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Five-Year Safety and Efficacy of a Novel Polymethylmethacrylate Aesthetic Soft Tissue Filler for the Correction of Nasolabial Folds

Steven R. Cohen, MD,* Carl F. Berner, MD,† Mariano Busso, MD,‡ Paul Clopton, MS,§ Douglas Hamilton, MD,‖ James J. Romano, MD,¶ Peter P. Rullan, MD,** Millard P. Thaler, MD,†† Zeena Ubogy, MD,†† and Thomas R. Vecchione, MD‡‡

BACKGROUND A novel soft tissue filler composed of polymethylmethacrylate (PMMA) microspheres suspended in a collagen gel matrix containing 0.3% lidocaine (ArteFill, Artes Medical, Inc.) was recently approved by the Food and Drug Administration for the correction of nasolabial folds. A randomized, multicenter, controlled pivotal trial performed in the United States established the safety and efficacy of this medical device throughout a 12-month study period.

OBJECTIVE The objective was to substantiate the long-term 5-year safety and efficacy of this novel soft tissue PMMA filler.

METHODS AND MATERIALS Attempts were made to contact all subjects treated with the PMMA filler that were enrolled in the original pivotal study. Safety was assessed by standard adverse event reporting methods. Efficacy was determined using a validated six-point facial fold assessment photometric grading scale using blinded observers' assessment of standardized photographs.

RESULTS Subjects ($n = 119$) demonstrated significant improvement in nasolabial folds comparing baseline (before any treatment) to 5 years after their last treatment ($p < .001$). Notably, subjects also demonstrated continued improvement between 6 months after their last treatment and Year 5 ($p = .002$). No serious unanticipated device-related adverse events were reported.

CONCLUSION This PMMA filler is the first soft tissue filler to demonstrate continued improvement and persistence of correction over a 5-year period posttreatment.

The study was sponsored by Artes Medical.

Biologic dermal fillers reliably and safely augment facial wrinkles and folds, but they necessitate retreatment after they have been resorbed, generally within a 12-month period.[1] A novel permanent implant (ArteFill, Artes Medical, Inc., San Diego, CA) was developed to address this shortcoming. This novel soft tissue filler is composed of polymethylmethacrylate (PMMA) microspheres suspended in a collagen gel matrix containing 0.3% lidocaine. It is a third-generation PMMA-based filler product that contains an optimized collagen matrix with microspheres, which have enhanced uniformity and consistency compared to the second-generation PMMA product Artecoll.

This novel filler has been approved by the Food and Drug Administration (FDA) for the correction of nasolabial folds, based on results of a U.S. pivotal trial with the second-generation predecessor product, Artecoll. Since the initiation of the pivotal trial, substantial improvements in the second-generation PMMA product have been made, resulting in a newer generation of product (Figure 1). Refinements in manufacturing have increased the uniformity in

*FACESplus Aesthetic Facility, La Jolla, California; UCSD Medical Center, San Diego, California; †Retired; ‡Private Practice, Miami, Florida; §PaxMed International, San Diego, California; ‖Department of Dermatology, UCLA School of Medicine, Los Angeles, California; ¶Private Practice, San Francisco, California; **Dermatology Institute, Chula Vista, California; ††Papillon Cosmetic Dermatology, PC, Mesa, Arizona; ‡‡Plastic Surgery Medical Clinic, San Diego, California*

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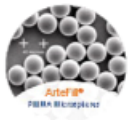
	3rd Generation	2nd Generation
Distributor/ Manufacturer	**Artes Medical** Dedicated U.S. GMP manufacturing facility	**Rofil Medical (Netherlands)** European Medical Contract Manufacturing
Composition	20% PMMA suspended in 80% bovine collagen gel, 0.3% lidocaine	
PMMA Characteristics	Round & smooth surface Uniform size  **Removal of PMMA microspheres < 20 microns**	Round & smooth surface Non-uniform size 
Regulatory Status	FDA approved (October 2006)	Not FDA approved, not in U.S. clinical trials

Figure 1. Third-generation PMMA enhancements compared to second-generation.

the size of the microspheres. The proportion of particles which are less than 20 μm in diameter has been reduced to <1% and, in fact, are typically nondetectable in the finished product. These manufacturing changes, made in cooperation with the FDA, are believed to have further improved the tolerability of the implant because smaller particle size elements (e.g., <20 μm) are thought to promote phagocytosis, which may be a possible cause of cutaneous adverse events associated with filler materials.[2] Furthermore, the product is now manufactured in the United States using bovine collagen sourced from a restricted closed herd in the United States. The data presented herein refer to subjects from the original pivotal study (treated with the second-generation PMMA product) that were followed for a 5-year period of time. For simplicity, in the balance of this publication the product will be referred to as the PMMA filler, unless otherwise noted.

The pivotal trial was a randomized, double-blind controlled study involving 251 men and women, comparing this novel PMMA filler ($n = 128$) to a collagen control filler (Zyderm 2 or Zyplast [Inamed Aesthetics, Santa Barbara, CA], $n = 123$). Efficacy was determined using a six-point facial fold assessment (FFA) photometric validated grading scale.[3] This scale was used for blinded observers' assessments of standardized photographs in which the mean score of three independent graders was designated as the primary efficacy measure. This same scale was also used for investigator nasolabial fold grading (secondary efficacy measure).

In this pivotal study, the subjects receiving the PMMA filler exhibited significant nasolabial fold correction, superior to that of the collagen control at both 3 and 6 months postinjection ($p < .001$, for both primary and secondary efficacy measures). The superiority of the PMMA filler was observed despite the fact that a substantially smaller quantity of material was utilized than in collagen control cases (0.82 mL/fold vs. 1.46 mL/fold; $p < .001$). The effect of the collagen control treatment virtually disappeared by 6 months. Nonetheless, in comparison to baseline (before any treatment) the PMMA filler demonstrated significant nasolabial fold correction at 12 months ($p < .001$, for both primary and secondary measures).

To further substantiate the durability of this novel implant material, a long-term 5-year follow-up safety and efficacy study of subjects enrolled in the original pivotal study was performed.

Materials and Methods

Study Design

This is a long-term follow-up study of PMMA filler–treated subjects that participated in the original multicenter pivotal study. The same method used in the pivotal trial to substantiate the safety and efficacy of the product was applied to evaluate the product in subjects 5 years after their last treatment. The primary objective of the study was to determine efficacy for nasolabial folds based on blinded observers' FFA evaluations and safety using unanticipated event assessments. Secondary objectives were to evaluate efficacy by means of investigators' FFA evaluations, investigators' success ratings, patients' satisfaction ratings, and blinded observers' FFA for 5 years versus 6 months.

Patients and Follow-up Visits

All of the investigators (eight U.S. sites) involved in the original pivotal trial participated in the study. Study candidates included those subjects initially randomized to be treated with the PMMA filler ($n = 128$) plus the subjects in the collagen control group who had elected to cross over to the PMMA filler therapy at the conclusion of their 6-month collagen control treatment period ($n = 106$), for a total of 234 potential subjects. On or about the 5-year anniversary date from their last treatment, investigators contacted their PMMA filler subject(s) by telephone and/or certified letter and encouraged them to be enrolled in the trial.

All subjects were asked to participate in a single follow-up visit. At this visit the following tasks were performed; investigator clinical grading (FFA scale and clinical success), facial photographs (for blinded observer assessments), subjects' ratings of satisfaction, recorded adverse events, and the documentation of any additional facial aesthetic procedures that had occurred since the last PMMA filler treatment. Investigators judged whether the additional aesthetic treatments had a possible or probable impact on effect of the novel PMMA filler's correction. Nasolabial folds were considered possibly affected by an intervening facial aesthetic treatment if it occurred in the same region as the PMMA filler injection or if it were applied to the entire face. Nasolabial folds were considered to be probably affected by an intervening facial aesthetic treatment if it affected the area of correction achieved by the PMMA filler injections. For all participating sites, the 5-year follow-up study protocol and associated consent were reviewed and approved by a central institutional review board. Informed consent was obtained from all subjects and the study protocol conformed to the guidelines of the 1975 Declaration of Helsinki.

Nasolabial Fold Correction

Assessment of nasolabial folds was based on grading using the FFA grading scale. The FFA scale is a validated six-point, photometric index of the severity of nasolabial folds, ranging from 0 (none) to 5 (severe).[3] The primary efficacy variable for this study was based on the review of standardized subject facial photographs using this measure. Photographs of subjects were taken using the same photography system and processed by the same film laboratory as in the pivotal trial. To minimize grader biases, photos from the pivotal study 6-month time point as well as the 5-year time point for each enrolled subject were evaluated. The photographs were provided to three independent blinded observers (board-certified dermatologist or plastic surgeon) in random order, to be evaluated during the same session using the FFA scale. The observers were blinded with respect to time point and treatment of the subjects in the photographs. The subject's facial fold severity score was then determined based on the mean of their three independent evaluations using the FFA scale. In the case of bilateral treatments, the ratings for the two sides were averaged. The change from pretreatment to 6 months was computed using the original set of 6-month photograph ratings. Change from 6 months to 5 years was computed using the new set of 6-month photograph ratings. Finally, the cumulative improvement over the 5-year interval

was computed as the sum of these two changes. This technique avoided any potential bias due to rater drift in the analyses. This FFA grading scale was also used by the investigator to clinically grade each subject's nasolabial folds as a secondary measure of correction.

Ratings of Success and Satisfaction

In addition to assessing the degree of nasolabial fold correction using the FFA scale, other methods were used to evaluate cosmetic correction. A 5-point ordinal scale was used by the investigators to rate the success of treatment with the novel PMMA filler, ranging from "not at all successful" to "completely successful." Likewise, subjects rated their satisfaction with the PMMA filler according to a similar 5-point scale ranging from "very dissatisfied" to "very satisfied" (Table 1).

TABLE 1. Scales for Rating Efficacy of Implant

Investigator success scale	*Patient satisfaction scale*
• Completely successful	• Very satisfied
• Very successful	• Satisfied
• Moderately successful	• Somewhat satisfied
• Somewhat successful	• Dissatisfied
• Not at all successful	• Very dissatisfied

Statistics

Efficacy data were analyzed for normal distribution by the Kolmogorov-Smirnov test. Paired *t*-tests were employed unless distributions were found to deviate significantly from normality, in which case the Wilcoxon matched-pairs signed-ranks test was used. Other statistical tests are identified individually under Results.

Results

Patient Demographics and Response Rates

From the original pivotal study subject pool, 145 subjects (145/234 or 62%) responded to queries to participate in the study. Three subjects, however, were excluded from the efficacy analysis because their long-term follow-up period was less than 4.5 years. Of the remaining 142 subjects, 15 were males and 127 females (mean age, 52.4 years), 82 subjects were from the original ArteFill group (64.1%) and 60 subjects in the crossover group (56.6%), with a mean follow-up period of 5.36 years (range, 4.53–6.32 years) after their final treatment with the PMMA filler. Comparison of the original PMMA filler and crossover groups revealed no significant difference in terms of follow-up rates (chi-square, $p = .245$).

During the pivotal trial, this PMMA filler had been used to treat a variety of other anatomic sites (e.g., glabellar folds, mouth corners, etc.). In this follow-up report, however, the focus was limited to the FDA-approved indication only, the treatment of nasolabial folds. In this group of 5-year follow-up subjects, 124 had nasolabial fold correction; most treatments were bilateral, and one was unilateral. These subjects provided the basis for the efficacy evaluation.

Blinded Observer Facial Fold Assessment Ratings of Efficacy at Five Years Compared to Baseline

The PMMA filler maintained significant cosmetic correction in nasolabial folds at 5 years after their last treatment compared to baseline ($n = 119$). Five of the 124 nasolabial fold subjects were excluded from this analysis because they did not have either baseline or 5-year photographs. Figure 2 shows an improvement of 1.01 points in blinded observer FFA for this time period ($p < .001$, paired *t*-test). Given that the FFA is a 0 to 5 scale, a change of 1 point represents a substantial improvement in cosmetic effect. Actual results are illustrated in photographs of a male (Figure 3) and female patient (Figure 4). Before treatment (baseline), the male patient exhibited a pronounced nasolabial fold, which was dramatically improved by 6 months and continued to improve at 12 months and 5 years. The inter-rater

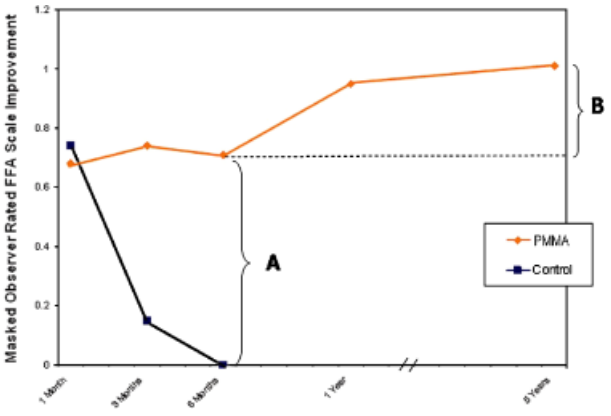


Figure 2. (A) PMMA filler shows marked improvement over "collagen" at 6 months ($p < .001$). (B) Continuous improvement of PMMA filler ratings between 6 months (0.71) and 5 years (1.01; $p = .002$).

agreement for nasolabial folds was found to be high (intraclass correlation coefficient, 0.845).

Secondary Measures of Efficacy at Five Years Compared to Baseline

Secondary efficacy measures also revealed favorable findings for the durability of the PMMA filler. Investigator FFA scores significantly improved at 5 years compared to baseline, by 1.67 points ($n = 122$, $p < .001$, paired t-test). These results were consistent with the 5-year success rated by investigators (90% described the cosmetic effect as "completely successful" or "very successful," $n = 123$) and satisfaction by the subjects (90% described themselves as "very satisfied" or "satisfied" with the cosmetic outcome, $n = 123$; Figures 5 and 6).

Efficacy at Five Years Compared to Six Months

The PMMA filler not only maintained nasolabial fold augmentation between baseline and 5 years; it also improved blinded observer FFA ratings by 0.20 points for the time period between 6 months and 5 years (Figure 2, Item B), indicating that the cosmetic effect improved gradually but significantly ($p = .002$, $n = 113$, paired t-test). This is evident in the patient photographs, particularly when comparing the 1- and 5-year time points (Figures 3 and 4). In a paired analysis of the group of crossover subjects ($n = 45$), the PMMA filler–induced improvement assessed 5 years after treatment with this novel filler (0.91 points) was significantly greater than the collagen-induced improvement measured at 6 months (0.01 points) as rated by blinded observer FFA ($p < .001$, paired t-test).

Potential Biases

The authors recognize that bias could potentially arise from a number of sources, including additional cosmetic procedures since the last PMMA filler injection. A total of 44 cosmetic procedures were documented to have occurred in this population. Table 2 details the cosmetic procedures performed and the investigators judgment if it was viewed as having a "possible" or "probable" impact on the nasolabial fold assessments. When this group was compared to the group that did not receive intervening treatments, no difference was discovered in change in blinded observer FFA rating at 5 years relative to 6 months ($p = .516$, t-test). In a separate

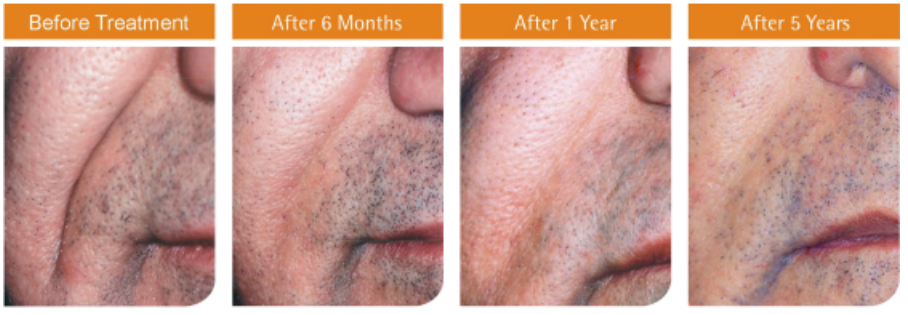


Figure 3. Male patient, before and after photos—baseline to Year 5. This subject had no additional cosmetic procedures during the 5-year follow-up period.[5]

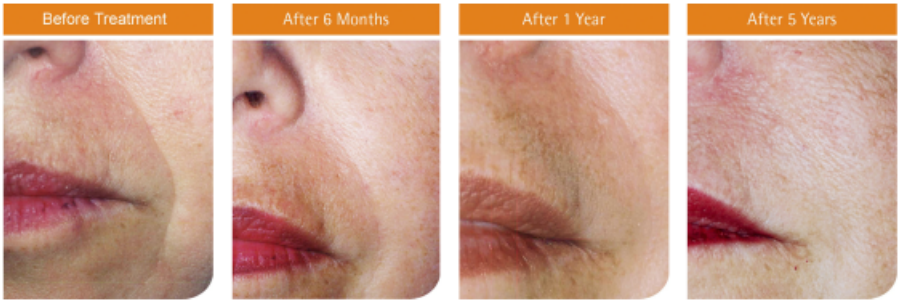


Figure 4. Female patient, before and after photos—baseline to Year 5, This subject had no additional cosmetic procedures during the 5-year follow-up period.

analysis, subjects were stratified into three subgroups, according to whether their impact from intervening treatments was possible, probable, or none. In no case did these subgroups differ significantly from each other (one-way analysis of variance). Furthermore, the improvement in blinded observer FFA scores from baseline to 5 years was still evident in subjects who had no impact from additional treatments ($p < .001$, paired t-test).

Efficacy data were also scrutinized for potential bias due to attrition. After stratification of subjects into groups with and without follow-up, no significant differences were found in terms of age ($p = .963$, t-test) or sex ($p = .170$, chi-square test). It is, however, important to note that the study subjects did achieve greater improvement at 6 months in contrast to the balance of the original PMMA filler subjects who did not participate in this study, potentially suggesting some selection bias ($p = .009$, t-test). When the participating study subjects were divided into two subgroups based on their 6-month findings, low responders (defined as those under 0.8 FFA points improvement) and high responders (defined as those with greater than 0.8 FFA points improvement) showed significant improvements in efficacy at 5 years compared to 6 months outcomes ($p < .044$ and $p < .024$, respectively, paired t-tests).

Safety Review

In this study, 145 subjects were evaluated for safety, 28 total adverse events were experienced by 21 subjects, and the 20 treatment-related events were distributed among 15 subjects (Table 3). Mild

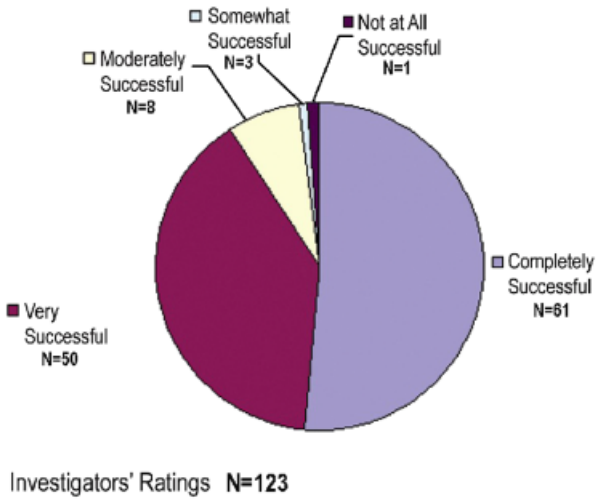


Figure 5. Investigators' success rating.

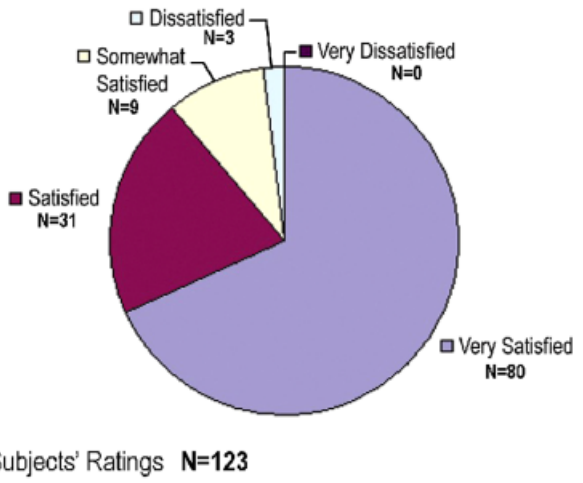


Figure 6. Subjects' satisfaction rating.

TABLE 2. Investigators' Judgment of Possible or Probable Impact on Nasolabial Fold Assessment of Various Cosmetic Procedures in Subjects Receiving Additional Cosmetic Procedures

	Nasolabial folds	
Treatment	*Possible impact*	*Probable impact*
Face-lift	6	5
Fillers		
Temporary	2	2
Semipermanent	0	3
Permanent	0	3
Microdermabrasion	4	0
Peeling		
chemical	10	1
laser	2	0
Noninvasive radiofrequency technology	0	0
Botulinum toxin A	0	0
Other	4	2

treatment-related events occurred in 8.3% of the total population; moderate events were reported in 1.4%, and severe related events in 0.7%. The most common treatment-related adverse event was lumpiness, of which 80% were deemed mild.

The investigators reported adverse events using standard categories. Using this standard reporting mechanism, in this study "granuloma or enlargement of the implant" was reported in two subjects. One subject presented with an inflammatory, lumpy area in the lip and in the melolabial fold 6 months after the last PMMA filler injection. The event was classified as being of moderate intensity by the investigator. The areas were treated with intralesional steroids followed by intraoral excision with apparently a satisfactory outcome; however, the subject did not consent to additional follow-up. The second subject presented with a lumpy, inflamed "nodule" in each of the nasolabial folds approximately 5 years after implantation. The event was classified as being of severe intensity by the investigator. The affected areas partially responded with intralesional steroid therapy. In neither case was histology available to substantiate a final diagnosis.

TABLE 3. Treatment-Related Adverse Events (AEs) 5 Years Postimplantation

	Related			*Not related*			
	Mild	*Moderate*	*Severe*	*Mild*	*Moderate*	*Severe*	*Unknown*
Lumpiness	8	1	1				
Increased sensitivity	2						
Persistent swelling or redness	1		1				
Sensitization reaction	1	1					
Granuloma or enlargement of implant*		1	1				
Other							
Mild prominence of implant	1						
Occasional pain when scrubbing face	1						
Basal cell carcinoma					2		
Scaly area mid right upper lip				1			
Systemic							
Breast cancer						3	
Death due to cardiac failure						1	
Alzheimer's							1
Totals	14	3	3	1	2	4	1
Number of subjects with AEs	12	2	1	1† (0)	2	4‡ (3)	1
Percent of subjects with AEs ($n=145$)	8.3	1.4	0.7 (0)	0.7† (0)	1.4 (2.1)	2.8‡ (2.1)	0.7

*Clinical enlargement of implant, but no histologic confirmation of foreign body reaction.
†Subject also had a related AE.
‡One subject also had a related AE.

Discussion

This novel PMMA filler is the only FDA-approved permanent soft tissue filler for the treatment of nasolabial folds.[5] It is composed of PMMA microspheres suspended in a collagen gel matrix containing 0.3% lidocaine. The proposed mechanism of action is based on microspheres stimulating the patient's fibroblasts to deposit collagen on and between the microspheres, eventually resulting in the replacement of the bovine collagen with the patient's own collagen. This yields a volume replacement matrix of the subjects' own collagen interspersed with small microspheres of PMMA. Given the more permanent nature of this implant material, subjects usually are fully corrected gradually over two or three treatment sessions spanning a several-month period to avoid overcorrection. Placement of this material can be achieved using a variety of injection techniques, although many prefer a tunneling method. In all cases, the material should be injected in the deep dermis to avoid superficial placement, which may lead to irregular skin surface changes. Given the importance of technique, the sponsor offers product training as an integral part of becoming an injector of this new filler material.

This 5-year follow-up study evaluated 145 of a potential 234 subjects treated with this PMMA filler that participated in the original pivotal study. Although it would have been ideal to evaluate all subjects, a retention rate of 62% (145/234) was impressive especially considering that the original trial had been completed years earlier and there were no plans to perform such a long-term follow-up study.

The study demonstrated significant improvement comparing baseline (before any treatment) to 5 years after treatment ($p < .001$) using both the blinded evaluator assessment of photographs and the investigator live grading of fold severity. The mean clinical improvement in investigator ratings at 5 years was 1.67 (on the 0 [none] to 5 [severe] FFA scale), in contrast to a 1.01 difference from the photo evaluations. This type of difference between live-grading assessment and photographic-based grading has been seen with other soft tissue filler studies. Notably, subjects also demonstrated continued improvement between 6 months after their last treatment and Year 5 ($p = .002$).

Both investigators and subjects were also asked to assess their overall impression of the treatment at the 5-years time point (Figure 2). Consistent with the quantitative nasolabial fold assessments, both the investigators and the subjects demonstrated very favorable qualitative impressions of the treatment. The investigators rated 90% of subjects within the top two responses (very successful or completely successful; Figure 5). Ninety percent (90%) of subjects rated their satisfaction within the top two responses (very satisfied or satisfied; Figure 6).

No serious unanticipated adverse events were reported, and the safety profile of the product is consistent with that of other soft tissue products (instructions for use package inserts for FDA-approved soft tissue fillers: Restylane, Juvéderm Ultra, Juvéderm Ultra Plus, and Radiesse, August 2007). Of note, such a comparison does not even take into account the potential safety impact of multiple treatments required by other soft tissue fillers to achieve a similar 5-year correction as demonstrated in this study. Nonetheless, two potential granulomatous reactions (no confirmatory histology) were identified in this study. Both cases improved with therapy. Granuloma formation is an adverse event that rarely occurs, but has been frequently attributed to the use of permanent fillers. It is, however, a phenomenon that has been documented to occur with other soft tissue fillers as well as demonstrated by the single-control collagen implant granuloma that occurred during the initial 6 months of the pivotal study.[1] In general, granulomas are most commonly treated with intralesional steroid therapy with good results as detailed in a recent publication by Gelfer and colleagues;[4] however, on rare occasion more aggressive therapy such as excision may be required.

Summary

The current follow-up study showed that the PMMA filler continued to maintain significant cosmetic correction for 5 years postinjection using both blinded observer photometric and clinical investigator methods of assessment. These results are unparalleled, because this is the only FDA-approved filler material with documented durability over a 5-year period. The product was well tolerated, and its safety profile was consistent with other soft tissue filler agents. Given its durability, the PMMA filler may also offer additional safety benefits in that few repeat treatments are needed. Two possible granulomatous reactions were noted in this study. These events appeared manageable and consistent with the incidence noted with other filler products, including the collagen control soft tissue filler. Improvements made to this third-generation PMMA product hold additional promise to further improve the safety profile defined by this study.

In summary, this novel PMMA filler offers an unprecedented durability of nasolabial fold correction not previously available with other filler agents. Safety concerns are consistent with other products in the category. The long-term nature of the correction, however, should be taken into consideration when discussing treatment alternatives with patients.

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Address correspondence and reprint requests to: Paul Clopton, MS, 5224 Lodi Street, San Diego, CA 92117, or e-mail: pclopton@ucsd.edu