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- Apyx Medical wants to present you with current scientific discourse. Specific usage outside of the cleared indications may not be safe or effective.

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As with any procedure, individual results may vary. As with all energy devices there are inherent risks associated with its use, refer to the IFU for further information.

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CLINICAL REPORTS

High energy, double pass helium plasma dermal resurfacing: A prospective, multicenter, single-arm clinical study

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Abstract

Background: A previous multi-center clinical study of low energy (20% power), single-pass helium plasma dermal resurfacing (HPDR) showed positive results but did not fully reveal the true potential of this novel technology. A second multi-center clinical study, reported herein, was therefore undertaken to evaluate efficacy and safety of high energy (40%), double pass HPDR for treatment of facial rhytids ([ClinicalTrials.gov](https://clinicaltrials.gov) Identifier: NCT04185909).

Methods: Fifty-five eligible subjects seeking improvement in facial rhytids were enrolled for study at one of four investigational sites. All subjects underwent full-face HPDR treatment. The forehead, nose, cheeks, and peri-oral treatment zones were treated at 40% power with two passes whereas the peri-orbital and jawline/mandibular zones were treated at 20% power (up to 40% for jawline/mandibular zone) and one or two passes. Photographic images of the face were captured using the VISIA-CR system. Three-month posttreatment Fitzpatrick Wrinkle and Elastosis Scale (FWS) scores were compared to baseline scores as determined by blinded independent photographic reviewers (IPRs) and study investigators.

Results: Blinded IPRs and study investigators observed a ≥ 1 -point FWS improvement in 100% of subjects with mean change in IPR FWS from baseline to the 90-day visit of $-3.6 (\pm 1.2)$. 96.4% of subjects indicated “improvement” in appearance at the 90-day visit utilizing the modified Global Aesthetic Improvement Scale. Evaluation of VISIA-CR data revealed statistically significant improvements in wrinkles, brown spots, and pore counts. Overall, 269 Adverse Events in 55 subjects were reported; most were mild-moderate in severity (99.3%), anticipated (86.2%), and of relatively short duration with most having resolved within 30 days (60.6%) of treatment.

Conclusion: Treatment of facial rhytids with high energy, double pass HPDR as detailed herein enables a marked improvement in FWS that parallels or surpasses competing technologies. VISIA-CR analysis demonstrates additional improvements in skin quality with statistically significant quantitative improvements in brown spots and enlarged pores as well as wrinkles. Effective rhytid effacement combines with high subject satisfaction and few unanticipated adverse events for a reasonable benefit-risk ratio.

KEYWORDS

facial rejuvenation, helium plasma, helium plasma dermal resurfacing, radiofrequency, rhytid, skin rejuvenation, skin resurfacing, wrinkle

INTRODUCTION

Helium plasma dermal resurfacing (HPDR) is a novel skin resurfacing technology that has been in clinical use (off-label) since 2012.¹ Helium plasma generation, similar to the predicate nitrogen plasma skin regeneration technology, occurs when radiofrequency (RF) current is applied to a flow of the appropriate medical grade gas over an electrode in the handpiece.² And although both devices may deliver similar energy densities to the skin's surface, it has been suggested that helium plasma's bimodal energy delivery with both top-down thermal convection/conduction and joule (RF) tissue heating may paradoxically enable more significant collagen remodeling and tissue contraction despite its more superficial depth of irreversible thermal damage.² Joule tissue heating results from the propagation of RF energy through the continuous flow of helium gas down to and into the tissue in a noncontact and non-chromophore-dependent manner.² Although RF energy is not visible, a violet white "beam" of light called the Lewis Rayleigh afterglow (from continuous de-excitation or neutralization of ionized helium plasma atoms across the length of the beam path) provides the user with a visual indicator of the active "radiofrequency bridge" during energy delivery.²

A previous multi-center clinical trial of the helium plasma device ([ClinicalTrials.gov](#) Identifier: NCT03286283) wherein 55 subjects underwent single pass, low energy (20% power) treatment of facial skin showed significant improvement of rhytids (per both Independent Physician Reviewers or IPRs and study Investigators), high subject satisfaction and a good safety profile with relatively few adverse events (AE).³ Further evaluation of VISIA-CR data from the study revealed significant improvements in wrinkle depth, brown spots, and pore size.⁴ The modest energy level (20% power) and energy delivery scheme (single pass) used in the initial clinical trial, however, was not sufficient to demonstrate the full potential of the new helium plasma technology or to adequately benchmark efficacy against clinically effective CO₂ and Erbium:YAG laser skin resurfacing devices currently in widespread use. As helium plasma energy is delivered to the tissue and tissue coagulation occurs, the electrical impedance of treated tissue increases causing RF energy to disperse peripherally to untreated tissue with lower electrical impedance—this phenomenon limits the depth of effect and potential for reduction of deeper rhytids from single-pass HPDR treatment.⁵

Although greater depth of effect may be achieved by increasing helium plasma device power even greater depth of effect may be achieved by additional energy delivery with a second pass over the tissue.^{5,6} The superficially coagulated/desiccated tissue may be left in place to serve as a biological dressing if only single-pass treatment is desired, however, it must be gently removed before a second pass is performed to reduce tissue impedance and thereby ensure adequate energy

delivery.^{5,6} The purpose of this multi-center clinical study ([ClinicalTrials.gov](#) Identifier: NCT04185909) is to demonstrate the effectiveness and safety of high energy (40% power), double pass HPDR treatment of facial skin.

METHODS

Study subjects

Eligible subjects from four participating study sites were healthy male and female adults ≥ 30 years old seeking improved appearance of facial wrinkles and rhytids.

Inclusion criteria

To be eligible for inclusion, subjects were required to have a facial wrinkle score ≥ 4 on the Fitzpatrick Wrinkle and Elastosis Scale,⁷ a Fitzpatrick Skin Scale score $\leq \text{III}$, and express their willingness to comply with protocol requirements, including abstaining from other facial cosmetic procedures through the 6-month follow-up visit. These included but were not limited to laser or chemical resurfacing, dermabrasion, neuromodulator and/or dermal filler injections, and aesthetic facial surgery.

Exclusion criteria

Reasons for exclusion from the study included: use of isotretinoin or other medication that can cause dermal hypersensitivity before treatment; active facial wound or infection (including herpes simplex virus-1); diabetes mellitus; autoimmune disease; bleeding disorders or blood-thinning medications including use of aspirin or nonsteroidal anti-inflammatory medications within 10 days before study treatment; connective tissue disease or active skin disease (including pre-cancerous lesions) in the planned treatment area; known susceptibility to keloid formation or hypertrophic scarring; a facelift procedure within 12 months of screening visit; RF microneedling, any facial treatment with an energy-based device or neuromodulator treatment within 6 months before screening visit; injectable facial filler treatment within 4 months of screening visit; chemical peel within 3 months of screening visit; hypersensitivity to anesthetics; a concurrent therapy that might place the subject at risk or jeopardize the study objectives; enrollment in another investigational trial and pregnancy or lactation.

Study design

Subject eligibility, physical examination, and wrinkle and rhytid assessments were completed at one of four investigational sites within 30 days before the study

procedure. All screening subjects were reviewed by the study sponsor before the study procedure to ensure that enrollment criteria were met and that study baseline images were of high quality. One or two urine pregnancy tests were obtained if the preprocedure screening and helium plasma procedure were not performed on the same day. In response to the ongoing coronavirus disease (COVID-19) pandemic, preoperative testing for COVID-19 infection status could be completed at the Investigators' discretion. Digital images of the planned treatment area were obtained to document pretreatment facial appearance (VISIA-CR 2.3 System; Canfield Scientific, Inc.). The same standardized imaging was obtained throughout the study at subsequent follow-up visits. Although discretionary, all subjects received medication for prophylactic treatment of bacterial and viral infections. Subjects also completed a Visual Analog Scale (VAS) pain assessment⁸ preprocedure and immediately postprocedure.

The face of each subject was divided into six zones: forehead, periorbital, nose, cheeks, perioral, and jawline/mandibular border (Figure 1). Topical anesthesia is not indicated for HPDR (interferes with the device to tissue RF coupling) and was not used.⁵ Subject comfort was facilitated with trigeminal nerve blocks, peripheral ring blocks and labial blocks (1%–2% lidocaine with 1:100,000 epinephrine) followed by sequential infiltration (using 70 mm 22 g spinal needle) of tumescent anesthesia into each treatment zone starting with the forehead, then nose and peri-orbital areas followed by right and left cheek areas and then peri-oral and jawline areas. Double Klein solution was prepared by adding each of the following to 500 cc USP injection grade normal saline: 50 cc USP injection grade 2% lidocaine and 0.5 cc USP injection grade 1 mg/ml epinephrine for final

concentrations of 0.2% lidocaine and 1:1,000,000 epinephrine. The total tumescent volume infiltrated was between 250 and 500 ml at the discretion of the investigators. Although times between completion of tumescent infiltration and start of HPDR procedures were not recorded, in most cases 15–30 min was allowed to elapse to obtain an adequate local anesthetic effect. Polycarbonate plastic eye shields coated with ophthalmic ointment were used during treatment.

Investigators were instructed to attach a 3 mm standoff device to the treatment tip assembly before all treatments, to use a steady movement of the plasma beam to ablate the tissue in each zone, not to wipe away treated tissue if only performing a single pass but to gently remove superficial coagulated/desiccated tissue resulting from the initial pass before completion of the second pass. Treatment of forehead, nose, cheeks, and perioral zones was performed with 2 passes at 40% power and helium gas flow rate of 4 L/min. The periorbital zone was treated at 20% power and helium gas flow rate of 4 L/min with 1 or 2 passes at the discretion of the investigators. The jawline/mandibular border zone was treated at 20% to 40% power and helium gas flow rate of 4 L/min with 1 or 2 passes at the discretion of the investigators.

Subjects underwent assessments immediately following the procedure and then at 1, 6, 10, 30, 90, and 180 days postprocedure.

Posttreatment care

For Days 1–3 posttreatment subjects were instructed to take tepid to cool showers multiple times each day, perform vinegar water soaks multiple times each day, and keep the

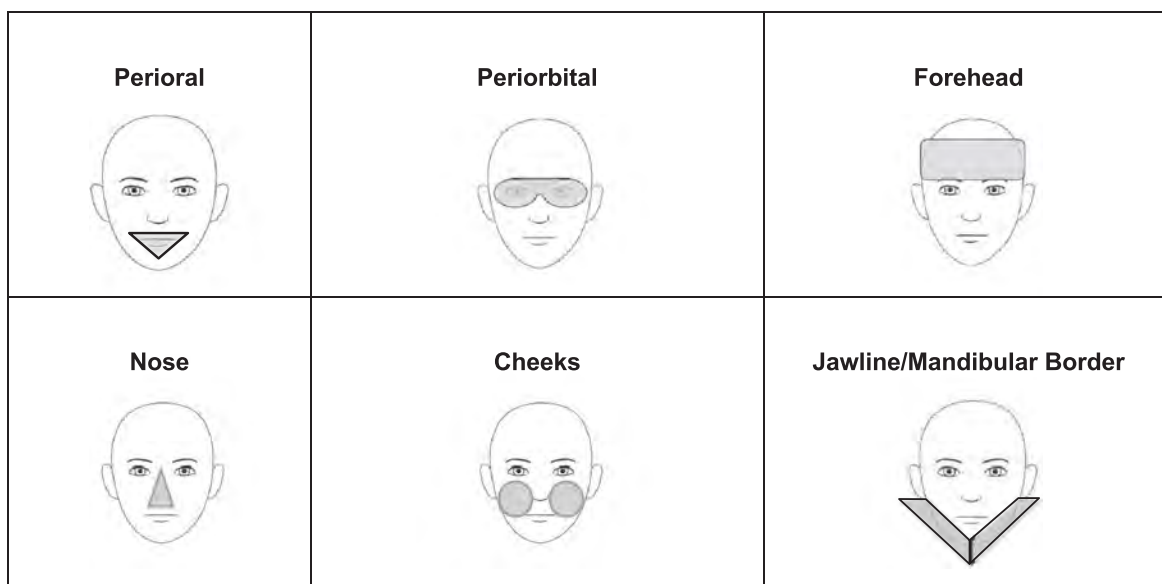


FIGURE 1 HPDR facial treatment zones. The face of each subject was divided into six zones: forehead, periorbital, nose, cheeks, perioral, and jawline/mandibular border. HPDR, helium plasma dermal resurfacing

facial skin moist at all times using Aquaphor. Cold vinegar water soaks (1 tablespoon white vinegar per cup of cold water) were to remain in place for approximately 30 min. For Days 4 to 14 posttreatment subjects were instructed to take tepid to cool showers multiple times each day, perform vinegar water soaks as needed, and keep the facial skin moist with Aquaphor, especially areas with slower healing. In addition, alcohol-free cleanser (Neutrogena Fresh Foaming Facial Cleanser) was provided along with sunblock (Neutrogena Sheer Zinc Oxide Dry-Touch Face Sunscreen with Broad Spectrum SPF 50) and a light moisturizer (Neutrogena Oil-Free Moisture Daily Hydrating Facial Moisturizer and Neck Cream) for use beginning day 15 posttreatment and beyond; they were also instructed to avoid any other topical products until they exited the study at Day 180 posttreatment.

Study assessments

Following the study procedure, subjects returned to the study site at 1 day, 6 days (4–8 days), 10 days (9–14 days), 30 days (23–37 days), 90 days (80–100 days) and 180 days (166–194 days) for VAS pain assessment, postprocedure assessments and to complete questionnaires. Digital images were obtained at each visit. Using daily diaries, subjects reported postprocedure complications and AE, daily VAS 0–10 scale pain scores, and the date when they first felt comfortable and willing to go out in public following treatment.

Assessment of subject wrinkle severity was made at baseline and at the 90-day posttreatment visit by three sourced, blinded, board-certified dermatologists or plastic surgeons (independent photographic reviewers [IPRs]) and at baseline and each follow-up visit by the Investigators using the Fitzpatrick Wrinkle and Elastosis Scale (FWS). The FWS is a clinically validated assessment tool used to assess skin wrinkle severity and elastosis on a scale from 1 through 9 (Table 1). Assessment of randomized baseline and 90-day follow-up images (right, front, and left views) was performed by the blinded IPRs. The IPRs assigned a single FWS score per subject for both the baseline and 90-day photos and ignored nasolabial folds, marionette lines, and artifacts (skin tissue bunching) from the chin rest. Sets of images were not arranged in any specific order.

Modified Global Aesthetic Improvement Scale (modified GAIS)

The Modified GAIS is a subjective rating of improvement in baseline appearance.⁹ Subjects and Investigators each rated subject appearance ranging from Very Much Improved to Very Much Worse (Table 2).

Study endpoints

The primary efficacy endpoint was the proportion of subjects achieving individual treatment success, defined as a ≥ 1 -point improvement on the FWS at the 90-day posttreatment visit by at least two out of the three blinded IPRs.

Additional efficacy endpoints included: correctly identifying 90-day posttreatment images from a pair of baseline and 90-day posttreatment images by at least two of three blinded IPRs; the magnitude of improvement as measured by the mean change in FWS from baseline to 90-day posttreatment visit as determined by the investigators; subject Modified GAIS as a measure of aesthetic improvement at Day 90 relative to baseline; investigator Modified GAIS as a measure of aesthetic improvement at Day 90 relative to baseline; subjects' satisfaction with the procedure at the 90-day visit as assessed by the Patient Satisfaction Questionnaire; assessment of re-epithelialization at the 10-, 30-, and 90-day posttreatment visits as reported by the study investigators; and, finally, mean duration until the subjects felt comfortable going in public after treatment as reported by the study subjects at the 10-day posttreatment visit.

The primary safety endpoint included evaluation of all AE up to the 90-day posttreatment visit. The secondary safety endpoint was the evaluation of change in pain and discomfort after treatment (baseline, within 60 min of procedure) as reported by the subjects on a validated 11-point VAS up to the 10-day posttreatment visit.

VISIA-CR image analysis

Standard images of the face were obtained using VISIA-CR 2.3 (Canfield Scientific, Inc.) before and 90 days after treatment. Right and left oblique and

TABLE 1 Fitzpatrick Wrinkle and Elastosis Scale

Class	Description	Score	Description
I	Fine wrinkles	1–3	Mild: Fine texture changes with subtly accentuated skin lines
II	Fine to moderate depth wrinkles, moderate number of lines	4–6	Moderate: Distinct popular elastosis (individual papules with yellow translucency under direct lighting) and dyschromia
III	Fine to deep wrinkles, numerous lines, with or without redundant skin folds	7–9	Severe: Multipapular and confluent elastosis (thickened, yellow and pallid) approaching or consistent with cutis rhomboidalis

Note: The FWS is a clinically validated assessment tool used to assess skin wrinkle severity and elastosis on a scale from 1 through 9. Study participants were required to have a wrinkle and elastosis score of 4 or above.

Investigators/subjects rating	Description
Very Much Improved	Optimal cosmetic result from this procedure in this subject
Much Improved	Marked improvement in appearance from the initial condition, but not completely optimal for this subject
Improved	Obvious improvement in appearance from the initial condition
No Change	The appearance is essentially the same as the original condition
Worse	The appearance is worse than the original condition
Much Worse	The appearance is worse than the original condition
Very Much Worse	The appearance is worse than the original condition

Note: The modified GAIS is a subjective rating of improvement in baseline appearance.⁹ Subjects and Investigators each rated subject appearance ranging from Very Much Improved to Very Much Worse.

TABLE 2 Modified Global Aesthetic Improvement Scale Evaluation (GAIS)

frontal views were captured using a standard procedure. Areas of interest were adjusted manually for each subject, view, and visit by the image analysis technician. Any areas with facial hair or artifacts were excluded. Brown spots, enlarged pores, and wrinkles were analyzed by one or more proprietary automated image processing algorithms with overall facial assessment determined as an average of the results from the left and right sides of the face. The absorption of UV light by melanin was used to count the number of brown spots and to determine the total area covered by brown spots. Enlarged pore count and total surface area with enlarged pores were determined using an algorithm able to detect circular objects with a prespecified diameter range and minimum circularity threshold. Mean thickness of and the total area covered by wrinkles were determined using oriented contrast-based filters to detect curvilinear features.

Statistical analysis

The sample size with a performance goal of 50% was chosen to provide sufficient power for a statistical comparison based on a power calculation. Categorical data was provided as proportions and counts while continuous data were presented with the mean, median, minimum, maximum, or standard deviation. Statistical analysis was performed by Technomics Research, LLC.

Ethics

Each subject provided signed informed consent before participating in any study-related activities and a required release of subject images including possible use in publications. This study was conducted under an Investigational Device Exemption (IDE) approval by the US FDA (G190179).

RESULTS

Fifty-five eligible subjects underwent the study procedure with the helium plasma device and completed the 6-month follow-up visit study requirements. The study cohort included 50 females (90.9%) and 5 males (9.1%) with an overall group average age of 64.5 years (± 7.0 SD) and a range of 46 to 81. Fitzpatrick Skin Scale Type I–III were enrolled: 4 (7.3%) Type I (white skin that never tans and always burns easily), 38 (69.1%) Type II (white skin that tans slightly and always burns easily), and 13 (23.6%) Type III (light brown skin that tans gradually and can burn moderately). All subjects enrolled in the study who had baseline FWS values were included in the full analysis set. The demographics and clinical characteristics of treated subjects are summarized in Table 3.

All 55 subjects underwent full-face treatment with all six zones treated (330 zones total) with one (20 of 330 zones including 4 of 55 periorbital zones and 16 of 55 jawline/mandibular border zones) or two (310 of 330 zones) non-overlapping passes of helium plasma with power of 20% (55 of 55 periorbital zones, 23 of 55 jawline/mandibular border zones), 30% (12 of 55 jawline/mandibular zones), or 40% (240 of 330 zones) and helium flow rate of 4 L/min (Table 4). The mean (SD) total volume of injected tumescent was 291.0 ml (104); mean volumes of tumescent per treatment area were also recorded (Table 4). At investigators' discretion, all subjects were given anxiolytic/sedative and/or pain medication before treatment. Mean (SD) procedure time (start of helium plasma treatment) was 65.2 (25.3) min and ranged from 25 to 117 min.

Fifty-five of 55 subjects returned for primary endpoint (Day 90) assessment and 54 of 55 subjects completed all posttreatment study visits. A total of 23 protocol deviations occurred in the study and none of the reported deviations were determined to affect the safety or welfare of the study subjects. Three of 23 protocol deviations were attributed to COVID-19 (two subjects were not seen for their 30-day posttreatment visit due to offices being closed due to

TABLE 3 Demographics and baseline characteristics

Characteristic	Summary
Sex	
Female	90.9% (50/55)
Male	9.1% (5/55)
Age	
<i>N</i>	55
Mean $\pm$ SD	64.4 $\pm$ 7.0
Median (IQR)	65.0 (61, 69)
(Min, Max)	(46, 81)
Race	
White	100% (55/55)
Tobacco Use	
None	69.1% (38/55)
Prior history	21.8% (12/55)
Current smoker	9.1% (5/55)
Fitzpatrick Skin Type	
Type I	7.3% (4/55)
Type II	69.1% (38/55)
Type III	23.6% (13/55)
Fitzpatrick Wrinkle and Elastosis Scale	
5	1.8% (1/55)
6	25.5% (14/55)
7	21.8% (12/55)
8	34.5% (19/55)
9	16.4% (9/55)

Note: Aggregate data from the full study cohort of 55 subjects were used to develop overall demographics and baseline characteristics.

COVID-19 and one subject refused to place her face on the chin rest for the VISIA-CR camera system for imaging due to COVID-19 safety concerns).

Ten of 20 non-COVID-19 protocol deviations involved subject diary compliance (nine diaries incomplete and one diary lost). One subject did not complete the 180-day posttreatment visit and was lost to follow-up. Seven subjects had follow-up visits outside of the visit window (5 days 90 visits and 2 days 180 visits). One subject failed to initial the VAS score on the clinical research form. One major protocol deviation occurred with the failure to place a grounding pad on the subject during treatment pass #1. Although electrical safety standards do not require the use of a grounding pad during HPDR energy delivery to ensure patient safety, not having the grounding pad in place reduces the amount of energy delivered to the tissue. The grounding pad was added before the second pass and the subject was deemed to be an effective success and did not have any severe or device-

related AEs. The subject with the major protocol deviation was nonetheless excluded from the “Per Protocol” analysis population.

Efficacy endpoints

The primary efficacy endpoint of ≥ 1 -point improvement in baseline FWS scores as assessed by blinded IPR at the 90-day posttreatment visit was achieved by 55 subjects (100%) in the full analysis population ($N = 55$) and 54 subjects (100%) in the per-protocol population ($n = 54$) (Table 5). The mean change in IPR FWS score from baseline to the 90-day visit was $-3.6 (\pm 1.2)$ with 96.4% of subjects improving on average at least 1-point, 92.7% of subjects improving at least 2 points, and a majority of subjects (74.5%) improving at least 3 points. Stratification of Day 90 posttreatment change in IPR FWS based upon baseline FWS showed a positive correlation with subjects with higher baseline FWS also achieving more change at Day 90 posttreatment (Table 5).

All three IPRs correctly identified the 90-day posttreatment image in 100% of subjects in pairs of baseline and 90-day images. The magnitude of improvement measured by the mean change in FWS from baseline to 90- and 180-day posttreatment visits as determined by investigators was $-4.4 (\pm 2.0)$ and $-4.8 (\pm 1.8)$, respectively (Table 5). Subjects' and Investigators' Modified GAIS were similar with “very much improved,” “much improved,” and “improved” aggregates of 96.4% and 97.8% versus 100% and 97.8% at 90- and 180-day posttreatment visits, respectively. Both Subjects' and Investigators' Modified GAIS also recorded “worse” at the 180-day posttreatment visit in one subject (1.8%) where a hypertrophic scarring AE in the perioral area still required ongoing treatment.

Subjects' satisfaction with the procedure at the 90-day visit as assessed by the Patient Satisfaction Questionnaire was positive with 96.4% “happy with results of procedure” and 83.6% “would recommend the procedure to a friend.” Complete re-epithelialization at the 10-, 30-, and 90-day posttreatment visits as reported by the study investigators was 5.5%, 87.3%, and 100%. Incomplete re-epithelialization at Day 30 posttreatment was observed in all treatment zones (forehead: $n = 3$, periorbital: $n = 1$, nose: $n = 2$, cheeks: $n = 4$, perioral: $n = 3$, and jawline/mandibular: $n = 3$). 50.9% (28 of 55) of subjects felt comfortable going in public as of the 10-day posttreatment visit with a mean of $9.8 (\pm 2.7)$ days until comfortable/willing and able to go out in public amongst those responding to this further query ($n = 28$).

VISIA-CR image analysis

A single HPDR treatment decreased the overall number of brown spots over the entire face by 59.2% at the 90-day follow-up visit ($p < 0.0001$); the decrease in the facial

TABLE 4 Treatment parameters

Zone	#Zones treated	Tumescent (cc, SD)	Helium flow (L/min)	% Power	Passes
1–6	330	291.1 (104)	4	20–40	1–2
1 (Perioral)	55	43.6 (13.2)	4	40	1 (55/55) 2 (55/55)
2 (Periorbital)	55	39.2 (23.0)	4	20	1 (4/55) 2 (51/55)
3 (Forehead)	55	60.0 (22.2)	4	40	1 (55/55) 2 (55/55)
4 (Nose)	55	18.2 (11.0)	4	40	1 (55/55) 2 (55/55)
5 (Cheeks)	55	77.9 (29.5)	4	40	1 (55/55) 2 (55/55)
6 (Jawline/ Mandibular Border)	55	52.2 (28.6)	4	20	1 (23/55) 2 (37/39)
				30	1 (12/55) 2 (0/39)
				40	1 (20/55) 2 (2/39)

Note: Aggregate data for each facial zone for volume tumescent used (ml), % power used and number of passes for subjects that underwent high energy, double pass HPDR treatment in each of the 6 different facial zones.

area (mm²) covered by brown spots was similar (58.4%, $p < 0.0001$). The total number of enlarged pores over the face decreased by 31.1% at the 90-day follow-up visit ($p < 0.0001$); the decrease in pore area (mm²) was similar (28.4%, $p < 0.0001$). The mean wrinkle thickness (mm) decreased by 9.1% ($p < 0.0001$) at the 90-day follow-up visit while the decrease in wrinkle area (mm²) decreased by 47.8% ($p < 0.0001$).

Primary safety endpoint

No serious AEs related to the study device or procedure occurred; one subject reported a serious AE (hospitalization for bowel obstruction) that was unrelated to either the study device or procedure. Two hundred and sixty-nine AEs and Expected Treatment Effects (ETEs) were reported in the 55 subjects in the study (Table 6). Most AEs were of “Mild” or “Moderate” severity (99.3%) with only two subjects experiencing “Severe” events, one of which was unrelated to the study device or procedure. Two hundred and fifty-seven AEs were related to the study device and procedure, 12 AEs were not related to the study device or procedure. Most AEs were also ETEs (81.8%) including crusting in 55 subjects, edema/swelling in 55 subjects, erythema/skin inflammation/

focal congestion in 56 subjects, pain/tenderness in 30 subjects, itching/pruritis in 14 subjects, post-inflammatory hyperpigmentation in 6 subjects, pinpoint bleeding in 2 subjects and rash/urticaria in 2 subjects. The majority of AEs resolved within 30 days (60.6%) with 75.8% resolved by Day 90 and 90.3% resolved by Day 180 posttreatment.

AEs that were not anticipated/expected included acne/milia (20 events in 16 subjects, 29.1%), hypertrophic scarring (8 events [4 mild, 3 moderate, 1 severe] in 8 subjects, 14.5%), telangiectasia (4 subjects, 7.3%), discoloration/hypopigmentation (3 subjects, 5.4%), prolonged wound healing (2 subjects, 3.6%), eye irritation (1 subject, 1.8%), and other (8 subjects, including nausea during procedure in 3 subjects, emesis/vomiting post-procedure in 2 subjects and drug reaction during the procedure, unilateral lower eyelid retraction and bowel obstruction each in 1 subject).

Secondary safety endpoint

Mean VAS Pain Scores were 3.7, 2.4, 2.9, and 1.1 within 1-hour postprocedure and at 1-, 6- and 10-day posttreatment visits with over 50% of subjects reporting a VAS pain score of 0 by the 10-day post-treatment visit.

TABLE 5 Efficacy endpoint data

90-Day endpoint measurement	Results
≥1-point improvement baseline IPR FWS	100% (55/55)
Mean change IPR FWS	−3.6 (±1.2)
Baseline FWS 4.67–5.33	−1.8 (±0.8)
Baseline FWS 5.67–6.33	−2.7 (±1.1)
Baseline FWS 6.67–7.33	−3.7 (±0.8)
Mean change Investigator FWS	−4.4 (±2.0) (−4.8 ± 1.8 @ 180 days)
IPR identification of 90-day posttreatment image	100% (55/55)
Modified GAIS (very much improved + much improved + improved)	
Subject	96.4% (53/55)
Investigator	97.8% (54/55)
Subject satisfaction	
“Happy with procedure”	96.4% (53/55)
“Would recommend procedure to a friend”	83.6% (46/55)

Note: 90-day endpoint measurements including percent achieving >1-point improvement in baseline IPR FWS, magnitude of change for baseline IPR FWS with stratification based on baseline FWS, magnitude of change for baseline Investigator FWS, IPR identification of 90-day posttreatment images, and Modified GAIS and subject satisfaction data.

Abbreviations: FWS, Fitzpatrick Wrinkle and Elastosis Scale; GAIS, Global Aesthetic Improvement Scale; IPR, independent photographic reviewer.

DISCUSSION

High energy (40% power) double pass HPDR treatment resulted in 100% (95% one-sided lower confidence level = 94.7% $p < .0001$) of subjects achieving the Primary Effectiveness Endpoint goal of demonstration of at least 1-point improvement from baseline in FWS at 90 days posttreatment based on IPR assessment of photographs. Although the mean change in IPR FWS from baseline to the 90-day posttreatment visit was -3.6 ± 1.2 stratification of change in IPR FWS based upon Baseline FWS showed a direct correlation with higher Baseline FWS scores obtaining greater change in 90-day posttreatment FWS scores (Table 5). Examples of high energy, double pass HPDR treatment effectiveness for wrinkle reduction for subjects with increasing baseline FWS are shown in Figures 2–5. The same primary effectiveness endpoint was achieved in only 64% of subjects in the single pass, low energy HPDR multi-center study.³ Blinded IPRs' ability to correctly identify 90-day posttreatment images from pairs of Baseline and 90-day images for each subject were similar in both multi-center studies (100% here vs. 98.2%).³

Mean change in FWS from baseline to the 90-day posttreatment Primary Effectiveness Endpoint was -4.4 ± 2.0 as determined by study Investigators. The modest increase in the magnitude of the observed improvement in FWS observed by study investigators may be related to the enhanced ability of the human eye to perceive three-dimensional change upon in-person evaluation as opposed to a comparison of two-dimensional digital images by the IPRs.³ Of note 5-point FWS improvement was the most common (range 1–8) degree of change noted by study investigators at 30, 90, and 180 days posttreatment (32.7%, 27.3%, and 33.3%, respectively). Both Subject and Investigator Modified GAIS scores were very high at 90 (96.4% and 100%) and 180 days (97.8% and 97.8%) posttreatment with the majority of subjects “very much improved”; 2 of 55 subjects reported, “no change” at day 90 and 1 of 45 subjects reported “worse” at day 180 (see following). As a further measure of subject satisfaction with the treatment 96.4% of subjects reported being happy with the results, 83.6% would recommend the treatment to a friend and 63.6% would consider having the treatment again, 78.2% indicated greater confidence, 77.8% noted improvement in mood, and 69.8% indicated that they feel more secure.

Similar to the foregoing single pass HPDR study,⁴ VISIA-CR analyses of facial skin following double pass HPDR treatment demonstrated statistically significant quantitative improvements in brown spots and pore counts as well as wrinkles at 90 days versus baseline. The observed magnitude of improvement was greater herein for changes in wrinkle thickness and wrinkle area but similar for changes in spots and enlarged pores. These findings suggest that single-pass treatment may be adequate to address dyschromia and pore visibility but that double-pass treatment is superior for wrinkle reduction.

Among the 269 AEs, the majority were related to the procedure (95.5%), the majority were of mild or moderate severity (99.3%), the majority were expected treatment effects (81.8%), and the majority resolved within 30 days posttreatment (60.6%). 75.8% of AEs resolved by Day 90 and 90.3% resolved by Day 180 posttreatment. No treatment-related AEs were observed that are unique to the novel helium plasma technology or to energy-based skin rejuvenation treatments. Using an 11-point VAS subject rated pain related to the high energy double pass HPDR treatment was similar to that of the previous low energy single pass study immediately posttreatment (3.7 vs. 4.3*) and at Day 10 posttreatment (1.1 vs. 1.8*).³

Despite slower facial skin re-epithelialization with the high energy, double pass versus low energy, single-pass treatments (complete re-epithelialization in 5.5% vs. 96.8%* at Day 10 and in 87.3% vs. 100%* at Day 30) the timeframe within which most subjects reported being comfortable going out in public was similar (10 days in 50.9% vs. 56.4%*³). The greater time required for re-epithelialization/wound healing in this high energy, double pass HPDR multi-center study versus the

TABLE 6 Expected Treatment Effects (ETEs) and non-anticipated adverse events

ETE	N	Severity			Duration Resolved by 180 days
		Mild	Moderate	Severe	
Erythema/skin inflammation/focal skin congestion	55 (100%)	11/55	44/55	0/55	54/55
Crusting	55 (100%)	9/55	46/55	0/55	55/55
Edema/swelling	55 (100%)	15/55	40/55	0/55	54/55
Pain/tenderness	30 (54.6%)	11/30	19/30	0/30	29/30
Milia/acne	16 (29.1%)	14/16	2/16	0/16	14/16
Pruritis/itching	14 (25.5%)	12/14	2/14	0/14	14/14
Post-inflammatory hyperpigmentation	6 (10.9%)	5/6	1/6	0/6	5/6
Telangiectasias	6 (10.9%)	5/9	1/6	0/6	3/6
Discoloration/hypopigmentation	3 (5.5%)	3/3	0/3	0/3	2/3
Pinpoint bleeding	2 (3.6%)	2/2	0/2	0/2	2/2
Prolonged wound healing	2 (3.6%)	0/2	2/2	0/2	2/2
Urticaria/rash	2 (3.6%)	1/2	1/2	0/2	2/2
Eye irritation	1 (1.8%)	0/1	1/1	0/1	1/1
Non-Anticipated AEs					
Hypertrophic scarring	8 (14.6%)	4/8	3/8	1/8	2/8
Emesis/nausea	5 (9.1%)	5/5	0/5	0/5	5/5
Bowel obstruction	1 (1.8%)	0/1	0/1	1/1	1/1
Lower eyelid retraction	1 (1.8%)	1/1	0/1	0/1	1/1
Drug reaction	1 (1.8%)	1/1	0/1	0/1	1/1
Self-inflicted superficial excoriation	1 (1.8%)	1/1	0/1	0/1	1/1

Note: ETEs and non-anticipated AEs by type with the number (and percent) of subjects, severity, and duration.

Abbreviation: AE, adverse events.

previous low energy, single-pass HPDR multi-center study may reflect both increased depth of treatment and greater impact on the papillary dermal vasculature in areas where the skin may be less vascular at baseline (e.g., peripheral areas of the forehead, temples, cheeks, jawline, and chin). Although “prolonged wound healing” was reported in two subjects (moderate severity; resolved in 2 and 7 days with continuation of posttreatment skincare per protocol), a secondary rescreening of all subject photos by IPRs did not identify any delayed wound healing AEs. Figure 6 shows the healing progression for one of the subjects with incomplete re-epithelialization of the chin, forehead, and peri-orbital areas at Day 10 (Figure 6A) and completed re-epithelialization in the same areas at Day 30 (Figure 6D).

Hypertrophic scarring ($n = 4$ mild severity, $n = 3$ moderate severity, $n = 1$ severe) occurred in focal areas of the forehead ($n = 3$), perioral ($n = 5$), jawline/mandibular ($n = 4$) treatment zones with multiple zones affected in several patients ($n = 3$). Hypertrophic scarring did not occur in the two subjects with delayed healing.

Hypertrophic scarring appeared to be related to unknown (possibly treatment-related) and nontreatment-related factors including secondary trauma/wounding and COVID-19 face-covering/mask use. Hypertrophic and even cicatricial scarring has been observed with other full field (e.g., CO₂ laser; erbiumYAG laser) and fractional (e.g., CO₂ laser) ablative skin resurfacing treatments as well as the predicate nitrogen plasma skin regeneration technology (personal observation, JDH)—possible contributing factors include excessive depth of treatment, excessive density of microscopic ablation zones (CO₂ ablative fractional resurfacing), excessive energy density with extensive residual thermal damage, secondary wounding of treated skin tissue, posttreatment infection of treated skin tissue, over-treatment of thinner and/or less vascular skin and delayed wound healing.^{5,10–14}

Moderate severity hypertrophic scarring in the left temple and jawline/mandibular border areas was diagnosed in one subject at the 90-day visit. These areas experienced secondary trauma from taping of an NG tube



FIGURE 2 Mild wrinkle improvement after HPDR treatment in a 68-year-old female, Fitzpatrick Skin Scale III. Before (A, B), 3-month (C, D), and 6-month (E, F) VISIA-CR photographs (front, left oblique). Double pass, 40% power all zones except periorbital (single pass, 20% power) and jawline/mandibular border (single pass). Baseline IPR FWS 6.3 (blinded reviewer average) with 3-month IPR FWS net change -0.7 . Significant improvement of dyschromia and photodamage along with modest improvement of skin texture with reduction of facial lines evident at Month 3 that is further improved at month 6. FWS, Fitzpatrick Wrinkle and Elastosis Scale; HPDR, helium plasma dermal resurfacing; IPR, independent photographic reviewers

to the skin tissue while undergoing treatment for bowel obstruction that developed 12 days after HPDR. The subject also noted wearing a face-covering/mask 2 days per week for work. The scarring was treated with silicone gel sheeting and topical steroid cream (betamethasone 0.05%) with significant improvement but incomplete resolution upon exiting the study at Day 180.

Another subject that underwent HPDR treatment just before the more stringent COVID-19 restrictions went into effect was not seen at the 30-day follow-up visit and did not contact the study site personnel regarding the onset of skin thickening in the perioral area before presenting for the 90-

day follow-up visit. The subject related that she experienced skin irritation in the perioral area from wearing a face-covering/mask and that an open abrasion in the perioral area may have been caused by scratching (secondary wounding) during sleep. This more severe scarring event was treated with serial intralesional triamcinolone (10–40 mg/ml) and/or 5-fluorouracil injections as well as occasional 532 nm/1064 nm pulsed laser treatments with significant improvement but incomplete resolution upon exiting the study at day 180.

Univariate tests using Fisher's exact test for categorical data and Student's *t* test for continuous data were



FIGURE 3 Moderate wrinkle improvement after HPDR treatment in a 49-year-old female, Fitzpatrick Skin Scale II. Before (A, B), 3-month (C, D), and 6-month (E, F) VISIA-CR photographs (front, left oblique). Double pass, 40% power all zones except periorbital (double pass, 20% power) and jawline/mandibular border (double pass, 20% power). Baseline IPR FWS 7.7 (blinded reviewer average) with 3-month IPR FWS net change -3.7 . Significant improvement of dyschromia and photodamage along with marked improvement of skin texture with reduction of facial lines evident at Months 3 and 6. Mild erythema in discrete areas continuing to resolve and some previously darker toned areas of peri-orbital and cheek skin remain evident by month 6 with no intervention other than sunblock (see Methods). FWS, Fitzpatrick Wrinkle and Elastosis Scale; HPDR, helium plasma dermal resurfacing; IPR, independent photographic reviewers

used to test for differences between study subjects with and without hypertrophic scarring. The analysis suggests that older subjects ($p = 0.0131$) with higher baseline IPR average FWS ($p = 0.1027$) may be at higher risk of hypertrophic scarring. This finding may be explained in part by older subjects having thinner skin and diminished healing capability in comparison to younger subjects.

The continuous nature of energy delivery used in the study, however, necessarily requires the user to maintain an appropriate treatment speed (velocity of movement of the treatment tip over the skin) of approximately 1 cm

per second during energy delivery. An inadvertent decrease in treatment speed would have inversely impacted energy density delivered to the tissue potentially increasing the risk for scarring AEs.² Of note, the energy density of 17.2 J/cm^2 occurs at 40% power with continuous energy delivery and treatment tip velocity of 1 cm/s —20% higher than the predicate nitrogen plasma skin regeneration device at 4.0 J/cm^2 and treatment speed of 2.5 Hz .²

The possibility of variance in technique contributing to some of the hypertrophic scarring events may be supported

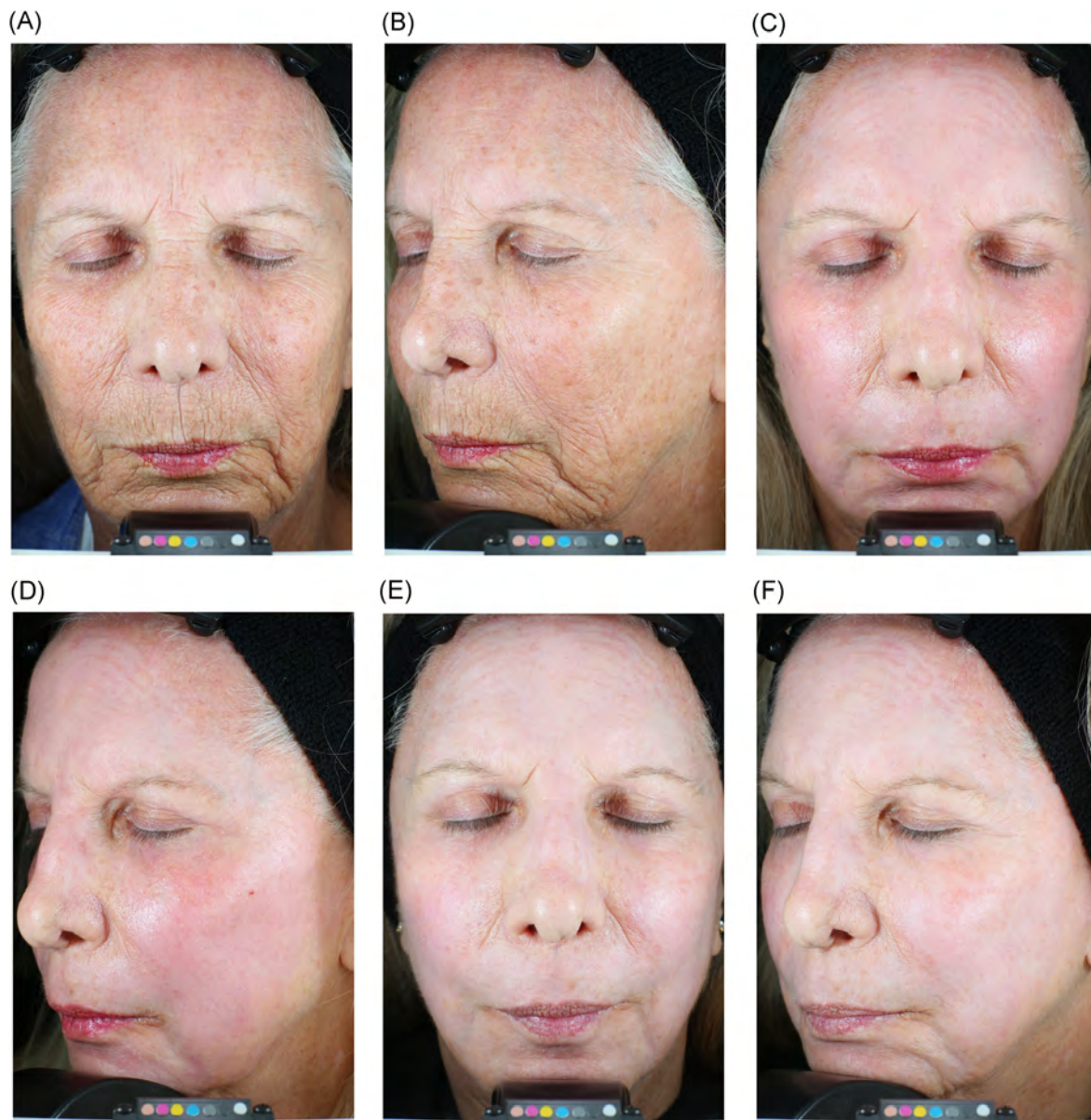


FIGURE 4 Marked wrinkle improvement after HPDR treatment in a 69-year-old female, Fitzpatrick Skin Scale II. Before (A, B), 3-month (C, D), and 6-month (E, F) VISIA-CR photographs (front, left oblique). Double pass, 40% power all zones except periorbital (double pass, 20% power) and jawline/mandibular border (single pass). Baseline IPR FWS 8.7 (blinded reviewer average) with 3-month IPR FWS net change -5.3 . Significant improvement of dyschromia and photodamage along with marked improvement of skin texture with reduction of facial lines evident at Months 3 and 6. Mild erythema of cheek areas and linear redness of upper forehead lines at Month 3 that is continuing to improve at Month 6. FWS, Fitzpatrick Wrinkle and Elastosis Scale; HPDR, helium plasma dermal resurfacing; IPR, independent photographic reviewers

by the fact that most of the patients ($n = 6$ or 75%) experiencing hypertrophic scarring occurred at a single study site. While at least one of the events at this study site was clearly related to secondary trauma from an unrelated medical procedure it is possible that a greater energy density was achieved in the areas of hypertrophic scarring during treatment (e.g., unintended overlap of beam path; decreased velocity of treatment tip). It is also possible that debridement of the desiccated skin tissue after the first pass was incomplete (resulting in focally increased tissue impedance and uneven energy delivery) or too aggressive (possibly leading to increased depth of tissue injury).

Beyond the treatment constraints imposed by this multicenter prospective study, primary prevention measures employed by practitioners performing off-label HPDR have included the use of pulsing, faster treatment speeds and feathering with decreased power and only a single pass at treatment areas in the periphery of the face (e.g., upper forehead, temples, jawline/mandibular border).^{5,6} Although each of these measures will reduce the energy-density delivered to the tissue the importance of appropriate posttreatment skin care and avoidance of secondary skin tissue trauma cannot be disregarded.



FIGURE 5 Marked wrinkle improvement with mild severity AE (focal hypertrophic scar left lateral upper lip and melolabial fold) after HPDR treatment in a 67-year-old female, Fitzpatrick Skin Scale II. Before (A, B), 3-month (C, D), and 6-month (E, F) VISIA-CR photographs (front, left oblique). Double pass, 40% power all zones except periorbital (single pass, 20% power) and jawline/mandibular border (single pass). Baseline IPR FWS 9.0 (blinded reviewer average) with 3-month IPR FWS net change -5.0 . Significant improvement of dyschromia and photodamage along with marked improvement of skin texture with reduction of facial lines evident at Months 3 and 6. Slightly visible and just palpable raised hypertrophic scar (mild severity) left lateral upper lip and melolabial fold evident by month 3 that is much improved by month 6 after several triamcinolone (10 mg/ml) injections. Mild erythema of left lower cheek with several telangiectasias present at month 3 improved by Month 6. FWS, Fitzpatrick Wrinkle and Elastosis Scale; HPDR, helium plasma dermal resurfacing; IPR, independent photographic reviewers

In the event of hypertrophic scar formation, common mitigation measures include early treatment with topical steroid cream, intralesional steroid and/or 5-fluorouracil injections, and laser treatment of hypervascular scar tissue.¹⁵ Another mitigation approach that remains under investigation involves the use of laser (ablative fractional) assisted topical drug delivery to enable both limited debulking of hypertrophic scar tissue and delivery of steroid and/or antimetabolite drugs to the remaining hypertrophic scar tissue.¹⁶ Subjects with hypertrophic

scarring in this study were treated with topical and/or intralesional steroids, intralesional 5-fluorouracil, and vascular laser therapy (532 nm/1064 nm) with resolution in two of eight subjects by the 180-day posttreatment visit (e.g., Figure 5); the remaining six AEs are responding to treatment and are expected to resolve with acceptable outcomes.

Acne/milia ($n = 17$ mild severity, $n = 3$ moderate severity) appeared to be related to COVID-19 face-covering mask use in some of the subjects as the lesions were in the area covered

FIGURE 6 Healing progression after HPDR treatment in a 53-year-old female, Fitzpatrick Skin Scale II. An additional 7 days (17 days total) was required for completion of re-epithelialization. Before (A), 6 (B), 10 (C), and 30 days (D) posttreatment. Incomplete re-epithelialization is an event at Day 10 (C) in the peri-oral area as well as other focal areas (left lateral brow, medial left upper eyelid) but complete by Day 30 posttreatment (D). HPDR, helium plasma dermal resurfacing



by the facial mask. No specific intervention/therapy was needed in 14 events whereas topical medication was used in two events and milia extractions were performed in two subjects (four events). Most (70%) acne/milia events were resolved by the 180-day posttreatment visit with the remainder having resolved subsequently. Telangiectasia ($n = 5$ mild severity and $n = 1$ moderate severity) resolved in 50% subjects by the 180-day posttreatment visit. One subject with ongoing telangiectasia was treated successfully with a pulsed 532 nm/1064 nm NdYAG vascular laser. Discoloration/hypopigmentation ($n = 3$ mild) resolved in two of three subjects by the 180-day posttreatment visit and was ongoing in one subject that completed and exited the study and maybe more

appropriately termed “relative hypopigmentation” due to contrast from baseline increased pigment in adjacent non-treated skin. Eye irritation ($n = 1$ moderate severity) was resolved by the 90-day follow-up visit with ocular lubricant drops as the sole intervention.

Although we do not yet have the benefit of a longitudinal perspective with lengthy follow-up, the novel HPDR technology using high energy, double pass technique appears to have relatively similar complication rates (with strict attention to treatment guidelines), healing times, and outcomes as other conventional deep skin resurfacing treatments including CO₂ ablative fractional resurfacing and full-field CO₂ and erbium YAG laser skin resurfacing.

Limitations of this study include the lack of an ideal internal control as is typically the case in facial skin resurfacing studies and certainly in single-arm studies, inability to precisely control energy density across study sites and between subjects, inability to ensure uniformity of aftercare measures employed by subjects as well as limited posttreatment follow-up of just 6 months.

CONCLUSION

High energy, double pass HPDR is an effective treatment for moderate to severe wrinkles in patients with Fitzpatrick Skin Types I, II, and III. Mean FWS improvement (−3.6 IPRs) was more than two grades higher than that previously observed with other skin resurfacing technologies including nitrogen plasma skin regeneration (−1.3)¹⁷ and CO₂ laser skin resurfacing (−1.1).¹⁸ VISIA-CR analysis confirms additional benefits of double pass HPDR treatment including significant reductions in brown spots, enlarged pores as well as improvement in wrinkle thickness. Subject satisfaction is similar to that for other skin resurfacing technologies and AE were predominantly mild to moderate ETEs that resolved in a reasonable time frame. While secondary wounding appears to be an important factor in the development of hypertrophic scarring events following HPDR treatment, primary prevention may be maximized via strict adherence to treatment guidelines. Overall, the benefit-risk ratio appears to be acceptable and relatively similar to that of other technologies of similar effectiveness.

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