Split-Face Comparison of an Advanced Non-Hydroquinone Lightening Solution to 4% Hydroquinone

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INTRODUCTION
Hyperpigmentation is a primary concern for many cosmetic patients because of its high rate of occurrence and significant impact on perceived age. While 4% hydroquinone has been the gold-standard of treatment, there is a growing interest in non-hydroquinone solutions however many of these newer solutions fail to deliver equivalent improvement.

METHODS
This double-blind, randomized, split-face study compares the effects of a new OTC non-hydroquinone lightening product (JM) to an available 4% hydroquinone lightening solution (OB) on the appearance of hyperpigmentation, texture and fine lines and wrinkles. Comparisons were determined by both physician assessment and subject self-assessment at baseline, 4, 8 and 12 weeks.

RESULTS
Physician assessment showed statistically equivalent improvement on both sides of the face with the JM side showing equivalent or superior improvement average improvement in all assessed categories. Subject self-assessment showed a significant preference for the JM product over the 4% hydroquinone and a substantially higher perception of overall improvement over 4% hydroquinone ($p=0.058$).

CONCLUSION
Overall, the results of this study show the JM product to be equivalent if not superior to 4% hydroquinone for results and patient satisfaction.

INTRODUCTION

Hyperpigmentation is a primary concern for cosmetic patients because of its high rate of occurrence and significant impact on perceived age. In the United States, as many as 90% of Caucasians over the age of 60 and 20% of Caucasians under the age of 35 experience lentigines.[1, 2] Further, 8.8% of individuals of Latino descent and up to 40% of persons of Asian descent experience melasma.[3]

Non-uniform color distribution is a visual indicator of perceived age and health. One study showed that, even in the absence of wrinkles, color distribution was highly positively correlated with the actual age of the person and perceived age. In addition, the homogeneity of pigment distribution on the face correlated positively with perceived attractiveness, healthiness, and youthfulness and was inversely correlated with perceived aging. Further, non-uniform color distribution could account for as much as 20 years of variance in perceived age.[4]

Hydroquinone has been the gold-standard topical solution for hyperpigmentation, due to consistency and quality of results. Additionally, studies have shown that concomitant use of hydroquinone and tretinoin is more effective than hydroquinone alone[5,6] functioning via multiple pathways to inhibit melanin production. Hydroquinone inhibits tyrosinase activity during melanin synthesis, while retinoids function upstream in the melanin production cycle by regulating tyrosinase transcription[7] and increase cellular turnover, helping to exfoliate pigmented skin.

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Additionally, retinoids are vital to the maintenance of optimal skin health and are utilized extensively by dermatologists. Retinoids have independently been shown to decrease the appearance of fine lines and wrinkles, increase epidermal proliferation leading to epidermal thickening, and increase compaction of the stratum corneum for greater luminosity of the skin and the biosynthesis & deposition of glycosaminoglycans to enhance collagen and elastin in the skin.

In response to consumer demand for non-hydroquinone lightening solutions, there is a continuous influx of new "lightening" products. Very few, however, combine the benefits of lightening agents and retinoids and many lack independent data to support their claims, instead relying on in-vitro or in-vivo data on individual ingredients to act as a surrogate for study data. Without testing the final formulation, however, it is impossible to know if the ingredients function as desired or if interactions in the final formulated product nullify anticipated benefits. Due to the lack of evidence and underwhelming results from many non-hydroquinone solutions, the gold standard recommendation for hyperpigmentation remains hydroquinone, often combined with a retinoid and/or in-office treatment.

This study investigates the effects of a new non-hydroquinone product combining two new lightening agents plus a host of established lightening technologies (Table 1) with all-trans-retinol to address multiple stages of melanin production for maximum results. One new ingredient, Nonapeptide-1, functions as an antagonist to Melanin Stimulating Hormone (MSH), effectively inhibiting melanin production upstream from classic tyrosinase inhibitors.[8] Another new ingredient, tetrahydrodiferuloylmethane (a colorless derivative of curcumin), is shown to function as a potent tyrosinase inhibitor and antioxidant and is shown to protect keratinocytes from hypoxanthine/xanthine oxidase injury in vitro. In addition, it is also shown to provide topical protection against UVB-induced inflammation and damage.[9]

METHODS

Twenty-nine subjects were enrolled in a 12-week, double-blind, split-face study comparing two products, Product JM (Marini Luminate Face Lotion MD, Jan Marini Skin Research) and Product OB (Obagi Nu-Derm Blender, 4% Hydroquinone, Obagi Medical).

Subjects were required to have mild-to-moderate hyperpigmentation (2-3 on a 0-4 scale) at baseline as determined by dermatologist assessment. Fine lines and wrinkles were assessed as part of the study but wrinkle score was not an enrollment criterion. Subjects were required to commit to the use of the study products, to follow protocol and to avoid significant intentional sun exposure over the course of the study.

Subjects were excluded from study participation if they were smokers, pregnant or nursing, used any prescription products on the areas undergoing treatment with the protocol items, used retinoids or tyrosinase inhibitors within three months of the study, had significant hormonal changes within three months of the study, demonstrated an inability to adhere to study protocols, had a known sensitivity or allergy to any of the ingredients, or had a conflicting condition.

Table 1: Key Ingredients Function and Mechanism of Action

Ingredient	Function	Reference
Reduce Melanin Stimulating Signaling		
Nonapeptide-1	Melanin Stimulating Hormone Antagonist	8
Inhibit Melanin Synthesis		
Tetrahydrodiferuloylmethane	Tyrosinase Inhibitor	11
Alpha-Arbutin	Tyrosinase Inhibitor	12
Hexylresorcinol	Tyrosinase Inhibitor	10
Retinol	Tyrosinase Transcription Inhibitor	7
Inhibit Tyrosinase Activity		
Dipotassium Glycyhrrizate	Tyrosinase Inhibitor	12
Glycyrrhiza Glabra	Tyrosinase Inhibitor	9, 12
Reduce Inflammation and Oxidative Damage		
Epigallocatechin Gallate	Antioxidant	13
Tetrahydrodiferuloylmethane	Antioxidant, anti-inflammatory. Protects keratinocytes from oxidative injury.	11
Alpha-Bisabolol	Anti-inflammatory	11
Glycyrrhiza Glabra	Antioxidant	9, 12

To prevent investigator bias during assessment, product labels were removed, product use was randomized to left/right application and the principal investigator was blinded

to product side usage. Subjects were randomized into two equal groups. Group 1 applied product JM to the right side of the face and OB to the left. Group 2 applied product JM on the left side of the face and OB on the right side. To control the remaining skin care routine, subjects used a generic gentle cleanser on both sides of the face, a generic moisturizer applied to each half of the face individually, with care to prevent the spread of products between sides, and a broad spectrum physical sunscreen (Marini Physical Protectant SPF 45), similarly independently applied to each half of the face.

Improvement was determined by direct physician assessment, subject self-assessment and Visia photography at baseline, 4, 8 and 12 weeks. Physician assessment rated three primary indicators on each side of the face: hyperpigmentation, fine lines, and wrinkles, using a 5-point increasing-severity assessment scale (4 = Severe, 3 = Moderate, 2 = Mild, 1 = Trace, 0 = None). Assessments of dryness, peeling and erythema were also recorded, using the same scale.

Subjects self-assessed the severity of discoloration, wrinkles and textural irregularities on each side of the face using a 5-point Severity Assessment (0= Very Significant Severity, 1=Significant Severity, 2=Neutral, 3=Minimal Severity, 4=flawless). Additionally, subjects were asked to rate their satisfaction with both the product and observed improvement using a similar 5-point scale (0=Highly Dissatisfied, 1=Dissatisfied, 2=Neutral, 3=Satisfied, 4=Highly Satisfied). Finally, to determine product preference, subjects were asked to identify a single preferred product "Overall, I prefer the product on this side of my face" and were asked whether or not they would choose to continue to use either product outside the study "Independent of this study, I would choose to continue to use the product on this side of my face".

RESULTS

Of the 29 enrolled subjects, 5 were lost to follow-up and one subject did not meet enrollment criteria with only trace pigmentation on one side of the face, resulting in a final "n" of 23 subjects.

Physician assessment showed statistically significant improvement vs. baseline in hyperpigmentation, fine lines and wrinkles at all time intervals for both sides of the face. Improvement in the appearance of hyperpigmentation, fine lines and wrinkles on the JM product side of the face is shown in Figure 1. Baseline and 12-week severity scores for improvement in the appearance of hyperpigmentation, fine lines and wrinkles are shown in Table 2. Irritation, dryness, peeling and erythema were also observed on both sides of the face with greater severity on Side A (the JM side). Average sensitivity scores for product JM were highest at week 4, deceasing by week 12. Maximum irritation was rated "trace" with a score of 1.35 (Trace = 1, Mild = 2).

Figure 1: Reduction in Hyperpigmentation by Physician Assessment

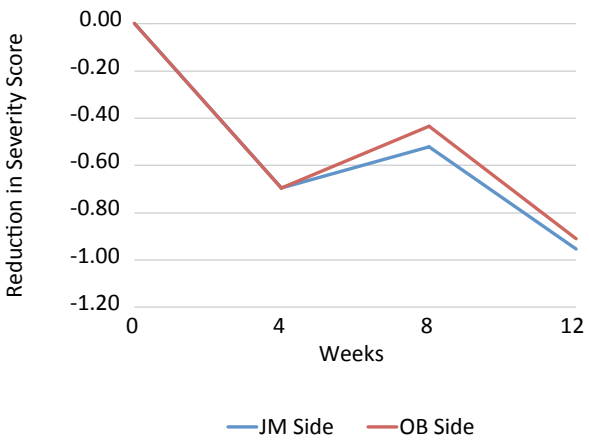


Table 2: Physician Assessed Severity Score & Statistical Significance (0-4 Scale)

	Product JM			Product OB		
	Base-line	12 Wks	p-value	Base-line	12 Wks	p-value
Hyperpig-mentation	3.00	1.96	0.0001	2.96	2.09	0.0002
Fine Lines	2.17	1.50	0.0152	2.17	1.55	0.0192
Wrinkles	2.09	1.50	0.0120	2.09	1.55	0.0194

- Figure 1: Compares the reduction in physician-assessed hyperpigmentation severity for both Products JM and OB.
- Figure 2: Shows the improvement in appearance of pigment, fine lines and wrinkles with product JM from baseline to week 12.
- Figure 3: Shows the improvement in appearance of pigment, fine lines and wrinkles with product OB from baseline to week 12.
- Figure 4: Measures subject-assessed satisfaction for both products.
- Figure 5: Shows the % of subjects preferring each product
- Figure 6: Shows the % of subjects indicating an intent to continue use for each product.
- Table 1: Shows key ingredient function and mechanism of action.
- Table 2: Shows the physician-assessed severity score for hyperpigmentation, fine lines and wrinkles.
- Table 3: Shows product acclimation severity
- Table 4: Measures subject assessed improvement across 4 factors.
- Table 5: Displays average product satisfaction and

improvement satisfaction at 4 and 12 weeks, along with significance of variance of the two sides at each time interval.

Figure 2: Improvement By Concern (JM Side)

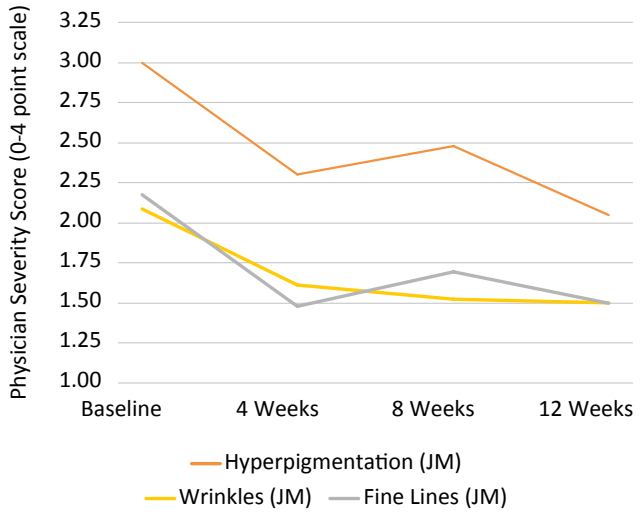


Figure 3: Improvement By Concern (OB Side)

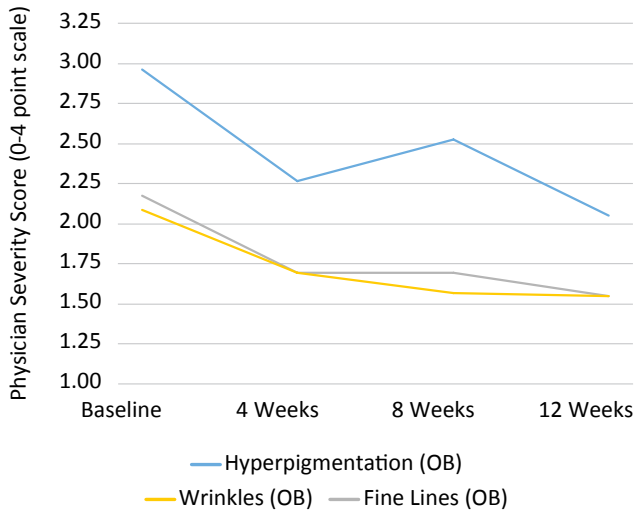


Table 3: Product Acclimation (0-4 scale)

	4 Weeks		8 Weeks		12 Weeks	
	JM	OB	JM	OB	JM	OB
Irritation	1.35	0.43	1.26	0.35	0.68	0.18
Dryness	1.17	0.35	1.43	0.35	1.05	0.27
Peeling	1.04	0.17	0.96	0.22	0.91	0.27
Erythema	1.04	0.35	0.74	0.17	0.55	0.05

Subject satisfaction (Figure 4) remained neutral (score range: 2.14 – 2.55) over the course of the study on the OB side of the face and progressed from neutral to satisfied (score range: 2.32 – 3.0) on the JM product side of the face. At the conclusion of the study, 57% of study participants stated that they preferred product JM over product OB. Further, a statistically significant difference was observed in the desire to continue to use each product with 80% of subjects indicating they would continue to use product JM and only 45% of subjects indicating they would choose to continue to use OB ($p = 0.03$) (Figure 5).

Figure 4: Subject Satisfaction

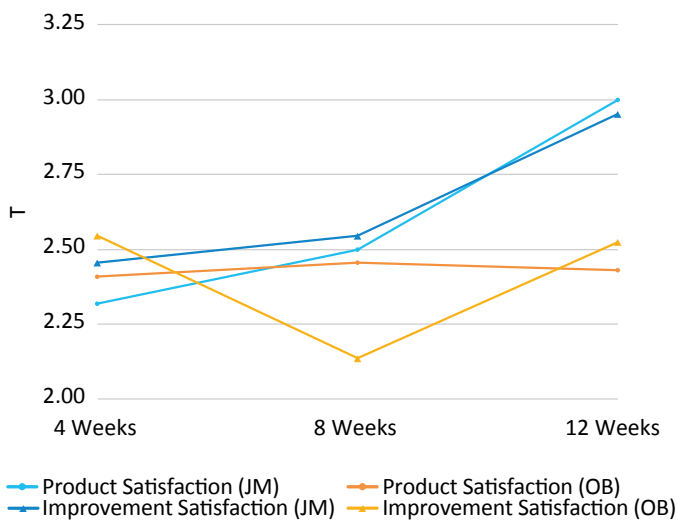
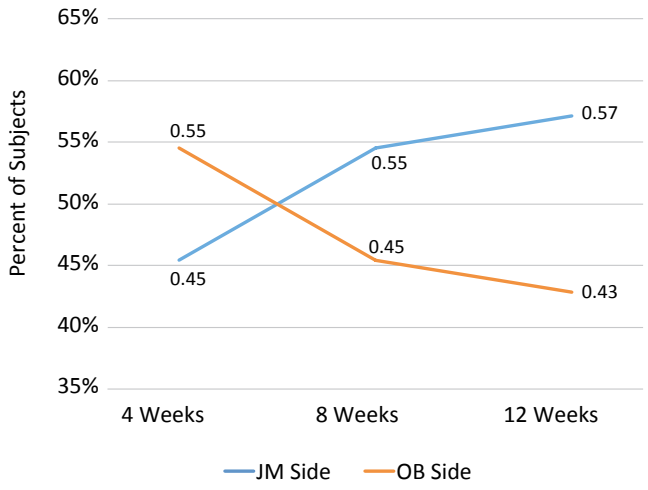


Figure 5: Overall Product Preference



DISCUSSION

This double-blinded, split-face study was designed to determine the efficacy of a new non-hydroquinone lightening solution vs. the gold standard lightening solution, 4% hydroquinone. Assessment by direct physician assessment and subject self-assessment show the test product (JM) to be equal or superior in all measured categories.

PHOTOGRAPHIC EVALUATIONS

BEFORE

AFTER | 12 WEEKS

BEFORE

AFTER | 12 WEEKS

Comparison of average physician-assessed hyperpigmentation scores on the two sides of the face showed slightly superior improvement on the JM product side of the face with an average improvement score of 0.91 compared to an average improvement score of 0.86 on the OB product side of the face (Figure 1). Improvement on both sides of the face were statistically significant with no statistically significant difference between the two sides of the face (p=0.77).

Physician assessment also showed rapid, statistically significant improvement in hyperpigmentation, fine lines and wrinkles, with a trend toward continued improvement over the course of the study on both sides of the face (Figure 2, Figure 3).

Average improvement in hyperpigmentation, fine lines and wrinkles was statistically significant on both sides of the face at weeks 8 and 12 (Table 2 shows results at week 12) with equivalent or superior average improvement scores on the JM product side of the face for all assessments at all time intervals. Only product JM, however, showed significant improvement in the appearance of wrinkles at week 4, indicating potentially more rapid anti-aging benefits. The observed faster response for wrinkles and greater overall improvement for the JM side may be attributable to its more comprehensive nature, as it includes 0.75% all-trans-retinol and multiple antioxidants in addition to lightening ingredients.

As expected, the high concentration of retinol in Product JM resulted in an acclimation period including greater irritation, dryness, peeling and erythema than that observed on the OB side. The OB side of the face did not include a secondary retinoid product as this study was designed to compare two single-product lightening solutions – an over-the counter product to a 4% hydroquinone product. Acclimation was most notable at the 4-week visit and decreased over the course of the study. It should be noted, however, that in practice it is not necessary to start individuals without prior retinoid usage on the studied 0.75% retinol formulation as another, less intense 0.3% formulation is available.

Subject satisfaction with improvement shows an increasing trend toward superior satisfaction on the JM product side of the face (Figure 4, Table 5) At the initial satisfaction assessment, average scores on both sides of the face were roughly equivalent (p=0.7) however, at 12 weeks, overall satisfaction on the JM side of the face increased notably while satisfaction on the OB product side of the face remained constant. While the difference between the two sides is not quite significant (p value = 0.058), there is a highly visible trend toward greater satisfaction on the JM product side of the face.

Subject assessment shows an increasing, and ultimately significant, preference for the JM product side of the face. At the 4-week visit there is a slight, non-significant (p=0.68) preference for the OB side of the face (Figure 5). Preference, however, changes to the JM side of the face at week 8, becoming statistically significant at week 12 (p=0.05). This study seems to show that when patients acclimate to both products, preference is highest for the JM side of the face.

Table 4: Subject-Assessed Improvement from Baseline (0-4 scale)

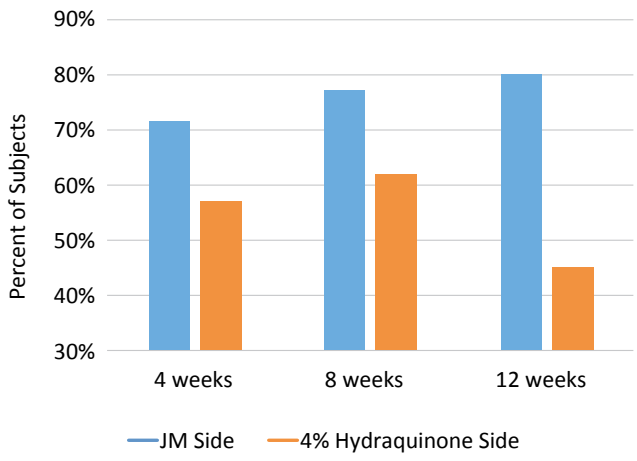
	JM	OB
Texture	0.81 (p<0.01)	0.76 (p<0.01)
Wrinkles	0.81 (p<0.01)	0.67 (p<0.01)
Pigment	0.90 (p<0.01)	0.90 (p<0.01)
Perceived Age	0.38 (p=0.10)	0.24 (p=0.23)

Table 5: Average Subject Satisfaction Scores

	4 Weeks			12 Weeks		
	JM	OB	p-value	JM	OB	p-value
Product Satisfaction	2.32	2.41	0.776	3.00	2.43	0.055
Improvement Satisfaction	2.45	2.55	0.715	2.95	2.52	0.058

Finally, the % of subjects indicating an interest in continuing to use each product outside the study showed a significant preference for the JM product (p=0.03 at 12 weeks) (Figure 6). Of particular interest is the divergent trend between the two products, with a continually increasing percent of subjects indicating intent to use the JM product.

Figure 6: Percent of Subjects Intending to Continue Use



One limitation of this study is the fact that the OB product is typically used in conjunction with prescription tretinoin. The goal of this study, however, was to compare the results of two comparably-priced, single-product lightening solutions with the only primary patient variable being an over-the-counter product vs. the gold-standard, 4% hydroquinone. This study shows superiority of the over-the-counter solution in many measured aspects. Further studies would be necessary to determine the results of more complete (and expensive) hydroquinone and OTC regimens.

CONCLUSION

Both direct physician assessment and subject self-assessment show equivalent to superior results for the over-the-counter study product (Product JM) vs. 4% hydroquinone (Product OB). Physician assessment showed statistically equivalent improvement in hyperpigmentation, texture and fine lines and wrinkles at 12 weeks with more rapid improvement noted in wrinkles on the JM product side of the face.

Subject-assessment showed superior satisfaction with both the JM product and their observed improvement on the JM product side of the face compared to use of 4% hydroquinone. Further, subjects showed a statistically significant preference for the test product and a greater preference to continue using the test product outside the study. Overall, the results of this study show the JM product to be equivalent if not superior to 4% hydroquinone for results and patient satisfaction.

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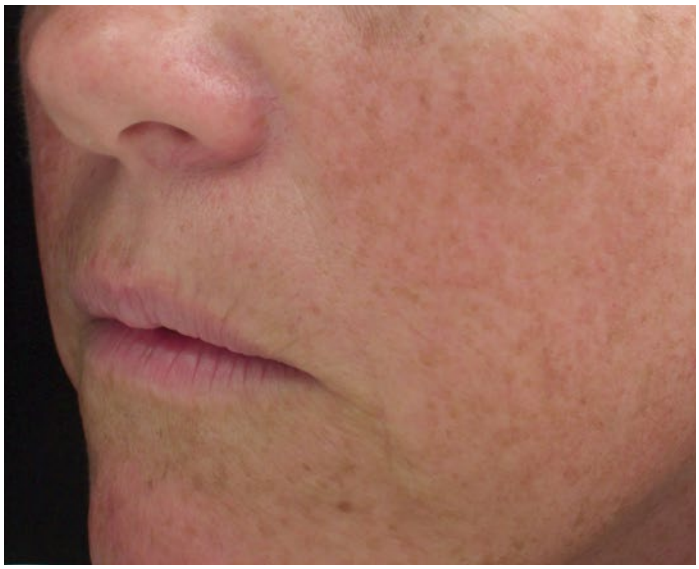
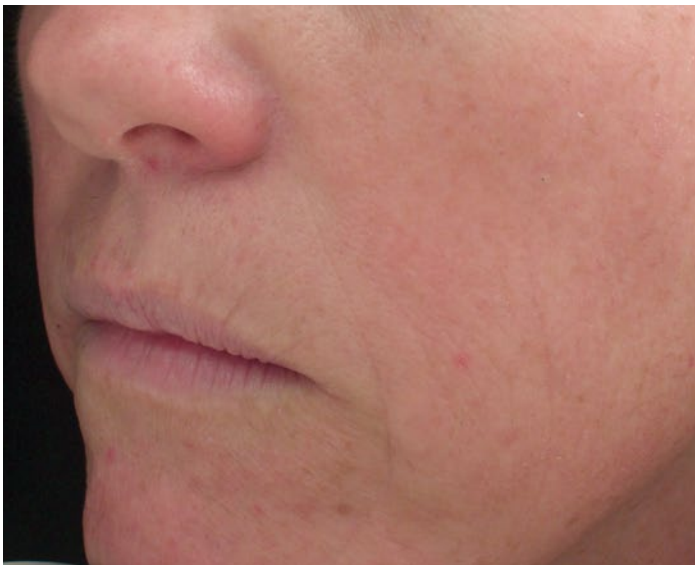
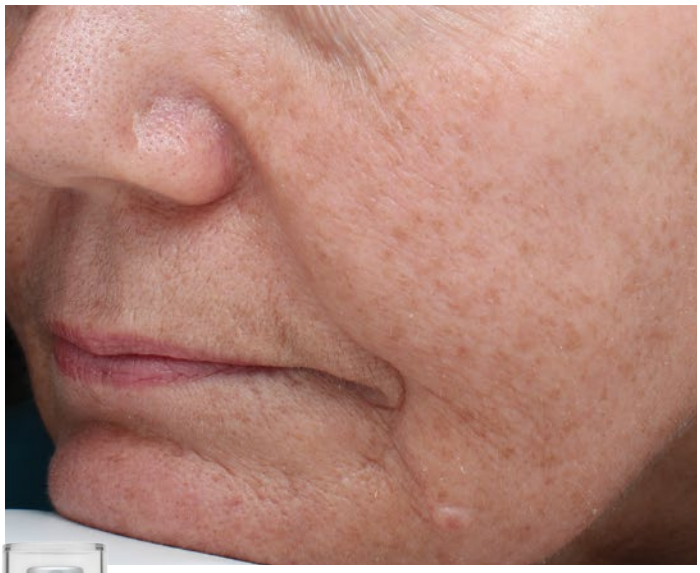
REDISCOVER RADIANT SKIN



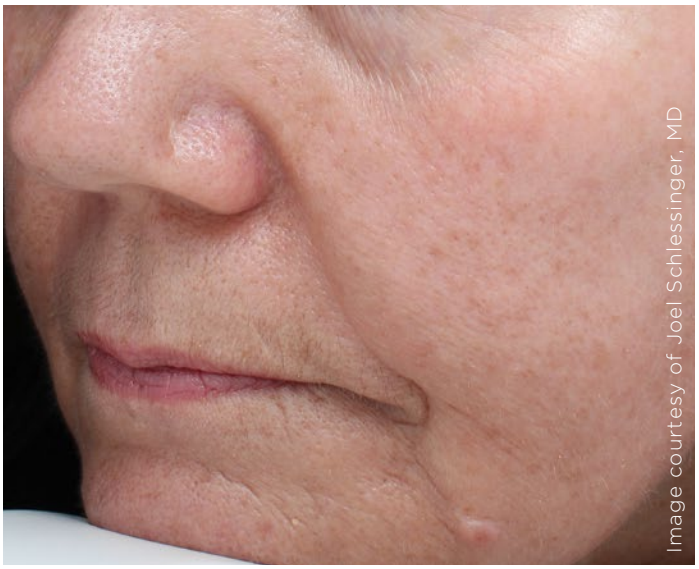
BASELINE



2 MONTHS



BASELINE



1 MONTH

Image courtesy of Joel Schlessinger, MD

Marini Luminate Face Lotion MD

Reveal brighter skin with this dynamic dual-purpose product that combines multiple non-hydroquinone technologies with concentrated all-trans-retinol to lighten the appearance of discoloration, reduce the appearance of fine lines and wrinkles and restore your skin's youthful complexion.

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