

Twelve-Month Persistency of a Novel Ribose–Cross-linked Collagen Dermal Filler

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BACKGROUND The porcine collagen–derived dermal filler Dermicol-P35 (Evolence, Colbar LifeScience Ltd, Herzliya, Israel) has low immunogenicity and the potential to provide a long-lasting corrective response for soft-tissue contour deficiencies and deformities.

OBJECTIVE The objective was to assess the persistence of the corrective response with Dermicol-P35 up to 12 months after obtaining an optimal cosmetic result (OCR) in a randomized, multicenter study comparing the efficacy and safety of Dermicol-P35 with the hyaluronic acid (HA) filler Restylane (Medicis Pharmaceutical Co.).

METHODS & MATERIALS Subjects with moderate to deep nasolabial wrinkles ($n = 149$) were randomized to injections of either Dermicol-P35 or HA on one side of the face and the alternative preparation on the contralateral side. If necessary, one touch-up injection could be given after 2 weeks to obtain an OCR.

RESULTS Although the mean Modified Fitzpatrick Wrinkle Scale score increased gradually after achieving the OCR with Dermicol-P35, 95.3 and 76.5% of subjects, respectively, met the criteria for persistence of the corrective response after 9 and 12 months. Persistency rates were similar regardless of the requirement for a touch-up injection at Week 2. No unexpected, severe, or serious injection-related adverse events were experienced.

CONCLUSION The effectiveness of Dermicol-P35 appears to be maintained for up to 1 year after achieving an OCR, both for touch-up and for non–touch-up subjects.

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Dermal fillers have been used to cosmetically improve soft tissue defects and deficiencies for more than 100 years, originally as injectable fat, but more recently as a variety of biocompatible soft tissue fillers. As more and more people seek to correct skin defects via techniques that do not require surgery, the use of these preparations has become increasingly common, especially for the correction of wrinkles and folds. Currently available dermal fillers include bovine and human collagens, hyaluronic acid (HA) preparations of animal or biosynthetic origin, poly-L-lactic acid products, polymethylmethacrylate, and calcium hydroxyapatite.^{1,2} Bovine collagen

preparations have been in use since 1981; various forms are available, including a glutaraldehyde cross-linked formulation (Zyplast, Allergan, Irvine, CA) designed to increase tissue persistence, but dermal correction with bovine collagen implants is generally of short duration requiring frequent reinjections, and hypersensitivity reactions are relatively common (occurring in around 1% to 3% of subjects).¹

Over the past decade, various HA dermal fillers in which the HA molecule is stabilized (cross-linked) through minimal chemical modification to improve

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its resistance to enzymatic degradation within the dermis have become available. These preparations can confer less risk of immunogenicity than bovine collagen, and skin testing prior to their use is not required.^{1,3} In comparison with cross-linked bovine collagen (Zyplast), HA has proved equally effective in correcting nasolabial folds and equally well tolerated, but the injection volume required to achieve an optimal cosmetic result (OCR) was lower with HA and the improvement was more durable.⁴ Another recent addition to the therapeutic armamentarium of soft-tissue fillers is Dermicol-P35 (Evolence, Colbar LifeScience Ltd, Herzliya, Israel), a porcine-derived collagen gel prepared via a process that includes enzymatic digestion to remove the most antigenic portions of the molecule and cross-linking with a naturally occurring sugar metabolite via Glymatrix technology to slow its resorption rate in vivo. Dermicol-P35 has demonstrated no evidence of cytotoxicity, delayed dermal contact sensitization, intracutaneous reactivity, systemic toxicity, mutagenicity, or genotoxicity in preclinical studies.⁵ A preliminary clinical study of a preparation containing a lower concentration of the same cross-linked porcine collagen (30 mg/mL; Evolence-30, Colbar LifeScience Ltd) in 12 subjects showed that it was equally effective in improving nasolabial folds as cross-linked bovine collagen (Zyplast), but provided a longer-lasting correction.⁶ No edema or ulceration occurred with either treatment, and the only adverse event observed was mild and transient erythema.

A previous publication⁷ has provided data on the efficacy and tolerability of Dermicol-P35 relative to that of the HA filler Restylane (Medicis Pharmaceutical Co., Scottsdale, AZ) up to 6 months after achievement of an OCR in subjects seeking correction of nasolabial folds. The data presented in this report indicate that the efficacy of Dermicol-P35 was noninferior to that of HA in these subjects and establish its good safety profile.⁷ The present analysis provides follow-up data on the persistency of the corrective response with Dermicol-P35 and its safety at 9 and 12 months after achieving the OCR. Owing to the sample size and lack of statistical power for

the 9- and 12-month data, a noninferiority analysis of Dermicol-P35 and HA could not be completed at these time points, and without appropriate statistical validation, it was not considered appropriate to compare the efficacy data for the two dermal fillers beyond the 6-month post-OCR assessment. Consequently, the focus of this report is on the persistence of the corrective response with Dermicol-P35 at 9 and 12 months after achieving the OCR. However, safety data for both dermal fillers for the second 6 months of follow-up are presented.

Methods and Materials

The study was a randomized, within-subject (split-face), evaluator-blinded trial performed at six centers in the US from November 2005 to April 2007 comparing Dermicol-P35 (cross-linked porcine collagen 35 mg/mL; Evolence), with HA (Restylane) in subjects seeking correction of bilateral moderate to deep nasolabial folds. The trial was approved by a central institutional review board, and was performed in accordance with the requirements of good clinical practice outlined in the International Conference on Harmonisation Guideline for Good Clinical Practice E6(R1) and directives on the protection of study participants contained in the Declaration of Helsinki and US 21 Code of Federal Regulations (Parts 50 and 56). Written informed consent was obtained from all subjects prior to screening.

Subjects and Treatment

Subjects eligible for participation in the study were adults (≥ 18 years of age) of either gender who presented with clinical evidence of bilateral aging defects in the nasolabial area with wrinkles rated as 2 or greater (i.e., ≥ 1 to 2 mm in depth) on the 7-point Modified Fitzpatrick Wrinkle Scale (MFWS; see Table 1)⁸ and a nasolabial wrinkle at least 50% of the anatomical nasolabial area length and who had completed the first 6 months of the noninferiority study of Dermicol-P35 and HA (the results of which have been published previously).⁷ All subjects

TABLE 1. MFWS⁸

Score	Description
0	No wrinkle: no visible wrinkle; continuous skin line
0.5	Very shallow yet visible wrinkle
1	Fine wrinkle: visible wrinkle and slight indentation
1.5	Visible wrinkle and clear indentation; less than 1 mm wrinkle depth
2	Moderate wrinkle: clearly visible wrinkle; 1 to 2 mm wrinkle depth
2.5	Prominent and visible wrinkle; more than 2 and up to 3 mm wrinkle depth
3	Deep wrinkle: deep and furrow wrinkle; more than 3 mm wrinkle depth

were required to abstain from exclusionary procedures affecting areas below the zygoma (e.g., face-lifts, full-mouth rehabilitation, further augmentation therapy, laser or chemical resurfacing) for the duration of the study. Exclusion criteria included pregnancy and/or lactation; a history of allergies and/or sensitivity to porcine collagen or HA; clinically significant organic disease; serious intercurrent illness; a history of autoimmune or collagen vascular disease; active skin disease or inflammation; clinically significant abnormal laboratory parameters; use of botulinum toxin A injections or radiofrequency skin-tightening in the lower half of the face; treatment with immunosuppressive drugs, chemotherapeutic agents, or systemic corticosteroids within the previous 3 months; use of over-the-counter wrinkle products; a history of bleeding disorders; presence of scars or facial deformities at the planned injection site; and absence of a requirement for treatment on both sides of the face.

Subjects not demonstrating hypersensitivity to pre-treatment skin testing with Dermicol-P35 and who met the inclusion/exclusion criteria were randomized to injections of either Dermicol-P35 or HA into the mid dermis of nasolabial folds on one side of their face with injections of the alternative preparation on the contralateral side. All injections were performed by investigators experienced in dermal filler corrections and were continued until the investigator had

determined that an OCR had been obtained; subjects could have received one “touch-up” injection of either Dermicol-P35 or HA or both at 2 weeks \pm 4 days after the first injection to achieve an OCR. At the end of the 12-month post-OCR response persistency evaluation, a further (optional) injection was permitted if the subject wished it. Corrections of contour deficiencies other than nasolabial folds were also permitted (e.g., corner of mouth or marionette lines), but these additional corrections were evaluated for safety only.

Assessments

Assessments of wrinkle severity, which were made by direct facial examination using the MFWS and aided by sets of reference photographs, were undertaken by blinded evaluators/assessors at 9 and 12 months after the OCR assessment (which was at 2 weeks after the original injection if no touch-up had been given or 1 week after a touch-up injection). The results at assessment visits prior to 9 months, at which both sides of the face were evaluated in the same manner, have previously been documented.⁷ In addition to wrinkle severity, the blinded investigators and the subjects also rated the overall treatment response at the OCR visit and each follow-up visit via the Global Improvement Assessment (GIA) scale. Using this scale, the aesthetic appearances of the nasolabial folds were rated as 1 = much better, 2 = better, 3 = no change, or 4 = worse compared with baseline (pretreatment).

Owing to the sample size and lack of statistical power, it was considered inappropriate to compare and contrast the persistency of the corrective responses with two products beyond the 6-month post-OCR visit. Therefore, the outcomes assessed for this analysis were 1) the persistence of the nasolabial fold correction with Dermicol-P35 injections at the 9- and 12-month post-OCR visits (i.e., the percentage of subjects with wrinkles exhibiting an improvement from baseline of at least 0.5 points in the MFWS at these times) and 2) the blinded investigator- and subject-rated global improvement ratings with

Dermicol-P35 injections at the 9- and 12-month post-OCR visits.

Safety (of both dermal fillers) was assessed via the occurrence of local and systemic adverse events, evaluation of the subjects' diaries (in which they were instructed to record levels of pain, swelling, redness, bruising, itching, tenderness, and other adverse events experienced up to 14 days after the last facial injection or event resolution), evaluation of facial sites, and standard laboratory test results. Enzyme-linked immunosorbent assay (ELISA) testing for antiporcine Type I collagen antibodies was performed for those subjects who were positive for antibodies at the 6-month post-OCR visit. The present analysis focuses on 1) adverse events occurring prior to the 6-month post-OCR visit that persisted at this visit, 2) adverse events with onset after the 6-month post-OCR visit, 3) adverse events occurring after recorection injections administered at the 12-month post-OCR visit, and 4) the occurrence of antiporcine Type I collagen antibodies postinjection.

Statistical Analysis

The percentage of subjects demonstrating persistency of the nasolabial fold correction (i.e., an improvement from baseline of at least 0.5 points in the MFWS at the 9- and 12-month post-OCR visits) was determined along with its two-sided 95% confidence interval (CI), using the normal approximation to the binomial distribution if the estimated parameter was > 10% and otherwise using exact binomial statistics. Changes in MFWS scores from baseline and the post-OCR visit were tested by using the Wilcoxon signed rank test at the two-sided 5% level of significance. GIA data were summarized by frequency count only.

Adverse events were summarized by treatment group, body system, the Medical Dictionary for Regulatory Activities (MedDRA) Version 9 preferred term, and relationship to the injected dermal fillers. Titters of antibodies to porcine Type I collagen

(immunoglobulin [Ig]G, IgE, IgM, and IgA) were summarized using descriptive statistics.

Results

A total of 164 subjects were screened and underwent pretreatment testing for hypersensitivity to porcine collagen. Of these, 149 subjects (intention-to-treat [ITT] population) were randomized and received treatment with the two dermal fillers; 148 attended the 6-month post-OCR assessment visit, 146 the 9-month post-OCR visit, and 145 the 12-month post-OCR visit. Four subjects were discontinued during the study, 1 because of an adverse event (unrelated to either dermal filler) and 2 because they were lost to follow-up, and 1 was discontinued on request. The demographic characteristics of the 149 subjects comprising the ITT population are shown in Table 2. Most were female and white and had a pale-white to white skin tone.

At the 12-month post-OCR visit, 123 subjects (82.6%) elected to have a recorection filler injection. Of these, 58 (47.2%) chose to receive an injection of Dermicol-P35, whereas 65 (52.8%) chose to receive an injection of HA. The mean recorection injection volumes of the soft tissue fillers were similar on the two sides of the face. For subjects

TABLE 2. Demographic Characteristics of Study Subjects (ITT Population; n = 149)

Characteristic	No. (%)
Age, years (mean \pm SD) [range]	55.7 \pm 8.3 [30.4–73.8]
Gender	
Male	12 (8.1%)
Female	137 (91.9%)
Race	
White	138 (92.6%)
Black or African American	4 (2.7%)
Asian	1 (0.7%)
Other	6 (4.0%)
Skin tone	
Pale-white/white (I–III)	121 (81.2%)
Light brown (IV)	22 (14.8%)
Brown (V)	6 (4.0%)

choosing Dermicol-P35, the mean recorection injection volume was 0.80 mL on the side originally injected with this preparation and 0.82 mL on the side originally injected with HA; for those choosing HA, the mean recorection injection volume was 0.69 mL on the side originally injected with this preparation and 0.71 mL on the side originally injected with Dermicol-P35.

Efficacy Assessments (Subsequent to the 6-Month Post-OCR Visit)

Mean MFWS scores at baseline and at subsequent assessments up to the 12-month post-OCR visit for Dermicol-P35–treated nasolabial folds (blinded investigator live assessments) are shown in Figure 1. At each assessment, the changes in MFWS scores from baseline were statistically significant ($p < .001$). Comparative data for HA injections up to the 6-month post-OCR visit have been reported previously.⁷

Persistence of the Corrective Response for Dermicol-P35–Treated Nasolabial Folds following the 6-Month Post-OCR Visit In comparison with the mean MFWS score at the OCR visit (0.53 ± 0.52)—which is indicative of shallow yet visible folds at this time (Table 1)—wrinkle severity scores were increased at subsequent follow-up assessments, but remained statistically significantly less than the baseline values at both the 9- and the 12-month post-OCR visits ($p < .001$; Table 3). The percentage of subjects in whom the corrective response persisted (i.e., the

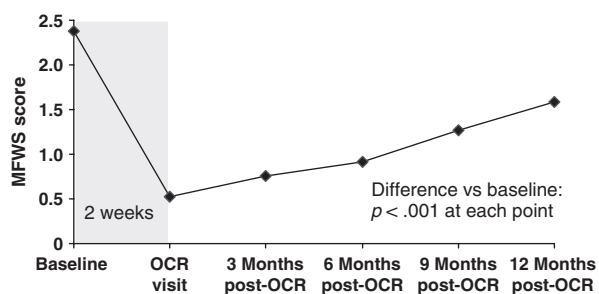


Figure 1. Changes in MFWS scores with Dermicol-P35 injections from baseline (pretreatment) to the 12-month post-OCR visit (ITT population, $n = 149$; blinded investigator assessment).

improvement from baseline in the MFWS was at least 0.5 points) was 95.3% at the 9-month post-OCR visit and 76.5% at the 12-month post-OCR visit; these proportions were similar in subgroups who had or had not received a touch-up injection (Table 3). Similar results were also recorded for MFWS scores by an independent blinded assessor performed via digital photographs of the subjects (data not shown).

Assessments of Global Improvement for Dermicol-P35–Treated Nasolabial Folds following the 6-Month Post-OCR Visit The aesthetic appearance of Dermicol-P35–treated nasolabial folds was rated by the blinded investigators as better or much better versus baseline in 97.3% of subjects at the 9-month post-OCR visit and 86.9% of subjects at the 12-month post-OCR visit. Similarly, 88.3 and 84.8% of subjects, respectively, rated the Dermicol-P35–treated nasolabial folds as better or much better versus baseline at these visits (Figure 2). Results in two subjects at 9 and 12 months typical of those achieved with Dermicol-P35 are shown in Figure 3.

Tolerability Assessment (Subsequent to the 6-Month Post-OCR Visit)

Adverse events reported by subjects after the first facial injections of the two dermal fillers, after the touch-up injections, and at the OCR visit have been reported previously.⁷ Local treatment-related adverse events appearing prior to the 6-month post-OCR visit that persisted at this visit, and those with onset after the 6-month post-OCR visit, are shown in Table 4. With Dermicol-P35, local injection-related adverse events that persisted at the 6-month post-OCR visit were noted in 3.4% of subjects (most commonly injection site induration, 2%), compared with 0.7% of subjects with HA injections. Local injection-related adverse events with onset after the 6-month post-OCR visit occurred in 1.4% of subjects with Dermicol-P35 injections compared with 0.7% with HA injections. On visual examination of subjects at the 9- and 12-month post-OCR visits, the only facial skin reactions noted by the investigators

TABLE 3. Changes in MFWS Scores from Baseline and the OCR Visit, and Persistence of the Nasolabial Fold Correction with Dermicol-P35 Injections at the 9- and 12-Month Post-OCR Visits (ITT Population, n = 149; Blinded Investigator Assessment)

Assessment	Dermicol-P35-Treated Nasolabial Folds	
	9-Month Post-OCR Visit	12-Month Post-OCR Visit
MFWS score (mean ± SD)		
Observed value	1.27 ± 0.65	1.59 ± 0.67
Change from baseline (mean 2.38 ± 0.36)	-1.11 ± 0.55*	-0.79 ± 0.62*
Change from OCR visit (mean 0.53 ± 0.52)	+0.74 ± 0.57*	+1.06 ± 0.72*
Persistence of nasolabial fold correction† (n; %) [2-sided 95% CI]		
Total ITT population (n = 149)	142 (95.3%) [91.9%–98.7%]	114 (76.5%) [69.7%–83.3%]
Subjects with touch-up injections (n = 72)	70 (97.2%) [93.4%–100.0%]	55 (76.4%) [66.6%–86.2%]
Subjects without touch-up injections (n = 77)	72 (93.5%) [88.0%–99.0%]	59 (76.6%) [67.2%–86.1%]

*p < .001 versus the baseline or OCR visit values (two-sided Wilcoxon signed rank test).

†Improvement from baseline of at least 0.5 points in the MFWS at the 9- and 12-month post-OCR visits.

with Dermicol-P35 were mild erythema in two subjects (1.4%) and mild nodule formation in 1 (0.7%).

Local treatment-related adverse events occurring after the recorection injections administered at the 12-month post-OCR visit are also shown in Table 4. With Dermicol-P35, 19% of subjects reported adverse events with the recorection injection (most commonly injection site swelling, erythema, and bruising) compared with 4.6% of those who received HA injections. All of these events were reported by

telephone to the investigator at one site; none was considered severe or serious and all were anticipated local adverse events.

Nonlocal injection-related adverse events did not occur in any more than one subject; no unusual or unexpected adverse events were observed, and their incidence did not increase. Serious adverse events were reported in four subjects during the trial (metastatic colon cancer, chronic myeloid leukemia, dehydration, and uterine prolapse in one subject each), but none of these was considered related to the dermal filler injections.

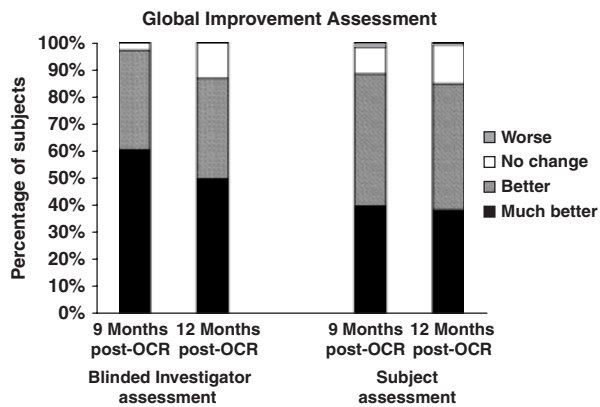


Figure 2. Global improvements versus baseline with Dermicol-P35 injections as assessed by blinded investigators and by subjects at the 9- and 12-month post-OCR visits (ITT population; n = 146 at 9 months, n = 145 at 12 months).

Antiporcine Collagen Antibody Titers Twenty-five subjects had elevated serum titers for one or more immunoglobulins at the 6-month post-OCR visit, and further serum samples were obtained in all of these subjects at the 12-month post-OCR visit. Few subjects changed status during this time. Most of the serum samples that were positive for antibodies to Type I porcine collagen at the 6-month post-OCR visit remained positive at the 12-month post-OCR visit. A significant increase in titer was observed in very few subjects. Subjects with the highest levels of antibodies did not display an unusual incidence of adverse events or adverse

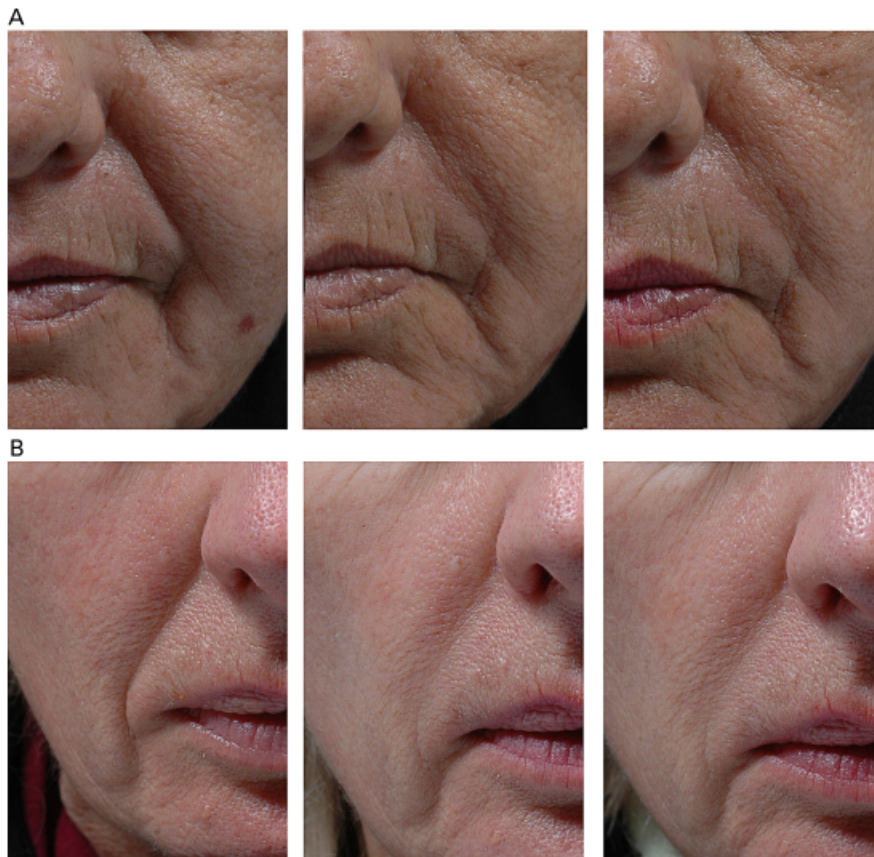


Figure 3. Improvements in nasolabial wrinkles in two subjects at the 9- and 12-month post-OCR visits. (A) Patient one, (B) Patient two.

events or other symptoms that were unusual in character.

Discussion

In a previous report, which presented data from the initial 6 months of this 12-month randomized, within-subject, evaluator-blinded study, no meaningful differences in efficacy were demonstrated between Dermicol-P35 and HA, either for changes in MFWS scores between baseline and the 6-month post-OCR visit or for global improvements in nasolabial folds at the 3- and 6-month post-OCR visits.⁷ The upper limit of the two-sided 90% CI for within-subject differences in MFWS changes from baseline between Dermicol-P35 and HA did not exceed 0.25, indicating that the efficacy of Dermicol-P35 was noninferior to that of HA. In addition, the two dermal fillers showed similar safety profiles, with

most adverse events taking the form of mild injection site reactions. Whereas the incidences of pain, swelling, and bruising were over 5% greater at the HA injection site, the incidence of induration, although low overall, was over 5% greater at the Dermicol-P35 injection site (12.1% vs. 5.4%, respectively). Although ELISA tests for antibodies against porcine collagen indicated the presence of antibodies in some subjects, most were also positive for the antibody at screening, and there were no unusual adverse events associated with elevated immunoglobulin titers. This included subjects (up to 10 in the case of IgG analyses) who exhibited a shift from a negative titer at screening to a positive titer during the 6 months of follow-up.⁷

The present report extends these findings for Dermicol-P35 filler injections in subjects ($n = 148$) who continued into the second 6 months of

TABLE 4. Subjects with Treatment-Related Local Adverse Events Occurring after the 6-Month Post-OCR Visit and following Recorrection Injections Given at the 12-Month Post-OCR Visit

Adverse Event	Dermicol-	
	P35	HA
<i>Local adverse events reported prior to the 6-month post-OCR visit and persisting at this visit</i>		
No. of subjects evaluated	148*	148*
No. with local adverse events	5 (3.4%)	1 (0.7%)
Injection site induration	3 (2.0%)	0
Injection site papules	1 (0.7%)	0
Skin discoloration	1 (0.7%)	1 (0.7%)
<i>Local adverse events with onset after the 6-month post-OCR visit</i>		
No. of subjects evaluated	148*	148*
No. with local adverse events	2 (1.4%)	1 (0.7%)
Injection site papules	2 (1.4%)	1 (0.7%)
<i>Local adverse events occurring after recorrection injections at the 12-month post-OCR visit</i>		
No. of subjects evaluated	58 [†]	65 [†]
No. with local adverse events	11 (19.0%)	3 (4.6%)
Injection site swelling	8 (13.8%)	1 (1.5%)
Injection site erythema	6 (10.3%)	0
Injection site bruising	4 (6.9%)	2 (3.1%)
Injection site irritation	1 (1.7%)	0
Injection site pain	1 (1.7%)	1 (1.5%)
Injection site pruritus	1 (1.7%)	0
*Numbers of subjects who attended the 6-month post-OCR follow-up visit.		
[†] Numbers of subjects who chose to receive recorrection injections at the 12-month post-OCR visit.		

follow-up, but does not compare and contrast the results achieved with those achieved with HA due to the lack of statistical power for the 9- and 12-month data collection time points. Although the mean MFWS score for Dermicol-P35-treated nasolabial folds increased gradually over this period, it remained statistically significantly lower than the baseline value at both the 9- and the 12-month post-OCR visits ($p < .001$) and the majority of subjects met the criteria for persistency of the corrective response (i.e., 95.3 and 76.5% of subjects, respectively). This finding was corroborated by assessments of global improvement by both the blinded investigators and the subjects themselves. At the 9- and 12-month post-OCR visits, the aesthetic appearance of Dermicol-P35-treated nasolabial folds

was rated by the blinded investigators as better or much better versus baseline in 97.3 and 86.9% of subjects, respectively, whereas 88.3 and 84.8%, respectively, of subjects rated their appearances as better or much better at these visits.

Tolerability findings in the second 6-month period indicated that the incidence of local skin reactions with Dermicol-P35 injections was low, with mild erythema and nodules occurring in only a small number of subjects ($n = 3$) and none experiencing any unexpected, severe, or serious adverse events, including hypersensitivity reactions. The ELISA immunoglobulin determinations indicated that multiple injections of Dermicol-P35 did not result in clinically significant development of antibodies against porcine Type I collagen. None of the subjects who were positive for antibodies, either in the enrollment phase or who became positive during the study follow-up, exhibited any unusual adverse events or other symptoms that were unusual in character. The reason for this is uncertain, but prior dietary exposure to porcine collagen may be a factor; this is a consideration for further studies of Dermicol-P35.

In comparison with HA, local adverse events appearing before the 6-month post-OCR visit and persisting at that visit were noted in 3.4% of subjects with Dermicol-P35 and 0.7% with HA. Local adverse events with onset after the 6-month post-OCR visit were also uncommon, occurring in 1.4% with Dermicol-P35 and 0.7% with HA. However, in subjects who elected to receive a recorrection injection of one of the two fillers at the 12-month post-OCR visit, local adverse events such as injection site swelling, erythema, and bruising were more common with Dermicol-P35 than with HA, occurring in 19 and 4.6% of subjects, respectively. Among these subjects ($n = 123$), no differences in the mean injections volumes of Dermicol-P35 and HA given on the two sides of the face were noted.

In conclusion, the data presented in this report indicate that the correction of nasolabial folds

achieved with Dermicol-P35 injection is maintained for up to 1 year after achieving an OCR. An important finding was that persistency of the corrective response was similar whether or not subjects received a touch-up injection. This may translate into greater subject tolerability and satisfaction without the requirement for repeated office visits to ensure a long-lasting OCR. The incidence of adverse events with Dermicol-P35 is very low; in most cases, adverse events take the form of mild and transient injection site reactions that do not lead to discontinuation of treatment. No evidence of immediate or delayed positive hypersensitivity reactions was noted in this study population, either during the pretreatment skin test phase or during the treatment phase of the study. Overall, Dermicol-P35 appears to be an efficacious and safe dermal filler for correction of moderate to deep nasolabial folds and has a long-lasting effect.

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