin) included patients with mild melasma. However, all these studies have limitations as they were open-label, and differences in patient characteristics and study design limit meaningful direct comparison.

A previous study investigated the additional benefits using the 4% HQ skin care regimen in combination with tretinoin 0.2%.³⁶ Melasma severity and pigmentation intensity was significantly reduced within four weeks. A study in patients previously treated with botulinum toxin Type A (BoNT-A) found that the use of a 4% HQ skin care system plus tretinoin can further enhance the improvements in facial appearance attained with BoNT-A, with significant improvement in fine lines/wrinkles and hyperpigmentation.³⁷ In addition, the use of a 4% HQ skin care system plus tretinoin 0.05% in patients undergoing intense pulsed light therapy for photorejuvenation was associated with significantly lower hyperpigmentation and laxity scores compared with placebo.³⁸

Unlike previous studies, our study included a good representation of patients who tend to be most at risk of melasma. A potential limitation of our study was that it was restricted to females. Melasma occurs more commonly in females,³⁹ and has a propensity for darker skin.⁴⁰ Some research suggests that there may be differences in the histopathology of melasma between males and females,⁴¹ but our inclusion criteria did not allow such study.

CONCLUSION

Using a 4% hydroquinone skin care system plus 1.0% retinol cream to treat mild-to-moderate melasma can significantly reduce melasma severity and pigmentation intensity within four weeks. In addition, this combination treatment can significantly improve all aspects of photodamage, including coarse wrinkling. Improved skin condition and high levels of patient satisfaction were also reported, and the treatment regimen was generally well tolerated.

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DISCLOSURES

The study was funded by Valeant Pharmaceuticals North America, LLC. Dr Rendon has been an investigator for Obagi Medical Products. Ms Barkovic was an employee of Valeant Pharmaceuticals when this study was completed.

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