Novel Hyaluronic Acid Dermal Filler: Dermal Gel Extra Physical Properties and Clinical Outcomes

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BACKGROUND Dermal gel extra (DGE) is a new, tightly cross-linked hyaluronic acid (HA)-based dermal filler containing lidocaine engineered to resist gel deformation and degradation.

OBJECTIVES To develop a firmer gel product (DGE) and compare the efficacy and safety of DGE with nonanimal stabilized HA (NASHA) for correction of nasolabial folds (NLFs).

METHODS DGE physical properties were characterized, and 140 subjects with moderate to deep NLFs were treated with DGE and NASHA in a randomized, multicenter, split-face design study. Efficacy, pain, and satisfaction were measured using appropriate standard instruments. Adverse events were monitored throughout the study.

RESULTS DGE has a higher modulus and a higher gel:fluid ratio than other HA fillers. Similar optimal correction was observed with DGE and NASHA through 36 weeks (9 months). Study subjects required less volume ($p<.001$) and fewer touch-ups ($p=.005$) and reported less injection pain ($p<.001$) with DGE treatment. Most adverse events were mild to moderate skin reactions.

CONCLUSIONS DGE is a firm HA gel that required significantly less volume and fewer touch-ups to provide equivalent efficacy to NASHA for NLF correction; both dermal gels were well tolerated. DGE will provide a comfortable and cost-effective dermal filler option for clinicians and patients.

This trial was sponsored by Mentor Worldwide LLC, Santa Barbara, CA and Genzyme Corporation, Cambridge, MA. Drs. Monheit and Gold are consultants to Mentor. David Burkholder, PhD, is an employee of PD Pharmaceutical Consulting Services, LLC, Guilford, CT. He is a Mentor writing consultant and was paid by the sponsors to provide assistance in the preparation of the manuscript.

Motivation for aesthetic facial rejuvenation derives from a range of factors, including disease, environmental exposure, trauma, and, perhaps most importantly, aging.[1] Classic emergence of unsightly skin folds and wrinkles during aging can be viewed as a three-dimensional process driven by redistribution of subcutaneous facial fat and loss of facial volume.[2,3] Reversing this process to yield smoother, younger-looking skin has been reported to improve self-image and even job performance.[4–6] Although the number of cosmetic surgical procedures has increased significantly during the past decade, nonsurgical treatment options increased 100% to 200% and accounted for 85% to 88% of the more than 10 million to 12 million surgical and nonsurgical procedures performed in the United States in 2009.[7,8] Minimally invasive dermal fillers used alone or in combination with botulinum toxin type A have accounted for much of the surge in nonsurgical facial rejuvenation procedures.[3,9] Because of good tolerability and low immunogenicity, hyaluronic acid (HA)-based fillers have emerged as the dominant choice for dermal filler applications.[10–12]

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Numerous HA filler reviews and consensus and guideline publications have appeared during the past few years.[1,3,9,13–15] The publications provide guidance and recommendations for appropriate application of HA fillers for aesthetic enhancement of facial features. A clear message is that not all fillers are ideal for all applications and that chemical and physical characteristics determine tissue compatibility and suitability for specific applications.[9]

HA-based dermal fillers available in the United States have distinct chemical and physical characteristics.[16,17] The chemical HA cross-linking process transforms uncross-linked HA polymers into a cross-linked gel more resistant to enzymatic and free-radical degradation, thus conferring longer residence time in the body.[15] The physical properties of dermal fillers (e.g., degree of cross-linking, degree of swelling, and HA-concentration) contribute to the elastic modulus (G') which is used to describe filler hardness.[16,17] A high G' (firmer) dermal filler may be more resistant to forces resulting from the movement of facial muscles.[16] Individually and taken together, the chemical and physical properties allow dermal gel development targeted to specific properties that may affect clinical performance.[18]

Dermal gel extra (DGE) (PREVELLE Lift, Mentor Worldwide LLC, Santa Barbara, CA and Genzyme Corporation, Cambridge, MA) is a novel divinyl sulfone (DVS) cross-linked HA-based filler formulated with 0.3% lidocaine engineered to form a tightly cross-linked gel resulting in a higher elastic modulus than other commercially available HA dermal fillers—characteristics selected to resist implant deformation and provide a long-lasting aesthetic correction. This article describes the physical properties of DGE and presents results of the first clinical study of this product.

Methods and Materials

Characterization of DGE Physical Properties

The gel:fluid ratio, concentration of HA, percentage of HA modification, percentage of swelling, and G' (elastic modulus: the amount of stress required to produce a given amount of deformation) of DGE were measured using previously described methods.[16]

Clinical Trial

Study Design: A prospective, randomized, subject- and evaluator-blinded, split-face design study (NCT00444626) was conducted in two phases at six U.S. sites. The objective of the initial study phase was to compare the efficacy and safety of DGE for the correction of moderate to severe nasolabial folds (NLFs) with that of a commercially available nonanimal stabilized HA (NASHA; Restylane, Medicis Aesthetics Inc., Scottsdale, AZ).[19] The objective of the repeat study phase was to determine whether an immune response results from repeat treatment with DGE. All subjects provided informed consent, and the study was conducted in compliance with the principles of the International Conference on Harmonization, adhering to Good Clinical Practice and to the principles that have their origin in the Declaration of Helsinki.

Subjects and Treatment: Study subjects were men and women aged 18 and older with moderately deep or deep bilateral NLFs measured using the Genzyme 6-Point Grading Scale (GGS; Table 1).[20] Subjects were excluded if they had had previous tissue augmentation at the NLF area within 24 weeks before study entry. In addition, subjects were restricted from undergoing tissue augmentation at the NLF area, as well as other cosmetic procedures (including botulinum toxin type A) in any area of the face for the duration of the study. Other exclusion criteria included pregnancy, plans for pregnancy

TABLE 1. Genzyme 6-Point Grading Scale

Grade	*Wrinkle Severity*
0	No wrinkles
1	Just-perceptible wrinkles
2	Shallow wrinkles
3	Moderately deep wrinkles
4	Deep wrinkles, well-defined edges
5	Very deep wrinkles, redundant fold

during the course of the study, history of bleeding or pigmentation disorders, and history of severe allergies or allergy to any of the test components. Immunocompromised or immunosuppressed subjects were also excluded.

DGE (22 mg/mL of cross-linked HA in a buffer solution with 0.3% lidocaine hydrochloride) and NASHA (20 mg/mL of cross-linked HA in phosphate-buffered saline solution)[19] were supplied as prefilled 1.0-mL syringes with 30-G needles. Investigators were instructed to use slightly more pressure on the DGE syringe with a slow injection and to avoid overcorrection.

During the initial study phase, enrolled subjects were treated with DGE and NASHA in opposing NLFs; assignment to NLFs was randomized. Before injection, topical anesthetic containing 2.5% lidocaine and 2.5% prilocaine (EMLA Cream, AstraZeneca, Wilmington, DE) was applied to both NLFs. At the initial study visit, each NLF was treated to optimal correction determined by the investigator. Injections were deep dermal and subcutaneous. A maximum of two touch-up injections was allowed at 2 and 4 weeks if optimal correction was not maintained for a 2-week period. If optimal correction for one or both NLFs was maintained at the 2-week follow-up visit, the prior visit was considered the date of optimal correction (DOC). Follow-up visits were scheduled at 4, 8, 16, 24, and 36 weeks (9 months) after the DOC.

If a subject completed the initial study phase, he or she entered into the repeat study phase (36 weeks after DOC) and was injected with DGE in both NLFs to optimal correction. A final visit for a safety assessment occurred 4 weeks after repeat treatment.

Assessments: Blinded evaluators assessed efficacy for NLF correction at weeks 4, 8, 16, 24, and 36 using the GGS (Table 1),[20] a modified version of the commonly used 6-Point Grading Scale for wrinkles.[21] All participating investigators (principal investigators and blinded evaluators) were trained before the study in the correct application of the GGS. The GGS was used each time the blinded evaluator and principal investigator performed a live wrinkle assessment for any given study time point. During the trial, live subject evaluations were performed using the GGS photographic scale.

The primary outcome of this study was improvement in wrinkle severity score (measured using the GGS) from baseline to week 24. Secondary outcomes were improvement in wrinkle severity score from baseline to week 36, duration of improvement at weeks 24 and 36, pain during injection and 15 and 30 minutes after injection, and product preference at weeks 24 and 36. The duration of improvement was defined as the percentage of subjects with improvement of 1 or more grades in wrinkle severity score from baseline to weeks 24 and 36. Subjects evaluated pain during injection and at 15 and 30 minutes after injection using a visual analog scale (VAS, 1–100 mm; 0 = no pain and 100 = extreme pain). Additional assessments included the volume of product used, the number of touch-ups needed to achieve optimal correction, and investigator and subject satisfaction with aesthetic result. The investigators and subjects assessed satisfaction at weeks 4, 8, 16, 24, and 36 using the Global Assessment of Satisfaction scale (−2 = much worse, −1 = worse, 0 = no change, 1 = better, 2 = much better). Efficacy analyses were performed on the full analysis set population, which included all randomized subjects who received both study treatments and were assessed for any posttreatment efficacy data.

Investigators evaluated adverse events after each study visit. Subjects completed symptoms diaries for up to 14 days posttreatment. Putative antibody titers (immunoglobulin (Ig)G, IgM, IgA) against DGE were measured at baseline and 4 and 36 weeks after initial treatment, and 4 weeks after repeat treatment to assess immunologic response. Blood samples were processed at a central laboratory. Serum antibody titer analysis was assessed using enzyme-linked immunosorbent assay (ELISA, Southern Research Institute, Birmingham, AL) validated to detect

anti-DGE antibodies in human serum. The safety population included all enrolled subjects who received treatment with DGE or NASHA.

Statistical Analyses: A sample size of at least 120 subjects was planned for the initial study phase to provide 90% power to compare the means for the primary efficacy end point between DGE and NASHA and to provide, with high probability, at least 100 subjects available for evaluation at the completion of the repeat study phase. Noninferiority of DGE treatment was considered to be demonstrated if the 97.5% lower confidence bound for the mean difference (DGE–NASHA) between the two treatments for the primary efficacy end point was greater than −0.5. The noninferiority analysis was performed using the data available. In addition, a sensitivity analysis was performed using multiple imputation for any missing data. The difference (DGE–NASHA) in improvement in the wrinkle severity score for each subject was analyzed according to Fitzpatrick skin type classification (I–III vs IV–VI), and the mean differences in improvement for these two classification groups were compared using the two-sample *t*-test. The pain assessments, volume of product used, number of touch-ups, and investigator and subject satisfaction of DGE and NASHA were compared using paired *t*-tests. Product preference assessments were compared using the sign test. Duration of improvement assessments, frequency of adverse events, and subject-reported symptoms were compared using the McNemar test. For all analyses, $p < .05$ was considered statistically significant.

Results

Characterization of DGE Physical Properties

The data in Table 2 show that DGE had different physical properties from currently available HA-based fillers.[16] DGE had a higher G' than NASHA (firmness; 1,800 vs 660 Pa), a higher gel component in formulation (19 vs 15 mg/mL), a higher gel:fluid ratio (85:15 vs 75:25), and a higher degree of HA cross-linking (7.0% vs 1.3%). DGE and NASHA both exhibited a high state of hydration that translated to relatively low dilution durability/% swelling of approximately 50%.

TABLE 2. Physical Properties of Dermal Gel Extra (DGE) and Nonanimal Stabilized Hyaluronic Acid (NASHA)

Properties	*DGE*	*NASHA*
Total HA concentration, mg/mL	22	20
Gel:fluid ratio	85:15*	75:25
HA gel concentration, mg/mL	19	15
Degree of HA modification, %	9	3
Cross-linked HA, %	7	1.3
Pendant-linked HA, %†	2	1.7
Dilution durability/% swelling	50	50
G' modulus, Pa	1,800	660

*The DGE formulation includes soluble hyaluronic acid (HA) to facilitate extrusion of a high-modulus gel from the syringe.
†Bifunctional (reactive group at each end) cross-linkers will often bond (link two HA strands) only at one end, leaving the other end free hanging (pendant). Thus, the total degree of modification can be defined as total % degree of modification = % cross-link + % pendant.

Clinical Study Subject Disposition

Of the 166 subjects enrolled, 140 were randomized and given at least one treatment with DGE and NASHA; 128 subjects completed the initial study phase, and 105 completed the repeat study phase. Subjects discontinued from the initial study phase for various reasons (lost to follow-up $n = 9$, voluntary withdrawal $n = 2$, adverse event $n = 1$); the most serious case was a subject withdrawal because of a diagnosis of colon cancer, classified by the investigator as unrelated to the study device or procedure. Withdrawals before repeat injection included voluntary withdrawal ($n = 7$), adverse events ($n = 3$, continued events from initial phase), and per protocol exclusions ($n = 13$). At baseline, all NLFs had moderately deep ($n = 161$; 57.5%) or deep ($n = 119$; 42.5%) wrinkles (according to the GGS). Baseline demographics are shown in Table 3. At baseline, 53 (37.9%) subjects had Fitzpatrick skin types IV to VI. Demographics of subjects in the repeat study phase were similar to the demographics for the baseline population.

TABLE 3. Subject Demographics at Baseline ($N = 140$)

Characteristic	*Value*
Age, mean ± standard deviation	52.7 ± 9.3
Female, *n* (%)	135 (96.4)
Race*, *n* (%)	
Caucasian	98 (70.0)
African American	22 (15.7)
Other or multiple races	17 (12.1)
Not available	3 (2.1)
Ethnicity, *n* (%)	
Non-Hispanic	108 (77.1)
Hispanic	30 (21.4)
Not available	2 (1.4)
Fitzpatrick skin type, *n* (%)	
I	6 (4.3)
II	44 (31.4)
III	37 (26.4)
IV	29 (20.7)
V	15 (10.7)
VI	9 (6.4)

*Multiple responses were possible for race.

Primary Efficacy Assessments

Similar improvements in wrinkle severity (mean improvement score (2 standard errors)) were seen for DGE- and NASHA-treated NLFs at week 24 (1.8 (0.2) for both products), and at Week 36 (1.3 (0.2) for both products; Figure 1A). Mean wrinkle severity scores for DGE- and NASHA-treated NLFs were similar at all time points (Figure 1B). The 97.5% lower confidence bound for the mean difference (DGE–NASHA) in improvement at 24 weeks was −0.140, which is greater than the prespecified noninferiority margin of −0.5; therefore, noninferiority of DGE to NASHA was demonstrated for the primary efficacy outcome: improvement in wrinkle severity 24 weeks after DOC.

Secondary Efficacy Assessments

The mean total volume for the initial treatment (initial plus touch-ups) of DGE required for optimal correction (1.31 (0.09) mL) was significantly ($p <$ .001) less than that for NASHA (1.52 (0.11) mL; Figure 2A). Mean initial injection volume (0.88 vs 0.97 mL, $p <$ .001) and mean first touch-up volume

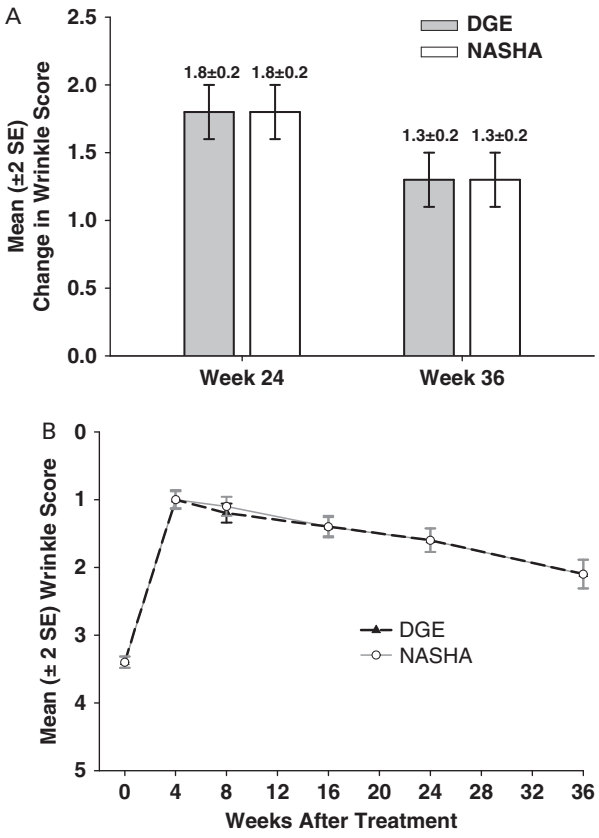

Figure 1. (A) Mean (± 2 standard errors (SEs)) change in wrinkle severity scores from baseline to weeks 24 and 36. (B) Mean (± 2 SE) wrinkle severity scores over time.

for subjects who had a first touch-up (0.57 vs 0.65 mL, $p = .002$) were significantly less for DGE than for NASHA. For the repeat study phase also, significantly ($p = .046$) less volume of DGE was required for NLFs originally treated with DGE than for NLFs originally treated with NASHA (mean 0.65 mL for DGE vs 0.69 mL for NASHA; Figure 2A).

During the initial treatment, 55.0% of NLFs injected with DGE received less than 1.0 mL, compared with 34.3% of NLFs injected with NASHA. The mean number of touch-ups required for optimal correction with DGE was 0.76 (0.13), compared with 0.90 (0.13) with NASHA ($p = .005$; Figure 2B).

Mean differences in change from baseline to week 24 in wrinkle severity score between the two NLFs of

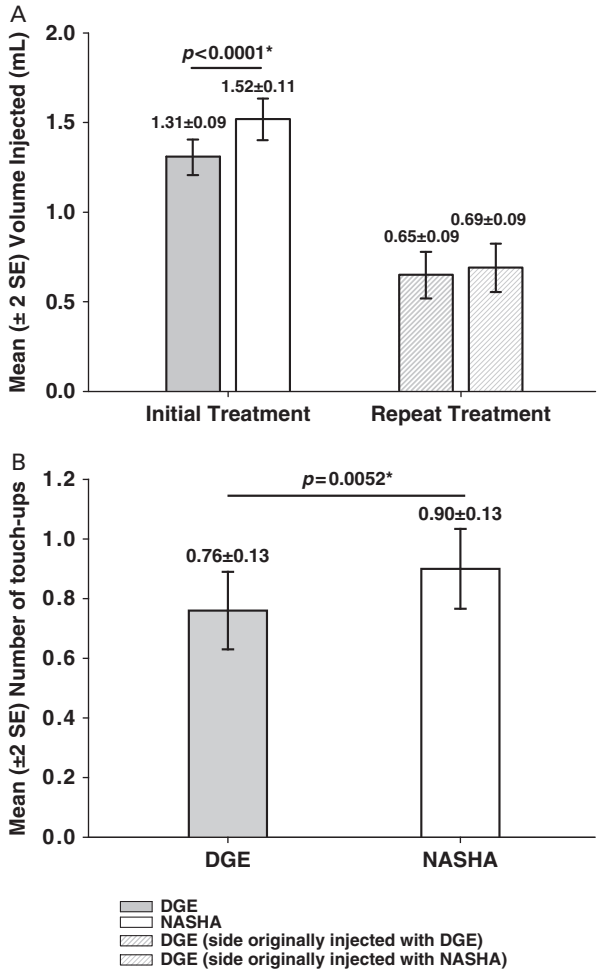

Figure 2. (A) Total volume of product injected. *p-value is based on paired t-test, dermal gel extra (DGE) vs non-animal-stabilized hyaluronic acid (NASHA). (B) Number of touch-ups needed for optimal correction. *p-value is based on paired t-test, DGE vs NASHA.

each subject were compared between subjects of Fitzpatrick skin type I to III and subjects of skin type IV to VI, and no significant difference ($p = .77$) was found.

Subjects experienced significantly less pain during injection with DGE than with NASHA, with mean VAS scores of 23.2 (3.3) and 48.9 (4.4), respectively ($p < .001$). The difference in pain scores was maintained 15 and 30 minutes after injection. The majority of NLFs maintained at least a 1-grade improvement in wrinkle severity at 24 (88.4% DGE, 87.6% NASHA) and 36 weeks (70.1% DGE, 69.3% NASHA (Figure 3). The difference between DGE and NASHA in duration of improvement was not significant at either time point ($p > .99$).

The results of the subject self-assessments, subject preference, and subject satisfaction were similar for DGE and NASHA at weeks 24 and 36. At 36 weeks, more subjects preferred DGE-treated sides (53.0%) than NASHA-treated sides (47.0%), although this difference was not statistically significant. Investigators rated more than 80% of all subjects' NLFs as much better or better at 24 and 36 weeks than at baseline; the distribution of the investigators' global satisfaction scores were similar for DGE and NASHA.

Safety Assessments

The most common treatment-emergent adverse events reported were injection site reactions, including swelling, pain, bruising, erythema, nodules, and pruritus (Table 4). There were no adverse events for which a statistically significant difference between treatments in the frequency of the adverse event was found. Twenty-eight (20.0%) subjects experienced non-NLF adverse events. Similar injection site reactions were reported in the repeat study phase (Table 4). Nine (8.6%) subjects

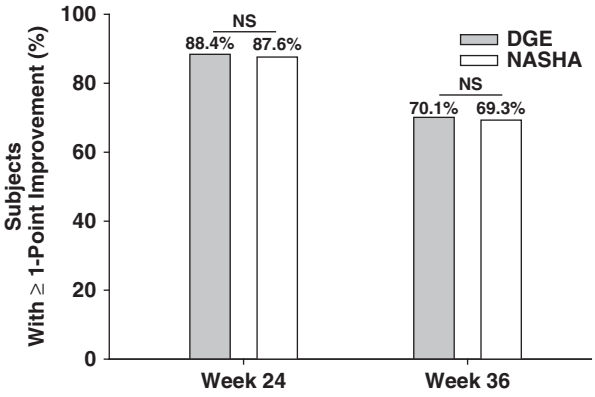

Figure 3. Comparison of duration of improvement with dermal gel extra (DGE) and non-animal-stabilized hyaluronic acid (NASHA). The duration of improvement was defined as the percentage of subjects with 1 grade or more improvement in wrinkle severity score from baseline to weeks 24 and 36 after date of optimal correction. NS = no statistically significant difference between DGE and NASHA.

TABLE 4. Treatment-Emergent Adverse Events Occurring in 5% or More of Subjects per Nasolabial Fold

	n *(%)*			
	*Initial Study Phase** (N = *140*)		*Repeat Study Phase* (N = *105*)	
Adverse event	*DGE*	*NASHA*	*Side originally treated with DGE*	*Side originally treated with NASHA*
Swelling	78 (55.7)	69 (49.3)	47 (44.8)	47 (44.8)
Pain	61 (43.6)	57 (40.7)	34 (32.4)	32 (30.5)
Bruising	35 (25.0)	29 (20.7)	23 (21.9)	23 (21.9)
Erythema	30 (21.4)	27 (19.3)	33 (31.4)	33 (31.4)
Nodule	12 (8.6)	6 (4.3)	3 (2.9)	0
Pruritis	11 (7.9)	8 (5.7)	6 (5.7)	7 (6.7)

*Dermal gel extra (DGE) vs nonanimal stabilized hyaluronic acid (NASHA). There were no statistically significant differences between treatments for any individual adverse event; statistical analysis was performed using the McNemar test.

experienced non-NLF adverse events after repeat treatment with DGE. The majority of adverse events resolved in 7 days or less and were mild or moderate in severity, with the most common severe reaction being injection site swelling. No serious treatment-related adverse events were reported during either study phase.

Although subjects with Fitzpatrick skin types I to III had a higher frequency of erythema than subjects with skin types IV to VI during the initial study phase, the overall frequencies of adverse events were similar for both subgroups. Hyper- or hypopigmentation, hypersensitivity, hypertrophic scarring, and keloid formation did not occur after treatment with either product.

Subject diary-reported symptoms on DGE-treated sides were slightly higher than on NASHA-treated sides in the initial study phase. Reported symptoms were swelling, redness, tenderness, pain, bruising, itching, and other (e.g., numbing or swollen feeling). Most diary-reported subject symptoms resolved in 7 days or less in both study phases. Subject-reported symptoms in the repeat study phase were similar to but reported at a lower incidence compared to the initial study phase.

DGE and NASHA did not have a clinically significant effect on hematology or blood chemistries during either treatment phase of the study. None of the subjects generated a high antibody titer to DGE after initial or repeat exposure.

Discussion

Ideally, clinicians should have an array of available dermal fillers with a range of properties to provide flexibility in selecting a treatment best suited to meet the needs of patients.[16] DGE (with lidocaine) has unique physical properties that distinguish it from currently available HA-based dermal fillers. The combination of high cross-linking (7.0% modified HA), high HA gel concentration in the formulation (19 mg/mL), and high gel:fluid ratio (85:15) resulted in a firm filler with a high elastic modulus (G' = 1,800 Pa). With a unique combination of physical properties, DGE was designed to resist enzymatic and free radical degradation and provide better support with a soft feel and more persistent correction.

Although DGE is firmer than other HA-based fillers, it is still much softer than the modulus of human skin.[22] The investigators in this study used an injection technique identical to that used with injecting other HA fillers and did not find a significant difference with the use of DGE.

This first clinical trial of DGE compared the efficacy and safety of DGE with that of NASHA, one of the

leading dermal fillers currently in use in the United States. Noninferiority of DGE was demonstrated at all time points: 4, 8, 16, 24 (primary study end point), and 36 weeks. The two dermal fillers were equally effective at correcting NLFs at all time points evaluated; clinically significant effects persisted for up to 36 weeks. Analysis of secondary efficacy variables indicated that significantly fewer touch-ups ($p = .005$) and less volume ($p < .001$) of DGE were required to achieve optimal correction. We postulate that the physicochemical profile of DGE (highly cross-linked, high-modulus gel) could lead to less gel migration and therefore less volume required to fill the localized intradermal space.[16] Assuming proper injection techniques, the lower volume of DGE and fewer number of touch-ups required for correction may contribute to a positive experience for patients and, ultimately, lower cost of treatment.

The advent of adding anesthetic lidocaine to dermal filler formulations represents an advance in patient comfort during injection procedures.[23,24] A greater than 50% reduction in pain during injection with lidocaine-containing formulations has been demonstrated to influence product preference.[23] Lidocaine-containing dermal gels are now widely available in the United States (Restylane-L, Medicis Aesthetics Inc., Scottsdale, AZ; Perlane-L, Medicis Aesthetics Inc., Scottsdale, AZ; Juvederm Ultra XC and Juvederm Ultra Plus XC, Allergan Inc., Irvine, CA).[25–28]

Clinician-reported and subject diary-reported treatment site reactions for both products during the initial phase of the study were similar in type and incidence to those reported previously for HA-based dermal fillers.[19,29–32] Although there was a higher incidence of subject-reported symptoms for DGE than NASHA in the initial study phase, the incidence of subject-reported symptoms was lower in the repeat study phase than in the initial study phase. The lower incidence of injection site reactions on repeat treatment may simply reflect investigator experience handling this new filler with physical properties substantially different from those of NASHA.[16]

More than one-third of the subjects enrolled in the present study were Fitzpatrick skin types IV to VI. Subgroup analysis revealed no difference in wrinkle correction between the two NLFs within each subject for darker skin subjects and in subjects with Fitzpatrick skin types I to III. Furthermore, the frequency and severity of adverse events experienced in subjects with skin types IV to VI were similar to those with types I to III. The results suggest that these HA-based fillers can be used safely and effectively when treating people of color.

Less volume and fewer touch-ups for DGE than NASHA provided partial translation of the differences in physical properties in the two dermal fillers to clinical outcomes, but a limitation of the study was that subjects were followed for only 36 weeks (9 months). A recent publication reported significant improvement in wrinkle severity for subjects treated with NASHA lasting up to 18 months after one retreatment at 4.5 or 9 months.[33] Investigators still rated more than 80% of all NLFs regardless of treatment as much better or better at 9 months in the current study. The question remains whether DGE, specifically engineered for greater implant durability, will provide greater longevity of correction than NASHA. Future studies must evaluate wrinkle correction and subject satisfaction with aesthetic results beyond 9 months after achieving optimal correction, with no retreatment, to evaluate its true duration of effect.

In conclusion, results from this study demonstrated that DGE was as effective as NASHA for the correction of NLFs for the 36-week (9-month) duration of this study. Both treatments provided aesthetic results that persisted for at least 36 weeks in most subjects, and both treatments were well tolerated. Subjects required less volume and fewer touch-ups for optimal correction with DGE than with NASHA. The data presented here suggest that DGE will be an effective and comfortable option for subjects seeking correction of moderate to severe facial wrinkles and folds.

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