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Cosmetic

Artecoll: A Long-Lasting Injectable Wrinkle Filler Material: Report of a Controlled, Randomized, Multicenter Clinical Trial of 251 Subjects

Foot

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Artecoll, an injectable wrinkle filler composed of polymethylmethacrylate microspheres and bovine collagen, is widely available outside the United States. For domestic availability, a multicenter Investigational Device Exemption study was required by the U.S. Food and Drug Administration. This study consisted of 251 subjects at eight centers who received injections of Artecoll or the currently approved collagen dermal filler (control) in 1334 wrinkles of the glabella, nasolabial fold, radial upper lip lines, and corner-of-the-mouth lines. The treatments were randomized, and follow-up safety, efficacy, investigator success rating, and subject satisfaction rating data were collected at 1, 3, and 6 months. The safety data, measured as adverse events and immunoglobulin G serum levels, were low and similar for both groups. The efficacy data, measured by masked observers using a photographic facial fold assessment scale, demonstrated a combined significant improvement with Artecoll compared with collagen at 6 months ($p < 0.001$). At 6 months, the investigator success ratings and the subject satisfaction ratings for each of the four injections sites were superior for Artecoll ($p < 0.001$). In the Artecoll group, 12-month follow-up was obtained for 111 subjects (86.7 percent) and showed persistence of significant augmentation. Artecoll had fewer adverse events reported throughout the 12-month safety study period than the control group did in 6 months, although the difference was not statistically significant. (*Plast. Reconstr. Surg.* 114: 964, 2004.)

Over the past several decades numerous attempts have been made to develop safe biological or synthetic materials to permanently fill wrinkles and scars.[1,2] Virtually all biological materials, however, are resorbed within 1 year, and previously used synthetic materials have been associated with side effects such as migration, granuloma formation, and late allergic reactions.[3] To overcome the problems with artificial skin fillers, Artecoll was developed in Germany to be a permanent, injectable implant.[4]

Artecoll consists of homogenous polymethylmethacrylate microspheres evenly suspended in a solution of partly denatured 3.5% collagen, which serves as a vehicle for deep dermal implantation. All microspheres have a defined size of 32 to 40 μm in diameter, are completely polymerized, and have a smooth, round surface. Because of the smooth surface of the microspheres, each microsphere becomes encapsulated by the patient's own collagen fibers, thereby preventing dislocation.

Artecoll consists of 20 volume% polymethylmethacrylate microspheres evenly suspended in 80 volume% U.S. bovine collagen per syringe. After deep dermal injection of Artecoll, the collagen carrier is degraded by the body within 1 to 3 months and completely replaced by the body's own collagen at a similar rate, ensuring a steady augmentation result. Because the microspheres are nonbiodegradable and too large to migrate or to be phagocytosed by macrophages, the tissue augmentation is expected to be permanent, consisting of 80 volume% autologous connective tissue.

Artecoll is approved and available in many countries in the world. Since its introduction in 1994, an estimated 200,000 patients have been

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treated with a reported complication rate of 0.01 percent.[4] On February 28, 2003, the U.S. Food and Drug Administration's General and Plastic Surgery Devices Advisory Panel recommended that Artecoll be approved, with conditions, for marketing in the United States. Artecoll is expected to become the first long-lasting injectable wrinkle filler to gain Food and Drug Administration approval since collagen was introduced in 1981. After approval, Artecoll will be marketed as "Artefill" in the United States, Canada, and Mexico.

MATERIALS AND METHODS

As an implant material, Artecoll is a class III device requiring Food and Drug Administration approval via the premarket approval route. This clinical trial was conducted in accordance with the Investigational Device Exemption regulations to obtain safety and efficacy data for inclusion in the premarket approval application to the Food and Drug Administration. The Investigational Device Exemption application for the Artecoll clinical trial received final approval by the Food and Drug Administration in August of 1999, and the trial was completed in September of 2001. The purpose of this study was to compare the safety and efficacy of Artecoll injections in the glabellar frown lines, nasolabial folds, radial upper lip lines, and corner-of-the-mouth (marionette) lines to the safety and efficacy of collagen (Zyderm II or Zyplast; Inamed Corporation, Santa Barbara, Calif.).

The primary objectives of the study were to compare the cosmetic correction provided by Artecoll at the end of 6 months to that of Zyderm/Zyplast over the same time period and to explore the safety of Artecoll at 6 and 12 months as an injectable implant for correction of contour deformities of the dermis of the face. The secondary objectives of the study were to characterize the physician's assessment of success with respect to how closely the treatment met the physician's expectations for correction and to characterize the subject's assessment of satisfaction with respect to the subject's personal expectations. Though physicians were not masked as to the identity of the treatment, subjects were not told which treatment they had received until after they had completed the 6-month evaluation.

The study was performed at eight centers (four plastic surgery centers and four dermatology centers) with institutional review board approval and informed consent from all subjects. The study was controlled and randomized, with potential subjects agreeing to be assigned to either the Artecoll or the control group. The subjects and evaluators were masked and unaware of which injection material was received (double-blinded). To be included in the study, a subject had to fulfill the following inclusion criteria: age 18 years or older, realistic expectation of benefits, willing and able to give informed consent, presenting for treatment in at least one of the four injection sites, and willing and able to comply with follow-up requirements. Exclusion criteria included pregnancy, treatment with botulinum toxin type A or collagen or any other wrinkle augmentation material within 6 months of the trial, anticipation of cosmetic surgery before completing the study, chemotherapy or corticosteroid treatment within 3 months of beginning the study, ultraviolet light therapy during the course of the study, anticoagulant therapy, autoimmune disorder or history thereof, atrophic skin disease, and extremely thin and/or flaccid skin. Additional exclusion criteria included known susceptibility to keloids, known lidocaine hypersensitivity, history of dietary beef allergy or undergoing desensitization, known allergy to collagen, severe allergies (history of anaphylaxis), cellulitis or infection at prior implant site, serum immunoglobulin G levels outside the normal range, and positive skin test to collagen or two equivocal tests.

Treatment and follow-up consisted of first screening the interested candidates and enrolling and randomizing them if they met the study criteria. A blood sample was then drawn for serum immunoglobulin G testing, followed by administration of the collagen skin test appropriate to the randomization assignment. If the subject met all criteria, treatment was initiated. Subjects were permitted to return for as many as two re-treatments over a maximum period of 1 month, with no limits on the volume of Artecoll or collagen injected. Follow-up appointments were then scheduled at 1, 3, 6, and 12 months, based on the final treatment date. Safety was assessed by recording all adverse events and by measuring serum immunoglobulin G levels at the 1-month visit, as well as at subsequent visits if it was elevated at the previous visit. Efficacy was measured by three masked observers using a Facial Fold Assessment Scale to rate wrinkles on the subject's photographs. Investigator assessment of suc-

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cess was recorded at 1, 3, and 6 months using the following scale: 1 = completely successful, 2 = very successful, 3 = moderately successful, 4 = somewhat successful, and 5 = not at all successful. Subject assessment of satisfaction was recorded at 1-, 3-, and 6-month intervals using the following scale: 1 = very satisfied, 2 = satisfied, 3 = somewhat satisfied, 4 = dissatisfied, and 5 = very dissatisfied.

Facial Fold Assessment Scale

The Facial Fold Assessment Scale used to grade wrinkles and furrows is a photographically based classification of mimetic wrinkles. It had been previously validated by "live" ratings, photographic ratings, and profilometric measurement of wrinkle depth.[5] The scale is an easy, consistent, and reliable tool for the assessment of wrinkle depth. Wrinkle depth is graded from 0 (least wrinkle depth) to 5 (most wrinkle depth). The six-point scale was used in the present study by three masked observers to objectively rate wrinkle severity before treatment and at 1, 3, and 6 months after treatment with Artecoll or collagen. Each rater compared standardized photographs taken at each study interval to reference photographs to assign a grade of 0 to 5 to each of the study wrinkles.[5] Rating was conducted in a randomized manner and raters were not informed of the treatment group or evaluation period (pretreatment or follow-up) for any photograph. Each of the three raters independently evaluated each photograph. Efficacy-dependent variables were expressed as the improvement of Facial Fold Assessment Scale ratings from baseline, averaged across the two facial sides in the case of bilateral treatment. A single overall improvement score was also computed for each subject and was also calculated by averaging the improvement across facial areas.

Injection Technique

AQ: 1 Before injection, topical EMLA cream (lidocaine 2.5% and prilocaine 2.5%; AstraZeneca, Wilmington, Del.) and, for the upper lip, local anesthesia were employed when indicated by the investigator. The dermal layer utilized for F1 Artecoll implantation is shown in Figure 1. The method of implanting Artecoll is more technique-sensitive than that for injecting collagen. The "tunneling technique" (i.e., moving the needle in a linear fashion back and forth just beneath the wrinkle) was utilized. Since the viscosity of Artecoll is three times higher than that of Zyplast, a higher constant pressure was applied throughout the injection procedure. A 27-gauge needle half an inch in length was utilized. The thickness of the needle and skin was used to help determine the depth of injection. The thickness of facial skin varies from 0.2 mm (eyelids) to 0.4 mm (nasolabial folds) to 0.8 mm (glabellar frown lines).[6] The thickness of the skin in a deep crease is diminished to about one quarter of its normal thickness. At the start of the procedure, the needle was tested by squeezing a small quantity of Artecoll out of the tip. Artecoll was then implanted deeply intradermally (e.g., into the reticular dermis just above the junction between the dermis and subcutaneous fat). If Artecoll was injected into the papillary dermis, causing a blanching effect, the injection was stopped and the needle was placed at a deeper level. At the end of implantation, the implant was evenly massaged with the fingernail and slight pressure was applied to any detected lump. Subjects were advised that there would be some swelling for the first 12 to 24 hours and that areas of light pink coloration along the injection sites might be present for 2 to 5 days. They were also advised to minimize mimetic activity for 1 to 2 days.

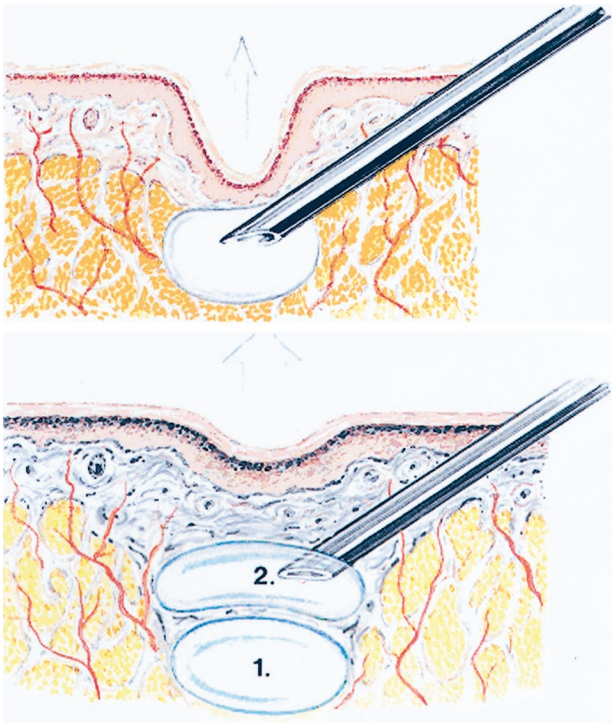

FIG. 1. The dermal plane of Artecoll implantation. (*Above*) The dermal thickness is diminished under a wrinkle. (*Below*) Artecoll is injected into the deep dermis to "fill" the wrinkle.

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Statistical Analysis

Adverse events were described by counts of events and counts of subjects experiencing adverse events. Counts of elevated immunoglobulin G levels were also provided. Tests for treatment group differences in number of treatments and quantity of product were made using independent *t* tests. Nonparametric tests were used for ratings variables. Groups were compared with Mann-Whitney *U* tests for improvements in observer-rated and investigator-rated Facial Fold Assessment Scale scores and for investigator success ratings and subject satisfaction ratings. Within-group tests for improvements in the Artecoll treatment group were made using Wilcoxon matched-pairs signed rank data to accommodate the 12-month observations. Rater reliability for observer Facial Fold Assessment Scale ratings was evaluated using intraclass correlation.

RESULTS

There were 251 subjects entered into the study. One hundred twenty-eight subjects received Artecoll (11 men and 117 women), while 123 subjects (11 men and 112 women) T1 received the collagen control (Table I). The mean age was 53.2 years (range, 28 to 82 years) for the Artecoll subjects and 51.2 years (range, 29 to 78 years) for the control subjects (Table I). Of these 251 subjects, 247 had at least one follow-up visit (98.4 percent) and 233 (92.8 percent) had a 6-month follow-up visit. In the Artecoll group, 12-month follow-up was obtained for 111 subjects (86.7 percent). Since Artecoll treatment was offered to all subjects in the collagen group at the 6-month follow-up, no 12-month follow-up could be obtained for the collagen group. Of the 116 collagen subjects who completed the 6-month follow-up evaluation, 106 (91 percent) were treated with Artecoll.

TABLE I
Subject Data

	Artecoll	Control	Total
Sex			
Male	11	11	22
Female	117	112	229
Total	128	123	251
Age			
Mean	53.2	51.2	52.2
Range	28–82	29–78	28–82
SD	10.3	11.3	10.8

Artecoll was injected into the glabellar frowns of 81 subjects, the nasolabial folds of 108 subjects, the upper lip lines of 69 subjects, and the mouth corners of 86 subjects; collagen was injected into the glabellar frowns of 86 subjects, the nasolabial folds of 104 subjects, the upper lip lines of 59 subjects, and the mouth corners of 87 subjects (Table II). In T2 total, 1334 wrinkles were injected: 320 glabellar frowns, 420 nasolabial folds, 253 lip lines, and 341 mouth corners were treated in the 251 subjects (Table II).

The number of treatments to each of the facial areas (i.e., glabellar frowns, nasolabial folds, radial upper lip lines, and corner-of-the-mouth lines) was not significantly different ($p = 0.316$ to 0.974) between the Artecoll and control groups (Fig. 2). Almost twice as much F2 collagen as Artecoll was used at each of the four injection sites (Fig. 3), a statistically signif- F3 icant difference ($p < 0.001$ in each case).

Results of Primary Objectives

Although adverse reactions were uncommon in both groups, more redness and swelling and more lumpiness at the injection site were noted in the collagen group. There were a total AQ: 2 of 27 adverse events in the Artecoll group compared with 38 in the collagen control group. These numbers were not statistically significant. One subject underwent "incidental" removal and/or drainage in the Artecoll group related to excision of an actinic keratosis in the vicinity of the previous Artecoll injection, and two subjects in the collagen group required removal and/or drainage for abscesses (Table T3 III).

Serum immunoglobulin G levels were elevated in one subject undergoing Artecoll implantation after 1 month. Levels were elevated in one subject at 1, 3, and 6 months after collagen injection (Table IV). T4

TABLE II
Treatment Data

	Artecoll	Control	Total
No. of subjects treated			
Glabella	81	86	167
Nasolabial fold	108	104	212
Lip lines	69	59	128
Mouth corners	86	87	173
No. of wrinkles treated			
Glabella	155	165	320
Nasolabial fold	214	206	420
Lip lines	137	116	253
Mouth corners	171	170	341

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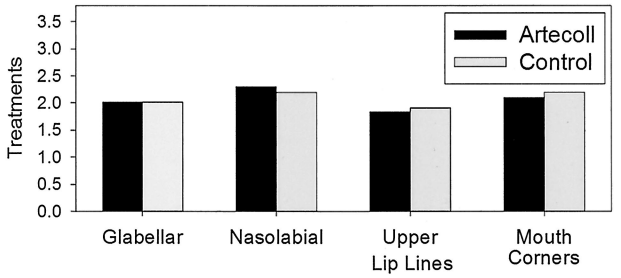

FIG. 2. During the 4 weeks after initial treatment, additional treatments were permitted. The number of treatments (mean ± SE) did not differ significantly between Artecoll and control collagen ($p = 0.974$, 0.316, 0.705, and 0.608, for the glabellar lines, nasolabial fold, upper lip lines, and mouth corners, respectively).

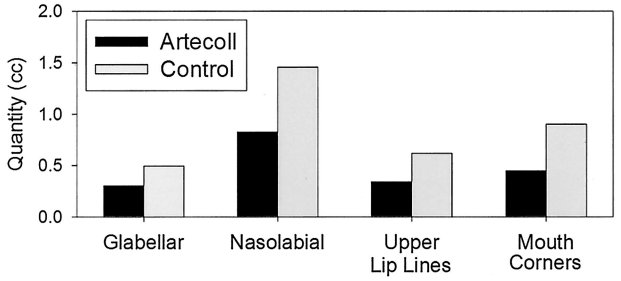

FIG. 3. The quantity of Artecoll injected (mean ± SE) was significantly lower than the amount of control collagen injected for each facial area ($p < 0.001$ in each case).

T5 Table V summarizes improvement over time in the masked observers' Facial Fold Assessment Scale ratings. Observations 1 month after injection showed no statistically significant difference between the two groups for nasolabial folds, upper lip lines, or mouth corners, while the control treatment was more effective ($p = 0.004$) than Artecoll for glabellar folds. By 3 months, the masked observers' ratings showed a statistically significantly greater improvement in the nasolabial folds ($p < 0.001$) and the corner-of-the-mouth wrinkles ($p = 0.001$) in the Artecoll group when compared with the collagen control group. Averaged across facial areas, the overall result was also significant ($p < 0.001$). At 6 months after injection, the Artecoll was statistically better ($p < 0.001$) than the collagen injection in the nasolabial fold and overall ($p < 0.001$). Facial Fold Assessment Scale reliability among the three masked raters ranged from 0.835 for the glabellar frowns to 0.900 for the corner-of-the-mouth lines.

Results of Secondary Objectives

T6 Table VI summarizes improvement in investigators' Facial Fold Assessment Scale ratings over time. Unlike masked observers who rated from photographs, investigators were not masked and rated their live experience with subjects against the reference photographs of the assessment scale. At 1 month, significantly greater improvement in glabellar folds was seen with control collagen than with Artecoll ($p = 0.034$), while significantly greater improvement in mouth corners was seen with Artecoll than with control collagen ($p = 0.041$). By 3 months, all facial areas except for the glabellar folds ($p = 0.317$) showed significantly greater improvement with Artecoll than with control collagen ($p < 0.001$ in each case). The overall average was also significantly greater for Artecoll ($p < 0.001$). By 6 months, all four facial areas and the overall average showed significantly greater improvement with Artecoll than with control collagen ($p < 0.001$).

Investigator success ratings over time are summarized in Figure 4. The ratings for the F4 two groups were similar at 1 month. However, by 3 months and 6 months, significantly more success was noted in the Artecoll group than in the control group ($p = 0.007$ to $p < 0.001$). By 6 months, Artecoll ratings were generally in the very successful range while collagen ratings were generally in the somewhat successful range.

A similar presentation for subject ratings of satisfaction is shown in Figure 5. No significant F5 differences between treatment groups were noted at 1 month. By 3 months, the subjects in the Artecoll group reported significantly greater satisfaction than subjects in the control group did ($p = 0.038$ to $p < 0.001$). At 6 months, the subjects in the Artecoll group continued to report significantly greater satisfaction than did the control group subjects ($p < 0.001$ in each case). By 6 months, the means for the Artecoll group were generally in the satisfied range while the means for the control group were generally in the dissatisfied range.

12-Month Artecoll Efficacy Analysis

Data on improvement at 12 months in Facial Fold Assessment Scale ratings were available for the Artecoll group only, per protocol, due to cross-over of collagen subjects to the Artecoll treatment at 6 months. Ratings from masked observers and from investigators were included.

Single-group tests were computed for masked observer ratings to determine whether efficacy could be detected 12 months after treatment. The results showed significant im-

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TABLE III
Adverse Events from Artecoll and Control Collagen Injections

Event	No. of Events			
	Artecoll		Control	
	Reported	Removal or Drainage*	Reported	Removal or Drainage*
Increased sensitivity	4		1	
Sensitization reactions	0		6	
Visibility of puncture site	0		2	
Granuloma or enlargement of the implant	0		1	
Persistent swelling or redness	7		13 (1†)	
Abscess	0		3	2
Infection	0		1	
Rash, itching more than 48 hours after injection	2		2	
Lumpiness at injection site >1 month after injection	8 (1‡) (1†)	1§	4	
Blurred vision (temporary)	1		0	
Recurrence of existing herpes labialis	1		0	
Flu-like symptoms	1		1†	
Other local complications	1		1†	
Other systemic complications	1†	0		
Severe illness, trauma, death	0		1†	
Adverse events	26	1	36	2
Total				
Total no. of subjects	21	1	16	2
Total no. of subjects evaluated	128	128	123	123
% of subjects	16.4	0.8	13.0	1.6

* Adverse events with removal or drainage are included in total reported.
† Not related to implant.
‡ Used contrary to protocol lip augmentation.
§ Pathology showed no foreign-body reaction. Diagnosis (seborrheic keratosis) not related to implant.

provement in Facial Fold Assessment ratings for the each of the four facial areas and the overall average ($p = 0.047$ to $p < 0.001$).

Similar tests were computed for investigator Facial Fold Assessment ratings. These showed significant results in all four of the treatment areas and overall ($p < 0.001$ in each case). These ratings for masked observers and investigators demonstrated effectiveness 12 months after Artecoll treatment.

Investigators ratings of success and subjects ratings of satisfaction in the Artecoll group at 12 months are presented in Figures 4 and 5, respectively. The success and satisfaction ratings remained high for the Artecoll group at 12 months.

TABLE IV
Abnormal Immunoglobulin G Levels in Artecoll and Control Groups

Treatment/Level	Follow-Up		
	1 Month	3 Months	6 Months
Artecoll			
Above	1	0	0
Below	0	0	0
Control			
Above	1	1	1
Below	6	3	1

DISCUSSION

The results of this study show Artecoll to be a safe and effective soft-tissue filler. Although Artecoll had fewer adverse events reported throughout the 12-month safety study period compared with collagen (Zyderm/Zyplast) in a 6-month study period, these results were not statistically significant. Artecoll was more effective than collagen for correction of nasolabial folds in masked observers' ratings at the 6-month effectiveness study period. No statistically significant difference was noted between masked observer ratings for Artecoll and collagen in the other injection sites; however, the quantity of Artecoll used was nearly half that of collagen. Investigators' success ratings for Artecoll were superior to those for collagen at 6 months for each of the four injection sites. Subjects' satisfaction ratings for the Artecoll group were also higher than for collagen in each of the injection sites at 6 months after implantation.

Zyderm was introduced as a dermal filler into the clinical arena in 1982.[7] It was initially very well received, but enthusiasm cooled because of its short duration of action. It is the general impression of many clinicians that virtually all biological materials eventually are ab-

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TABLE V
Improvement in Masked Observers Ratings Using the Facial Fold Assessment Scale

	Artecoll				Control				
	No.	Mean	SD	SE	No.	Mean	SD	SE	*p*
1 Month									
Glabellar folds	64	0.17	0.69	0.09	77	0.49	0.68	0.08	0.004
Nasolabial folds	91	0.75	0.76	0.08	91	0.74	0.73	0.08	0.713
Upper lip lines	58	0.31	0.55	0.07	53	0.48	0.60	0.08	0.205
Mouth corners	71	0.46	0.74	0.09	76	0.30	0.65	0.07	0.179
Overall	109	0.53	0.59	0.06	108	0.59	0.55	0.05	0.422
3 Months									
Glabellar folds	65	0.25	0.80	0.10	75	0.35	0.60	0.07	0.348
Nasolabial folds	87	0.81	0.81	0.09	88	0.15	0.79	0.08	<0.001
Upper lip lines	53	0.18	0.64	0.09	51	0.25	0.52	0.07	0.454
Mouth corners	64	0.45	0.80	0.10	77	0.01	0.66	0.07	0.001
Overall	102	0.53	0.61	0.06	107	0.02	0.48	0.05	<0.001
6 Months									
Glabellar folds	71	0.34	0.79	0.09	79	0.32	0.68	0.08	0.971
Nasolabial folds	92	0.77	0.87	0.09	91	0.00	0.90	0.09	<0.001
Upper lip lines	55	0.08	0.62	0.08	50	0.22	0.48	0.07	0.176
Mouth corners	69	0.26	0.76	0.09	79	0.09	0.74	0.08	0.316
Overall	107	0.50	0.67	0.06	110	0.16	0.57	0.05	<0.001
12 Months									
Glabellar folds	69	0.41	0.73	0.09					
Nasolabial folds	90	0.95	0.95	0.10					
Upper lip lines	56	0.24	0.64	0.09					
Mouth corners	70	0.17	0.81	0.10					
Overall	108	0.55	0.71	0.07					

sorbed. To provide permanent tissue augmentation, polymethylmethacrylate, a substance widely used as a permanent implant, was combined with a temporary collagen carrier to deliver smooth, round polymethylmethacrylate microspheres into the deeper skin layers.[8] Once in position, the bovine collagen carrier is replaced by autologous connective tissue which individually encapsulates each of the microspheres, creating a bulk augmentation that is

TABLE VI
Improvement in Investigator Ratings Using the Facial Fold Assessment Scale

	Artecoll				Control				
	No.	Mean	SD	SE	No.	Mean	SD	SE	*p*
1 Month									
Glabellar folds	67	1.16	0.79	0.10	79	1.56	1.07	0.12	0.034
Nasolabial folds	91	1.66	0.92	0.10	93	1.59	1.05	0.11	0.405
Upper lip lines	61	1.47	0.74	0.09	54	1.32	0.90	0.12	0.338
Mouth corners	74	1.50	0.97	0.11	76	1.16	0.94	0.11	0.041
Overall	111	1.50	0.68	0.06	111	1.47	0.79	0.07	0.593
3 Months									
Glabellar folds	67	1.14	0.90	0.11	74	0.90	1.07	0.12	0.317
Nasolabial folds	88	1.84	0.94	0.10	89	0.51	0.99	0.11	<0.001
Upper lip lines	58	1.28	0.69	0.09	51	0.43	0.89	0.12	<0.001
Mouth corners	68	1.40	1.25	0.15	75	0.48	0.77	0.09	<0.001
Overall	106	1.50	0.83	0.08	108	0.59	0.73	0.07	<0.001
6 Months									
Glabellar folds	73	1.12	0.95	0.11	82	0.46	1.04	0.12	<0.001
Nasolabial folds	96	1.91	1.01	0.10	96	0.01	0.86	0.09	<0.001
Upper lip lines	60	1.34	0.95	0.12	54	0.05	0.98	0.13	<0.001
Mouth corners	72	1.28	1.41	0.17	80	0.02	0.83	0.09	<0.001
Overall	112	1.51	0.95	0.09	115	0.17	0.74	0.07	<0.001
12 Months									
Glabellar folds	69	1.29	1.01	0.12					
Nasolabial folds	91	2.07	1.06	0.11					
Upper lip lines	58	1.41	1.02	0.13					
Mouth corners	72	1.51	1.23	0.14					
Overall	109	1.68	0.94	0.09					

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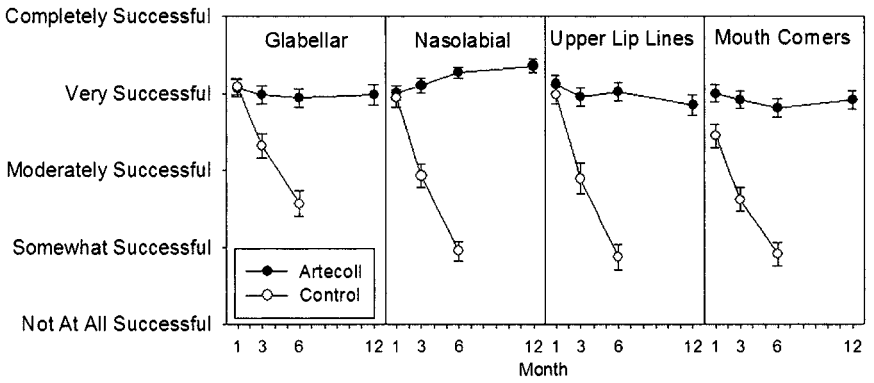

FIG. 4. The investigators' success ratings (mean ± SE) for Artecoll and control collagen were similar at 1 month (p = not significant in each case except for mouth corners, $p = 0.011$) and significantly higher for Artecoll than for control collagen at both 3 and 6 months ($p < 0.001$ in each case except 3-month glabellar, where $p = 0.007$). Artecoll success ratings remained high at 12 months.

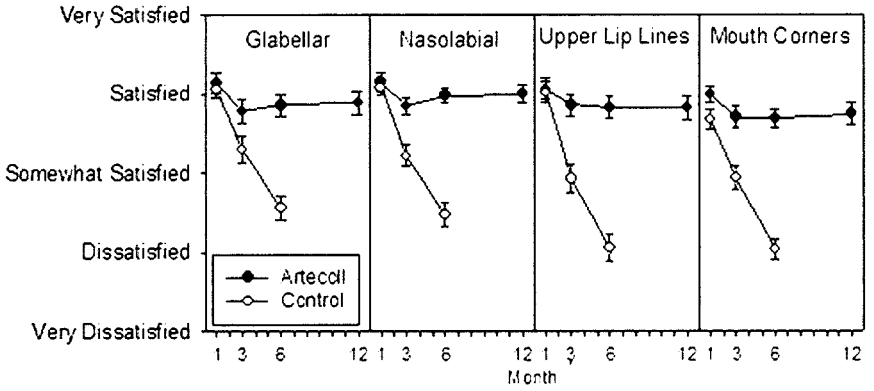

FIG. 5. The subjects' satisfaction ratings (mean ± SE) for Artecoll and control collagen were similar at 1 month (p = not significant in each case) and significantly higher for Artecoll at 3 and 6 months ($p < 0.001$ in each case except for 3-month glabellar, where $p = 0.038$). Satisfaction ratings for Artecoll remained high at 12 months.

approximately 20 percent synthetic and 80 percent the patient's own collagen.

A preliminary product used in humans by the same inventor, before Artecoll, was called Arteplast.[9] The original suspension consisted of 30- to 42-μm-diameter polymethylmethacrylate microspheres in gelatin. The first clinical trials were conducted under the supervision of the Ethical Commission of Frankfurt University in 1989. One hundred eighty-seven volunteers received Arteplast subdermally. In this group, plus in the 400 subjects who received Arteplast up until its replacement by Artecoll in 1994, a total of 15 subjects (2.5 percent) developed foreign-body granulomas from 6 to 18 months after injection.[4] The majority of these granulomas were treated with intralesional steroid injection and rarely with surgical excision. In 1994, a new purification and washing technique was introduced.[4] The sieving process was changed from a nylon fabric mesh to a metal mesh, and a complex washing and ultrasound procedure was devised that removed virtually all nanoparticles and electrical surface charges, which were thought to be the cause of foreign-body reactions and granuloma formation. Another change made at the same time was the use of collagen as a carrier to replace the gelatin carrier, which is resorbed too quickly and thereby permits clumping of the particles.

The improved product, named Artecoll, was brought onto the market by Rofil Medical International, Breda, Holland, in 1994, and it has since been used in an estimated 200,000 patients with a reported granulomatous reaction rate of less than 0.01 percent.[4]

In evaluating the literature on safety of permanent injectable fillers, it is critical for the clinician to differentiate between Arteplast and Artecoll. Arteplast and Artecoll have been con-

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fused with each other in the past, making accurate communication about the safety and efficacy of Artecoll difficult.[10] Electron microscopy views of the polymethylmethacrylate microspheres contained in Artecoll clearly demonstrate the absence of microparticles in the Artecoll microspheres (Fig. 6). F6

Biocompatibility

The chemical inertness and biocompatibility of polymethylmethacrylate has been well accepted since Judet[11] introduced the first hip prosthesis made from polymethylmethacrylate in 1947. Animal experiments have documented that an important key to biocompatibility in the skin is the round shape and smooth surface and the size of the polymethylmethacrylate microspheres.[12,13] In comparison, other synthetic fillers, such as Teflon and silicone particles, have irregular surfaces and cause a chronic granulomatous reaction.[14] Microscopically, the predominant cells seen in the reaction to Teflon or silicone particles are foreign-body giant cells. In contrast, in the rare case of foreign-body reaction to Artecoll, histologically, the true granulomas show broad bands of collagen fibers between microspheres, which are pushed apart, with rare lymphocytes, macrophages, and giant cells.[15] These granulomas almost always respond to intralesional injection with corticosteroid.[4,16]

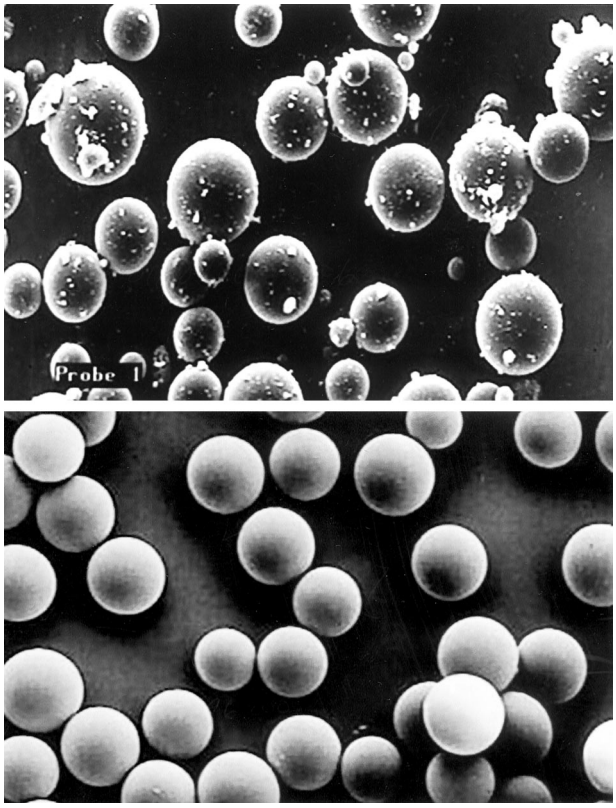

FIG. 6. Comparison of scanning electron microscopy images of polymethylmethacrylate bone cement (*above*) and Artecoll polymethylmethacrylate 32- to 40-μm-diameter microspheres (*below*). Note the absence of nanoparticles on the surface of Artecoll microspheres as a result of the washing procedures.

Most materials that are used as biological fillers to increase the thickness of the dermis in a wrinkle line are phagocytosed within a few months. Therefore, a lasting effect can be achieved only by using either an autogenous material that becomes vascularized and survives as a graft or nonresorbable synthetic substances. There are six million polymethylmethacrylate microspheres in each 1 cc of Artecoll. Beneath the wrinkle crease, the microspheres stimulate fibroblasts to encapsulate each individual microsphere. Collagen is used as a carrier substance that prevents clumping during injection and favors tissue ingrowth. The 20 volume% polymethylmethacrylate microspheres provide the scaffold for the 80 volume% autologous connective tissue deposition. The Artecoll serves as a filler that seems to "splint" the wrinkle crease, preventing further folding and allowing the dermis to regenerate in the wrinkle fold.

Treatment Areas

The glabellar lines posed little problem with injection since the dermis is thick and the underlying connective tissue provides good support for the implant (Fig. 7). Slight overcorrection may be necessary and deeper lines may require repeated injections. It is difficult to explain the lack of statistical difference between collagen and Artecoll in the glabellar frown region using masked observer ratings. Initial overcorrection was common for collagen treatment. However, there was a general reluctance among U.S. clinical trial investigators to inject as much Artecoll as collagen in each of the four study areas due to its permanent effect, which may account for the absence of clear-cut statistical significance, with the exception of nasolabial folds. Nevertheless, subject satisfaction ratings and investigator success ratings were higher for Artecoll at the 6-month point in each of the four study areas. F7

The results of nasolabial fold augmentation with Artecoll were excellent (Figs. 8 and 9). Nasolabial creases are best supported by two to three bands of Artecoll implanted parallel and F8,F9

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FIG. 7. Glabellar lines before (*above*) and 6 months after (*below*) treatment with Artecoll.

medial to the fold. During the first several days after implantation, Artecoll can be moved laterally by facial muscle movement. Care must be taken not to place the Artecoll too superficially. Otherwise, in patients with thin skin the implant may appear erythematous for several weeks and the implant may be visualized as small white granules. A second session is often necessary, especially in the inferior aspect of the nasolabial crease.

Radial lip lines extend upward or downward from tiny notches in the vermilion-cutaneous border. In younger patients with nice projection of the white roll, each wrinkle can be treated individually. In patients with four or more vertical lines and in whom the projection of the white roll is diminished, Artecoll can be injected transversely along the entire white roll as well as beneath the individual vertical lines (Fig. 10). There is a natural pocket between F10 the white roll and the orbicularis oris muscle that is easily filled centripetally from the corners of the mouth. Injection into the upper and lower lips may be painful, and field or nerve blocks with local anesthesia may be helpful. Artecoll is not intended for injection into the vermilion of the lip.

Wrinkles at the corners of the mouth and marionette lines may be difficult to treat, but they often yield excellent results. First, the lower white roll itself is treated horizontally about 1 cm in length from the corner. Next, five to 10 vertical and horizontal threads of Artecoll should be implanted using a criss-crossing technique (Fig. 11). This supports the

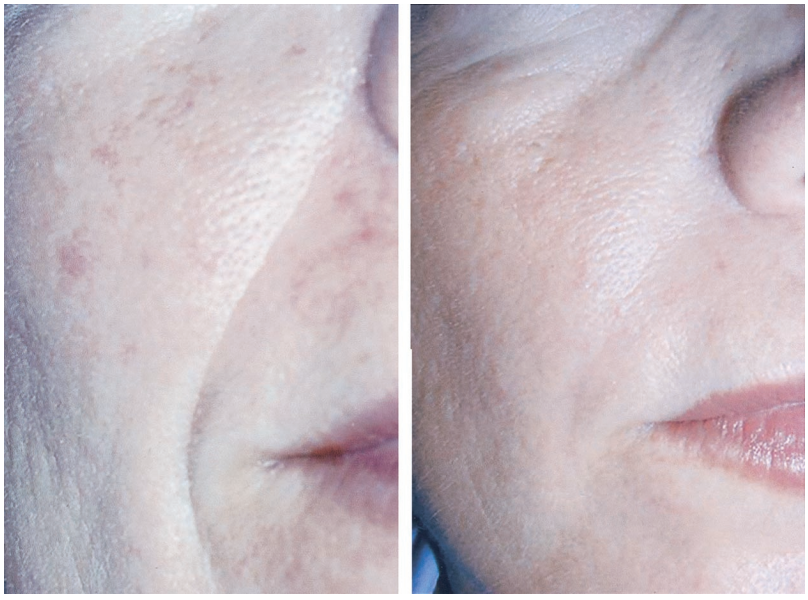

FIG. 8. Nasolabial fold before (*left*) and 12 months after (*right*) treatment with Artecoll.

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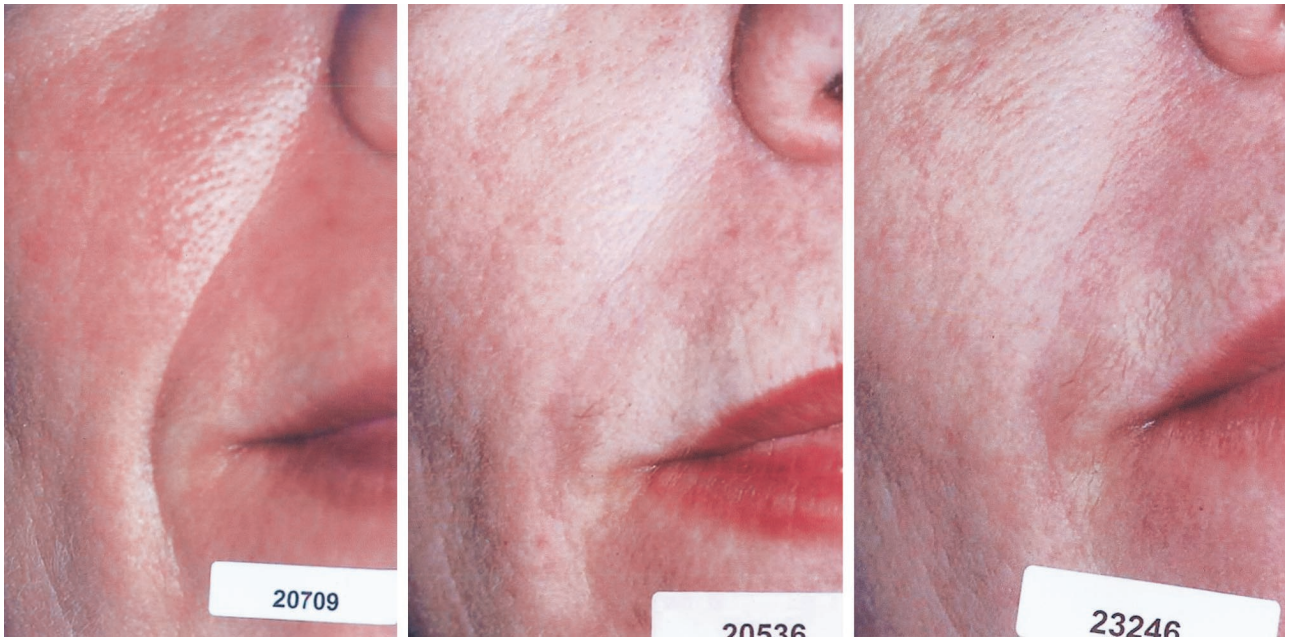

FIG. 9. Nasolabial folds before (*left*), 6 months after (*center*), and 1 year after (*right*) treatment with Artecoll.

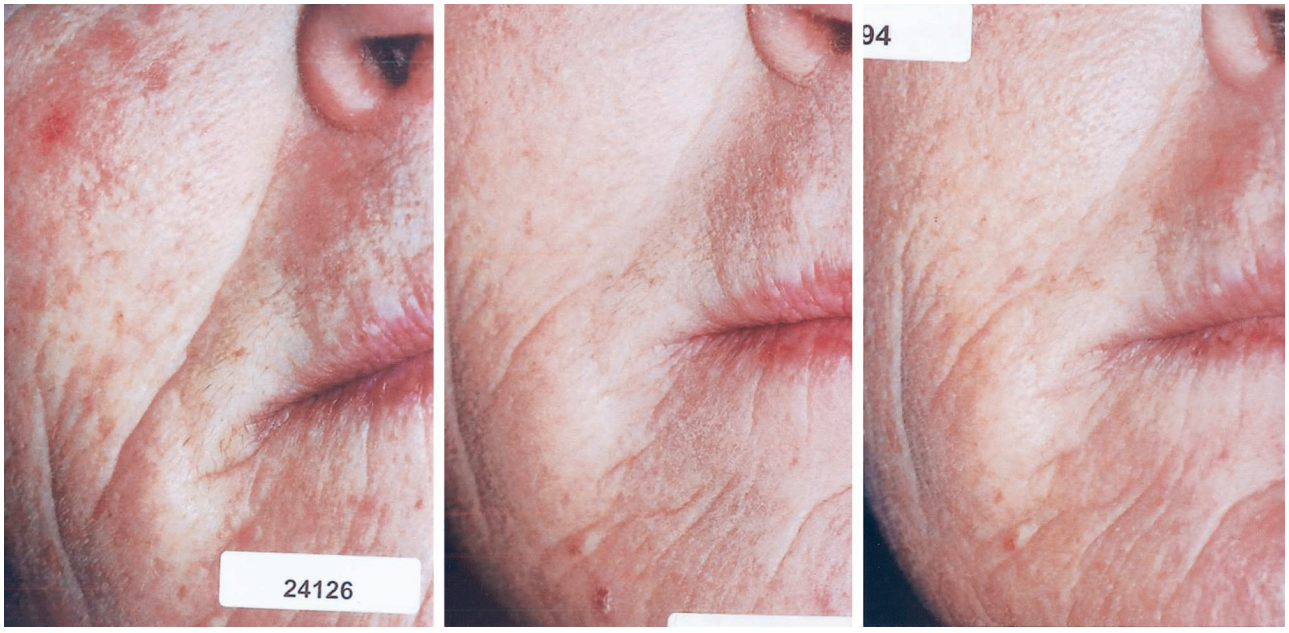

FIG. 10. Upper lip lines, marionette lines, and nasolabial folds before (*left*), 6 months after (*center*), and 12 months after (*right*) treatment with Artecoll.

region and slightly lifts the corners of the mouth. The skin is thin in this area and superficial injection may lead to telangiectasias. Preferably, Artecoll should be implanted in many different tunnels in two or more sessions. Injection of Artecoll into the orbicularis oris muscle is to be avoided as it may result in the formation of nodules that can be palpated in the wet mucosa. The marionette lines that extend vertically from the corners of the mouth down to the mandibular border can be improved by linear threading combined with deep intradermal criss-cross injection of Artecoll.

CONCLUSIONS

The ability to measure the effect of cosmetic treatments, such as wrinkle fillers, has suffered from the lack of a validated objective rating scale. The authors hope that the successful

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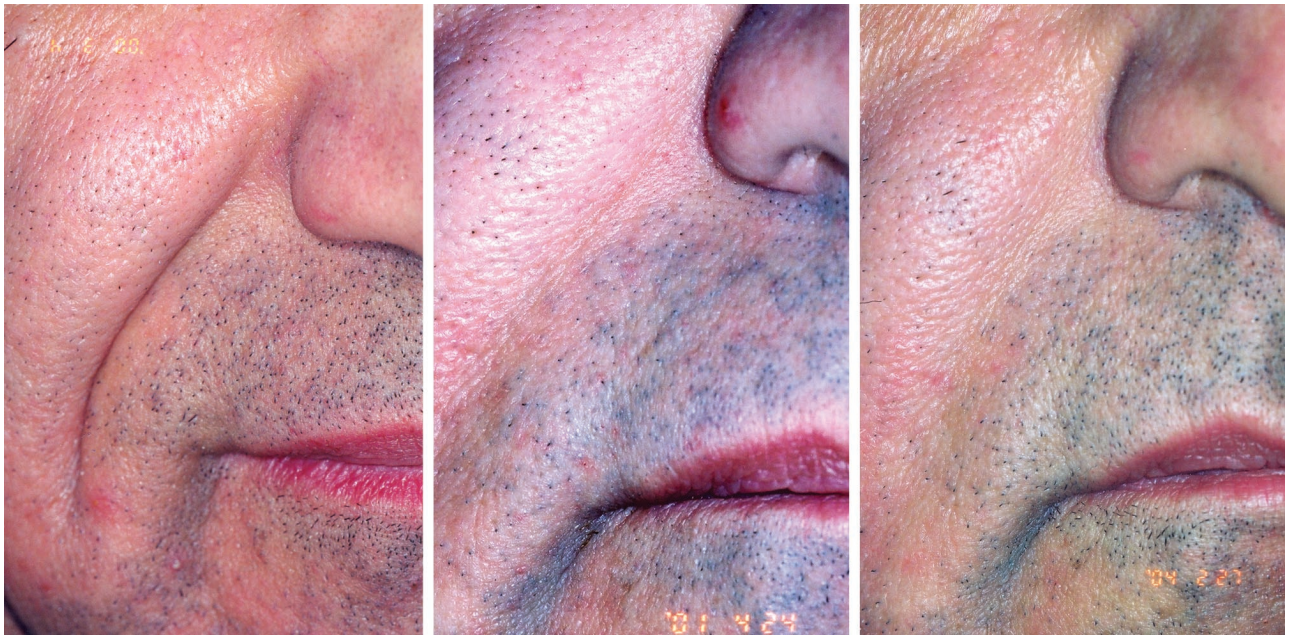

FIG. 11. Extreme nasolabial folds before (*left*), 1 year after (*center*), and 4 years after (*right*) treatment with Artecoll.

utilization of a photographic facial fold assessment scale for this Food and Drug Administration study will encourage development and adoption of similar scales for cosmetic treatment evaluations.

This study has demonstrated the safety of Artecoll relative to collagen control, as measured by relative rates of adverse events. It has demonstrated the effectiveness of Artecoll relative to collagen control for the treatment of nasolabial folds, as measured by the objective rating scale using masked raters. The effectiveness of Artecoll was demonstrated for all areas treated, using the important outcome measures of investigator success rating and subject satisfaction.

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