A Novel Tyrosine Amino Acid Derivative as a Topical Wrinkle Filler

Barbara A. Green, RPh, MS,[1] Brenda L. Edison, BA,[1] Irina Brouda, MA,[1] Anthony D. Gonzalez, BS,[2] Uma Santhanam, PhD,[2] Raaj Khusial, PhD,[2] Ronni L. Weinkauf, PhD[1]
[1]NeoStrata Company, Inc., Princeton, NJ USA; [2]Avon Products Inc., New York, NY USA

Introduction

Wrinkles result from repetitive motion in combination with damage from free radicals following exposure to sunlight and pollution. These visual signs of aging can be mitigated with various dermal fillers and botulinum toxins for patients willing to undergo injectable therapies. However, for patients who prefer topical anti-wrinkle treatments over injections, a new compound derived from the amino acid tyrosine may provide a topical benefit.[1] In a preliminary investigation, topical use of the new tyrosine derivative increased viable epidermal thickness and built volume in the dermal matrix with the potential for a faster and more potent skin plumping effect than alpha hydroxy acids. Additionally, the new tyrosine derivative was found to have high oxygen radical absorbance capacity (ORAC value = 5149 µmol TE/g), making it a superior antioxidant to Vitamin C (ORAC value = 650) and comparable to CoffeeBerry (ORAC value = 5700).[2] The new tyrosine derivative may provide an alternative treatment for those patients who are reluctant to use injectable therapies and/or are in a maintenance phase. This poster presents a summary of pre-clinical and clinical studies evaluating the safety and the benefits of the novel tyrosine derivative as a topical wrinkle filler.

Safety Studies

Test Performed With Tyrosine Derivative	Result	Conclusion
Pre-Clinical		
Ames Bacterial Reverse Mutation Test	Negative	Non-mutagenic
Chromosomal Aberration Test in Cultured Human Peripheral Blood Lymphocytes	Negative	Non-mutagenic
Ocular Irritation Test (Topical Application on EpiOcular Human Cell Construct)	Negative	Not an ocular irritant
Neutral Red Uptake Phototoxicity Assay in Fibroblasts	Negative	Non-phototoxic
Clinical		
Ophthalmologist Evaluation of Eye Irritation During Topical Periocular Use (2% in gel)	Negative	Not an eye irritant, safe with contact lens use
Repeated Insult Patch Test (2% in gel)	Negative	Not a dermal irritant or allergic contact sensitizer
Human Photocontact Allergenicity Assay (1.25% in cream)	Negative	Not a photosensitizer

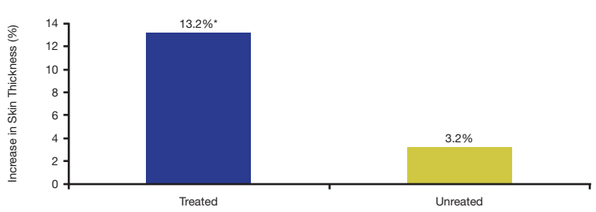
Penetration and *In Vitro* Cellular Studies

Evaluation Parameter	Test Model/Test Substance/Method	Result	Conclusion
Skin Penetration Capacity	**Franz cell diffusion model** Tyrosine derivative, 1.75%, tested in oil-in-water emulsion, water-in-silicone emulsion, and aqueous serum vehicles	Tyrosine derivative was detected in stratum corneum, epidermis, and dermis after 48 hours	Tyrosine derivative penetrates into and through *ex vivo* human skin
Hyaluronic Acid (HA) Stimulation Capacity	**HA expression in cultured human fibroblasts and chondrocytes** Tyrosine derivative (0.001% to 0.1%) tested vs. water (negative control)	Tyrosine derivative, 0.001% to 0.02%, was non-cytotoxic and significantly increased HA expression in fibroblasts and chondrocytes, $P<0.05$	Tyrosine derivative can stimulate hyaluronic acid production in human dermal and cartilage tissues
Collagen Stimulation Capacity	**Collagen gene expression in cultured human fibroblasts** Tyrosine derivative (0.05% to 0.1%) tested vs. DMSO (vehicle control)	Tyrosine derivative, 0.05% and 0.1%, was non-cytotoxic and significantly increased collagen gene expression, $P<0.05$	Tyrosine derivative can stimulate collagen production in human dermal fibroblasts

Pilot Skin Thickness Study

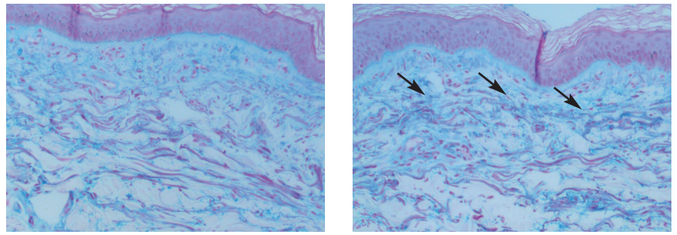
Eight Caucasian women, 40-65 years old, treated 1 forearm twice daily with 2% tyrosine derivative serum + vehicle cream for 4 weeks, then with 2% tyrosine derivative serum + 1.25% tyrosine derivative cream for 4 weeks. Skin thickness of treated and untreated forearms was measured at weeks 0 and 8 with digital calipers (Figure 1). Punch biopsies of one treated and one untreated area were performed at week 8 and histologically examined for differences in glycosaminoglycans (GAGs) and pro-collagen (Figures 2, 3).

Figure 1. Increase in Forearm Skin Thickness With and Without Topical Tyrosine Derivative Treatment



*Mean change is significant versus baseline, $P<0.05$.
No statistically significant differences between treatments.

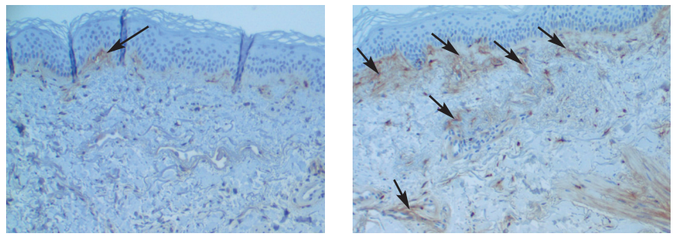
Figure 2. Differences in GAGs* Between Untreated Skin and Skin Treated With Tyrosine Derivative



Untreated Treated

*GAGs are stained blue.
Note increased density of the blue stain in the slide of tyrosine derivative-treated skin.

Figure 3. Differences in Pro-Collagen* Content Between Untreated Skin and Skin Treated With Tyrosine Derivative



Untreated Treated

*Pro-collagen is stained brown.
Note increased brown cytoplasmic stain in dermal fibroblast cells in the slide of tyrosine derivative-treated skin.

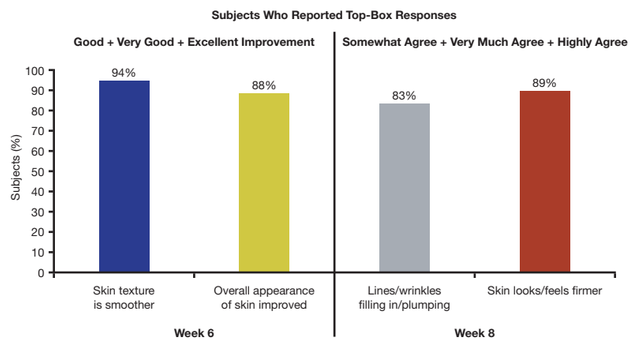
Facial Skin Plumping Study

Method: 18 women, 35-65 years old, Fitzpatrick skin phototype I, II, and III, with mild to moderate facial photodamage, including clearly defined lines and wrinkles, used 2% tyrosine derivative gel + placebo cream for 4 weeks, followed by 2% tyrosine derivative gel + 1.25% tyrosine derivative cream for 4 weeks. The gel was applied to target lines and wrinkles, and the creams were applied to the entire face twice daily. The subjects completed self-assessment questionnaires and were photographed at weeks 0, 4, 6, and 8.

Results:

- Subjects reported improvement to skin texture, wrinkles and firmness during topical tyrosine derivative treatment (Figure 4).
- Clinical photographs showed visible improvement in the appearance of nasolabial folds, glabellar lines, forehead lines, periocular lines, and crow's feet (Figures 5-8).

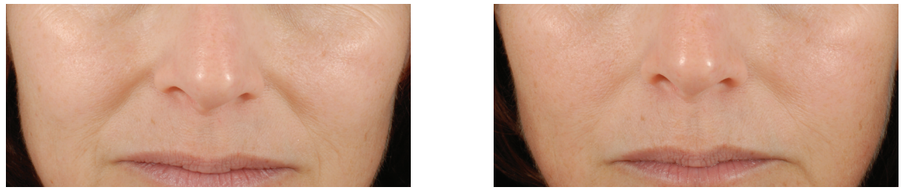
Figure 4. Self-Assessment



Clinical Photography

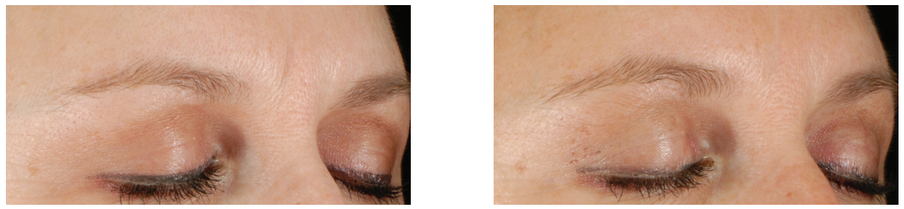
All subjects used a topical tyrosine derivative regimen for up to 8 weeks

Figure 5. Improvement in Nasolabial Folds



Baseline Week 6

Figure 6. Improvement in Glabellar Lines



Baseline Week 4

Figure 7. Improvement in Forehead Lines

Baseline Week 6

Figure 8. Improvement in Periocular Lines and Wrinkles

Baseline Week 8

Conclusions

The Novel Tyrosine Derivative Topical Wrinkle Filler

- **Is safe and well-tolerated in topical preparations without irritation or sensitization effects**
- **Is able to penetrate all skin layers, stimulate cellular production of collagen and hyaluronic acid, and provide measurable and visible skin plumping benefits**
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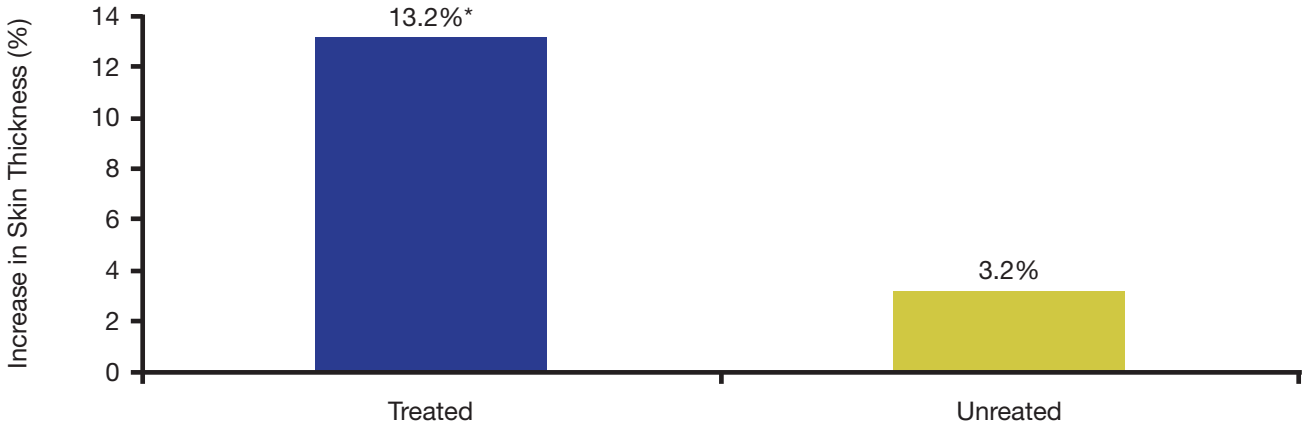

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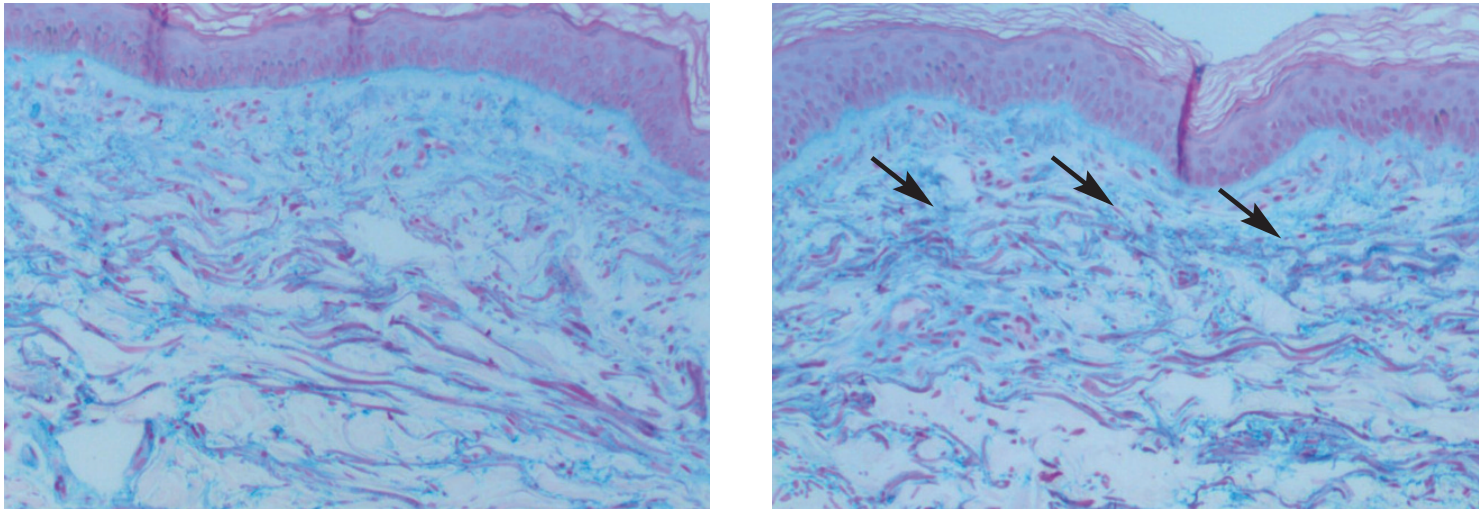

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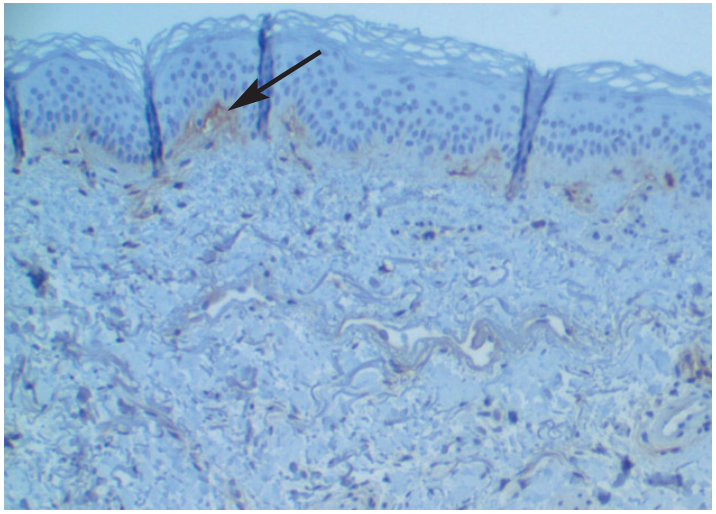
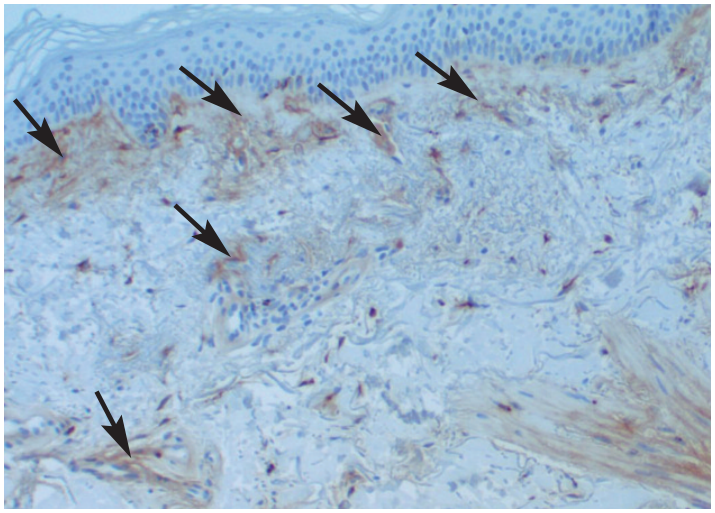


Untreated



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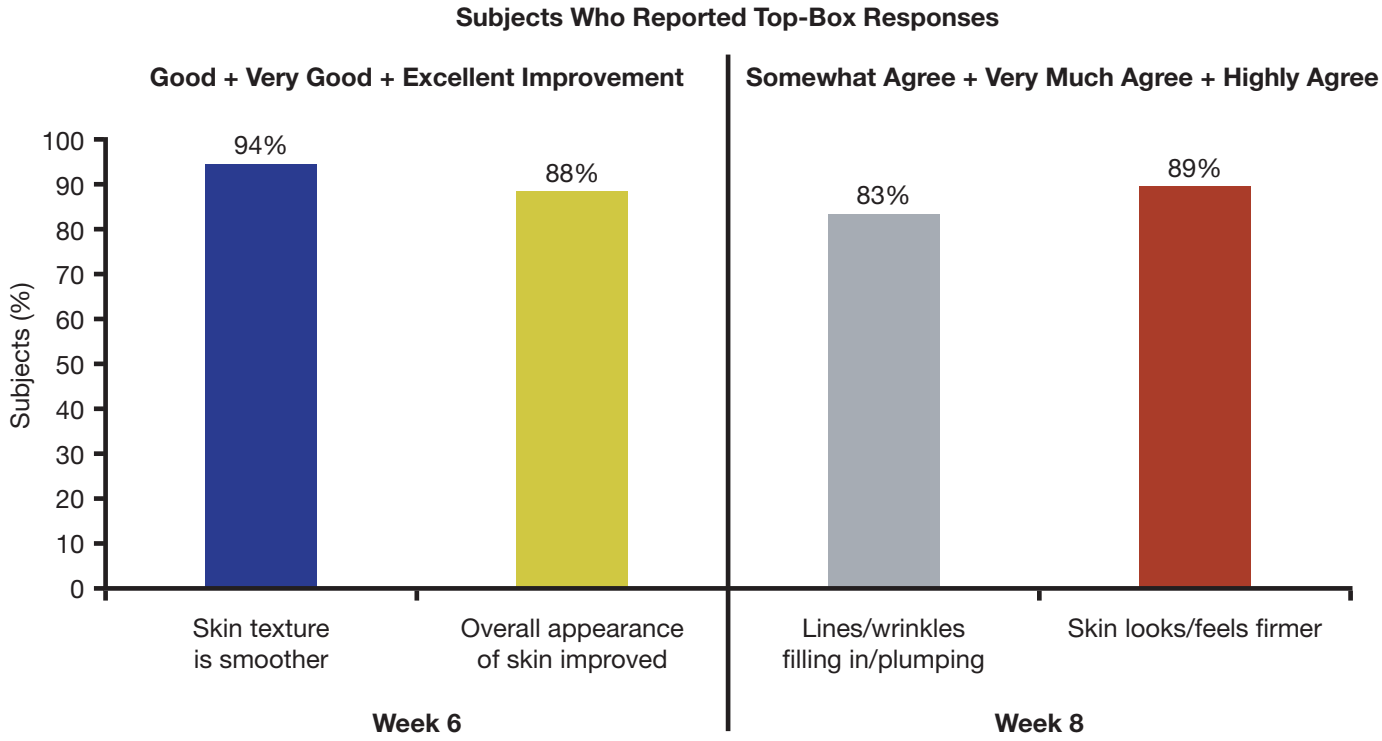

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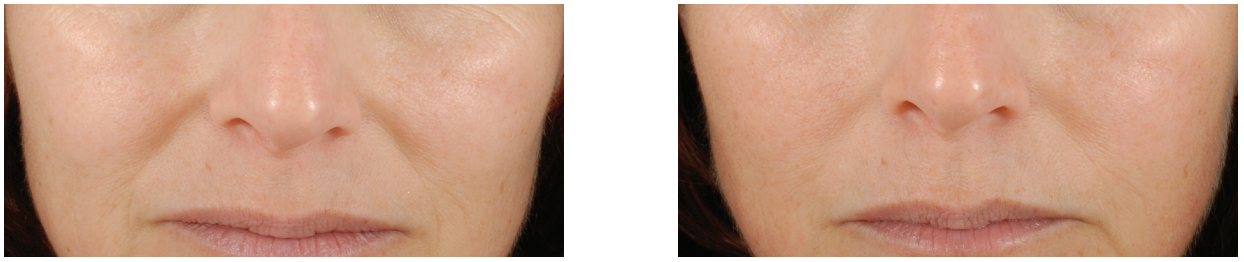

Baseline Week 6

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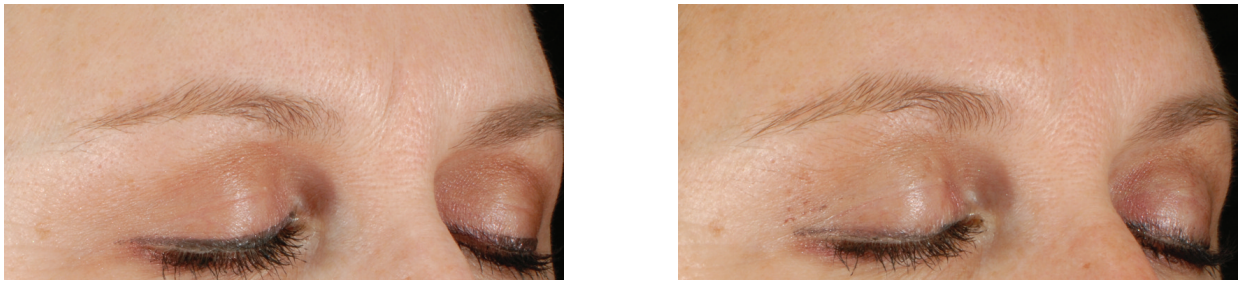

Baseline Week 4

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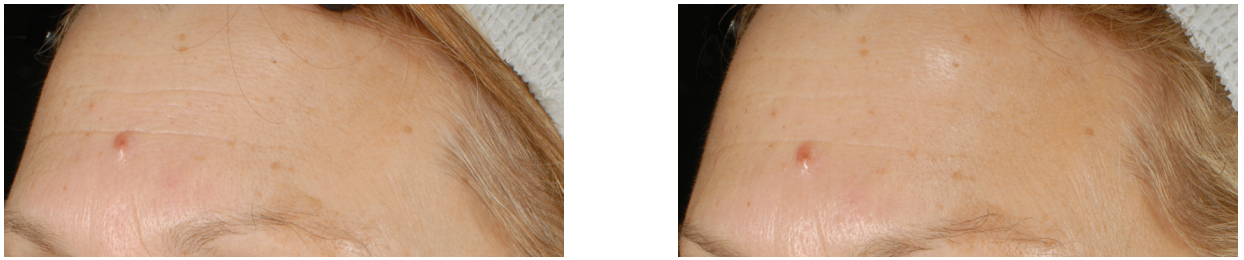
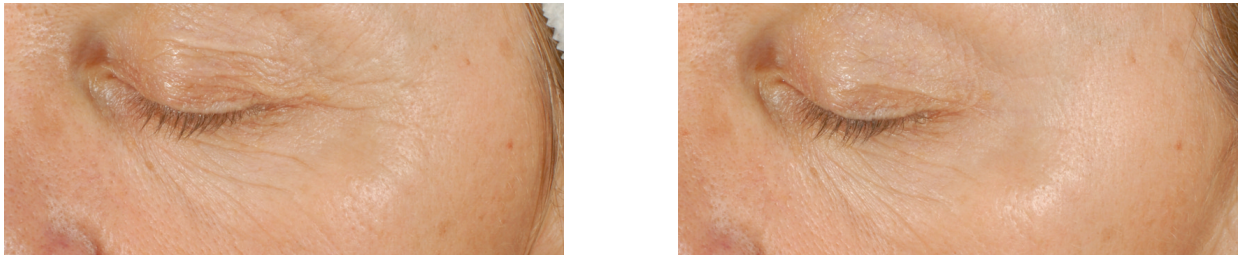


Baseline Week 6

Figure 8. Improvement in Periocular Lines and Wrinkles



Baseline Week 8

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