

I. General Information

- A. Device generic name:** Dermal Implant
- B. Device trade name:** Artecoll™, PMMA/Collagen Implant
- C. Applicant's name and address**
- ARTES MEDICAL, INC.
4660 La Jolla Village Drive, Suite 825
San Diego, CA. 92122 USA
- D. PMA number***
- E. Date of Panel recommendation***
- F. Date of notice of approval to the applicant***

(*to be completed by FDA)

II. Indications for Use

Artecoll is indicated for the correction of contour deficiencies of soft tissue.

III. Device Description

Artecoll is composed of PMMA microspheres, 30 to 42 microns in size, suspended in a water based carrier gel composed of 3.5% bovine collagen, 96.5% buffered, isotonic water for injection including 0.3% lidocaine.

0.5 cc syringe contains	
Polymethylmethacrylate	120 mg
3.5% Bovine Collagen Solution	0.4 cc
Bovine Collagen	3.5%
Phosphate Buffer	2.7%
Sodium Chloride	0.3%
Lidocaine Hydrochloride	0.3%
Water for Injection	93.2%

IV. Contraindications, Warnings, and Precautions**A. Contraindications**

Artecoll must not be injected if the patient has a positive response to the required Artecoll Test Implant. Refer to Artecoll Test Implant Package Insert for complete instructions for administration and evaluation of the test implant.

Artecoll must not be used in patients with severe allergies manifested by a history of anaphylaxis, or history or presence of multiple severe allergies.

Artecoll contains lidocaine and must not be used in patients with known lidocaine hypersensitivity.

Artecoll must not be used in patients with a history of allergies to any bovine collagen products, including but not limited to injectable collagen, collagen implants, hemostatic sponges and collagen based sutures, because these patients are likely to have hypersensitivity to bovine collagen in Artecoll.

Artecoll must not be used in patients undergoing or planning to undergo desensitization injections to meat products, as these injections can contain bovine collagen.

Artecoll is contraindicated for use in breast augmentation, and for implantation into bone, tendon, ligament, or muscle.

B. Warnings

An Artecoll Test Implant must be administered and evaluated prior to soft tissue deficiency correction using Artecoll. Refer to Artecoll Test Implant Physician Package Insert.

Artecoll must not be implanted into blood vessels. Implantation of Artecoll into dermal vessels may cause vascular occlusion, infarction, or embolic phenomena.

Artecoll should be used with caution in patients with histories of allergic reactions to other substances, as injectable collagen use has been associated with allergic hypersensitivity responses, especially in patients with such histories.

Use of Artecoll at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives) or infection is present should be deferred until the inflammatory process has been controlled.

The safety of Artecoll for use during pregnancy, in breastfeeding females or in patients under 18 years has not been established.

Artecoll should be used with caution in patients on immunosuppressive therapy.

Patients who are using substances that interfere with platelet function or have any condition that reduces coagulation may experience increased bruising or bleeding at injection sites.

C. Precautions

The injection of Artecoll carries an inherent, yet minimal, risk of infection, as does any transcutaneous procedure. The usual precautions associated with injectable materials should be followed.

After use, treatment syringes and needles may be potential biohazards. Handle accordingly and dispose of in accordance with accepted medical practice and applicable local, state and federal requirements.

Artecoll has an opaque, off-white appearance. In the event that the content of a syringe shows signs of separation and/or appears clear (like water) after being melted, do not use the syringe and notify Artes Medical, Inc. at (858) 550-9999, or toll-free at (866) ARTESINC.

V. Alternative Practices and Procedures

Alternatives to treatment with Artecoll may include:

- ??no treatment
- ??treatment with injectable bovine collagen fillers (Zyplast, Zyderm; McGhan Medical Corp., Santa Barbara, CA)
- ??injection of processed cadaver tissue (Cymetra; Lifecell Corp., The Woodlands, TX) (Fascian; Fascia Biosystems, LLC, Beverly Hills, CA)
- ??injection of autologous fat
- ??injection of botulinum toxin (Botox; Allergan, Inc., Irvine, CA)
- ??laser resurfacing

Of these alternatives, treatment with injectable bovine collagen fillers that do not contain PMMA microspheres has been shown to require retreatment at regular intervals to maintain the desired effect. Processed cadaver tissue is estimated to last three to six months. Autologous fat injections need to be repeated because only a low percentage (<5%) of implanted cells find connection to subcutaneous capillaries of the recipient bed, which is essential for transplant survival. Botulinum toxin injections paralyze the movement of facial muscles for three to six months. They are regarded as safe, but are intended for use only in the upper face. Laser resurfacing can reduce the fine lines and wrinkles that may result from skin aging, but is not intended for treatment of the deep folds for which Artecoll is indicated.

VI. Marketing History

The predecessor of Artecoll, Arteplast (PMMA microspheres suspended in gelatin), was developed in Frankfurt, Germany in 1989 and was used in clinical trials in over 600 patients. In order to significantly reduce the rate of side effects, Artecoll was developed, with a change in the PMMA microsphere sieving procedure and use of collagen as a suspension medium. Rofil Medical International B.V., Breda, The Netherlands, began marketing Artecoll worldwide (not in the U.S.) in 1994. In September 1996, Artecoll was certified for the CE mark as a Class III medical device. Artecoll was approved in Canada in September 1998, and is marketed by Canderm Pharma, St Laurent, QC. In Mexico, approval was granted May 1999, and the device is marketed by Grupo Venta Int., Guadalajara, Jal.

VII. Potential Adverse Effects of the Device on Health

No implant-related severe illness, trauma or death occurred among the subjects treated with either Artecoll or the commercially available Control implants in the clinical studies described in Section IX. The Artecoll open label U.S. clinical trial included 157 subjects. One-year safety evaluations were available for 126 subjects. The Artecoll controlled, randomized U.S. clinical trial involved 128 subjects treated with Artecoll and 123 subjects treated with either of two commercially available Control implants. For the controlled, randomized trial, follow-up periods for both safety and efficacy were at one, three and six months, with a final 12-month safety evaluation.

A. Observed Adverse Events

Table 1 reports all of the adverse events (treatment-related and non-treatment-related) reported for Artecoll and the established Control group subjects during the controlled, randomized trial, in order of reported frequency for Artecoll group subjects. Table 2 reports

all of the adverse events (treatment-related and non-treatment-related) reported for Artecoll subjects during the open label trial, in order of reported frequency.

TABLE 1.

Adverse events reported in controlled, randomized clinical trial of Artecoll

Event	Number of Events							
	Artecoll				Control			
	Severity of Event, as determined by investigator			Removal or Drainage*	Severity of Event, as determined by investigator			Removal or Drainage*
	Mild	Moderate	Severe		Mild	Moderate	Severe	
Lumpiness at injection area more than one month after injection	6(1 ^{**}) (1 ^{****})	2	0	1 ^{***} (mild)	1	1	2	
Persistent swelling or redness	5	2	0		9(1 ^{****})	3	1	
Increased sensitivity	4	0	0		0	0	1	
Rash, itching more than 48 hours after injection	2	0	0		0	2	0	
Blurred vision	0	1	0		0	0	0	
Flu-like symptoms	0	1	0		1 ^{****}	0	0	
Recurrence of existing herpes labialis	1	0	0		0	0	0	
Sensitization reactions	0	0	0		2	3	1	
Abscess	0	0	0		0	1	2	2 (severe)
Visibility of puncture area	0	0	0		0	2	0	
Granuloma or enlargement of the implant	0	0	0		0	0	1	
Infection	0	0	0		0	0	1	
Other local complications	1	0	0		1 ^{****}	0	0	
Other systemic complications	0	1 ^{****}	0		0	0	0	
Severe illness, trauma, death	0	0	0		0	0	1 ^{****}	
Total AEs	19	7	0	1	14	12	10	2
	26				36			
Total subjects with AEs	21			1	16			2
Total subjects treated	128				123			
% of subjects with AEs	16.4			0.8	13.0			1.6

* AEs with removal or drainage are included in Mild/Moderate/Severe counts

** Used contrary to protocol (lip augmentation)

*** Pathology showed no foreign body reaction. Diagnosis, seborrheic keratosis. Not related to implant

**** Not related to implant

TABLE 2.**Adverse events reported in open label trial of Artecoll**

Event	Number of Events				
	Severity of Event, as determined by investigator				Removal or Drainage*
	Mild	Moderate	Severe	Unknown	
Lumpiness at injection area > one month after injection	1	1**	0	3	1 (moderate)**
Persistent swelling or redness	2	0	0	1	
Increased sensitivity	0	0	0	1	
Rash, itching more than 48 hours after injection	2	0	0		
Sensitization reactions	1	0	0	1	
Granuloma or enlargement of the implant	0	0	1		1
Other local complications	0	1***	0	1***	
Other systemic complications	1***	0	0		
Severe illness, trauma, death	0	0	1***		
Total AEs	7	2	2	7	2
	18				
Total subjects with AEs	17				2
Total subjects evaluated	126				126
% of subjects with AEs	13.5				1.6

* AEs with removal or drainage are included in Mild/Moderate/Severe/Unknown counts

** Used contrary to protocol (lip augmentation)

***Not related to implant

B. Potential Adverse Events

Based on the literature and experience with Artecoll outside the United States, possible adverse events that might occur but have not been reported in the U.S. clinical trial include hypersensitivity to bovine collagen, nodule formation, infection, abscess, and possible vascular occlusion. In case of lumpiness due to displacement of implant or late granuloma formation, the treatment of choice is multiple triamcinolone acetonide injections intralesionally (1).

VIII. Summary of Preclinical Studies

A. Laboratory Studies

Morhenn, et. al. , conducted an experimental study at the University of California, San Diego to determine which sizes of polymethylmethacrylate (PMMA) microspheres are phagocytosed by three human cell lines in tissue culture (2). Human macrophages U-937, Langerhans cells XS 106 and XS 52, and human keratinocytes HaCaT were able to phagocytose PMMA microspheres 20 µm or smaller. Microspheres larger than 20 µm were not ingested by any cell line. Microparticles made of silicone or polymethacrylate, on the other hand, were phagocytosed, possibly because of their different physical shape.

B. Animal Studies

G. Lemperle, et. al., in a study conducted at the University of Frankfurt, demonstrated in experiments on rats the safety and biocompatibility of PMMA microspheres (3). Histological specimens up to seven months after intradermal and subdermal implantation revealed a modest tissue reaction, forming a delicate fibrous capsule around each individual microsphere. No breakdown, corrosion, phagocytosis or migration of the spheres was observed at seven months.

In another experimental study at the University of California, San Diego, ten soft tissue filler substances, which were widely used outside the U.S., were injected subdermally in mice (4). At one, three, six and nine months, implantation sites were excised and microscopically inspected together with local lymph nodes, lungs, liver and spleen. The different materials caused different patterns of foreign body reactions, which were examined according to the Duranti classification. The least tissue reaction around particulate material was observed in the Artecoll implants. In mice, no migration or transportation of any of the injected particulate filler substances to lymph nodes or filter organs could be detected at any of the four time points. Apparently, macrophages with high numbers of phagocytosed small microspheres or particles were unable to migrate to lymph nodes or filter organs.

IX. Summary of Clinical Studies

A. Controlled, Randomized Trial

1. Study design

The Artecoll clinical trial was a prospective, multi-center, controlled, randomized, double-masked trial. Subjects were randomized (1:1) to either Artecoll or a commercially available collagen implant (Zyderm 2[®] for glabellar folds, Zyplast[®] for others, collectively termed "Control").

a) Primary Objectives

- ??To determine whether the cosmetic correction provided by Artecoll at the end of a six month period following injection is superior to that provided by a commercially available collagen implant at the same time period
- ??To determine the safety of Artecoll as an injectable implant for correction of contour deformities of the dermis of the face

b) Secondary Objectives

- ??To characterize the initial quality of the cosmetic correction provided by Artecoll and the commercially available collagen implant
- ??To characterize investigator assessment of success with respect to how closely the treatment met the investigator's initial expectations for correction
- ??To characterize subject assessment of satisfaction with respect to the subject's personal expectations

A total of 251 subjects were injected with either Artecoll (128 subjects) or with the the established Control device (123 subjects) at eight dermatology or plastic surgery centers in the U.S. Follow-up periods for both safety and efficacy were at one, three and six months, with a final 12-month safety evaluation.

2. Patient assessment

Treatment effectiveness was assessed at each follow-up visit. Photographs were taken at the time of pre-treatment evaluation and at each post-treatment evaluation. From the photographs, independent, masked observers classified each fold according to the Facial Fold Assessment (FFA) Scale, a scale that was created and validated for this study. Standardized reference photographs were used by the masked observers for comparison. For evaluation of secondary objectives, investigators rated success of treatment and subjects indicated satisfaction ratings.

3. Demographic data

Twenty-two men and 229 women between the ages of 28 and 82 were enrolled in the study. Study centers all were located in the U.S. The overall mean age was 52.2 years. The age distributions for the two treatment groups and the sample as a whole are summarized in Table 3. The groups did not differ significantly in mean age ($t = 1.42$, $df = 249$, $p = .157$).

Table 3.**Age distribution of subjects by treatment group**

Treatment	Artecoll	Control	Total
N	128	123	251
Mean	53.2	51.2	52.2
Std.Dev.	10.3	11.3	10.8
Std.Err.	0.9	1.0	0.7
Minimum	28	29	28
Maximum	82	78	82
Range	54	49	54
Variance	105.6	128.3	117.2

The gender distributions for the two treatment groups and for the sample as a whole are summarized in Table 4. Most of the subjects treated (91.2%) were female. The gender distribution did not differ significantly between treatment groups (Yates corrected chi-square = 0.00, $p=1.000$).

Table 4.**Gender distribution of subjects by treatment group**

Gender	Artecoll		Control		Total	
	Number	Percent	Number	Percent	Number	Percent
Male	11	8.6%	11	8.9%	22	8.8%
Female	117	91.4%	112	91.1%	229	91.2%

4. Data analysis and results

a) Primary objectives

For the first primary objective, the comparison of Artecoll and Control in terms of improvement in masked observer FFA Scale ratings at the 6-month follow-up observation was completed using Mann-Whitney U tests since improvement data were not normally distributed. The results for objective 1 are summarized in Table 5. The difference for Nasolabial Folds was statistically significant. The means and mean ranks indicate that Artecoll treatment resulted in greater improvement than Control in these cases. Thus, the alternative hypothesis was accepted for Nasolabial Folds. There were no significant differences between Artecoll and Control for Glabellar Folds, Upper Lip Lines, or Mouth Corners.

Table 5.**Improvement in masked observer FFA Scale ratings from pre-treatment to six months for each fold area by treatment group – Objective 1**

Treatment Area	Treatment	N	Mean	Std.Dev.	Std. Err.	Mean Rank	Mann-Whitney U Test	
							U	p
Glabellar Folds	Artecoll	71	0.34	0.79	0.09	75.4	2795.0	.971
	Control	79	0.32	0.68	0.08	75.6		
Nasolabial Folds	Artecoll	92	0.77	0.87	0.09	113.8	2176.5	<.001
	Control	91	0.00	0.90	0.09	69.9		
Upper Lip Lines	Artecoll	55	0.08	0.62	0.08	49.2	1164.5	.176
	Control	50	0.22	0.48	0.07	57.2		
Mouth Corners	Artecoll	69	0.26	0.76	0.09	78.3	2465.0	.316
	Control	79	0.07	0.74	0.08	71.2		

For the second primary objective, that is, total number of subjects with any adverse events, Artecoll and Control were compared using the chi-square test with correction for continuity. The result was not significant (chi-square=0.338, p=.561) indicating that the two treatments did not differ in adverse event rates.

Only one Artecoll and two Control subjects required follow-up removal or drainage. The treatment difference in this rate is not significant (Fisher Exact Test p = .485). A total of 128 subjects received Artecoll injections. No unanticipated adverse device effects were reported. Adverse events reported for the Artecoll subjects were similar to but lower in number than the adverse events reported for the Control group. No implant-related severe illness,

trauma or death occurred among the subjects treated with either Artecoll or the Control implant.

b) Secondary objectives

The quality of the initial treatment result was characterized using the FFA Scale at one month and three months post-treatment, comparing severity with pre-treatment ratings. The initial quality of the cosmetic correction provided by Artecoll and Control was compared by use of non-parametric Mann-Whitney U tests. Using masked observer FFA Scale ratings, improvement from pretreatment values at one month was greater for Control than for Artecoll for Glabellar Folds and not significantly different between treatment groups for the other treatment areas. By three months, improvement was greater for Artecoll than for Control for Nasolabial Folds and for Mouth Corners and the treatment groups were not significantly different for the other treatment areas.

Table 6 summarizes the initial progress at one month post-treatment. The difference in improvement between Artecoll and Control was significant for Glabellar Folds. Means and mean ranks indicate that this initial improvement was greater for Control than for Artecoll. No other treatment area showed a significant difference between Artecoll and Control.

Table 6.

Improvement in masked observer FFA Scale ratings from pre-treatment to one month

Treatment Area	Treatment	N	Mean	Std.Dev.	Std. Err.	Mean Rank	Mann-Whitney Test	
							U	p
Glabellar Folds	Artecoll	64	0.17	0.69	0.09	60.3	1777.5	.004
	Control	77	0.49	0.68	0.08	79.9		
Nasolabial Folds	Artecoll	91	0.75	0.76	0.08	92.9	4010.0	.713
	Control	91	0.74	0.73	0.08	92.1		
Upper Lip Lines	Artecoll	58	0.31	0.55	0.07	52.3	1323.0	.205
	Control	53	0.48	0.60	0.08	60.0		
Mouth Corners	Artecoll	71	0.46	0.72	0.09	78.9	2351.5	.179
	Control	76	0.30	0.65	0.07	69.4		

Table 7 summarizes the progress at three months post-treatment. The difference in improvement between Artecoll and Control was significant for Nasolabial Folds and Mouth Corners. Means and mean ranks indicate that improvement at three months was greater for Artecoll than for Control. The other treatment areas showed no significant difference between Artecoll and Control.

Table 7.**Improvement in masked observer FFA Scale ratings from pre-treatment to three months**

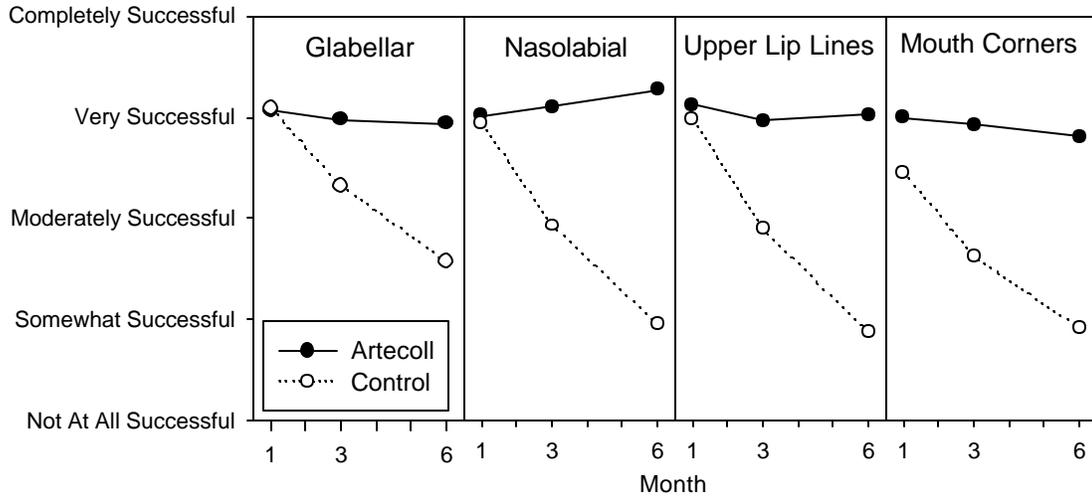
Treatment Area	Treatment	N	Mean	Std.Dev.	Std. Err.	Mean Rank	Mann-Whitney Test	
							U	p
Glabellar Folds	Artecoll	65	0.25	0.80	0.10	67.1	2213.0	.348
	Control	75	0.35	0.60	0.07	73.5		
Nasolabial Folds	Artecoll	87	0.81	0.81	0.09	107.0	2173.5	<.001
	Control	88	0.15	0.79	0.08	69.2		
Upper Lip Lines	Artecoll	53	0.18	0.64	0.09	50.3	1236.5	.454
	Control	51	0.25	0.52	0.07	54.8		
Mouth Corners	Artecoll	64	0.45	0.80	0.10	83.6	1657.5	.001
	Control	77	0.01	0.66	0.07	60.5		

To determine investigator assessment of success with respect to how closely the treatment met the investigator's initial expectations for correction, the investigator's assessment (not masked) of success was rated using a five-point scale, with 1 corresponding to "completely successful" and 5 to "not at all successful", at one, three and six months post-treatment. Descriptive statistics were used to characterize the investigator ratings. Table 8 summarizes the findings and the means are illustrated in Figure 1. By month three, ratings that are more successful were obtained for Artecoll than for Control in each treatment area. Mean investigator ratings of Artecoll were roughly at the "very successful" level at all follow-up points. Mean investigator ratings of success for Artecoll treatment were in the "very successful" range at all follow-up points while less successful for Control at months three and six.

Table 8.**Investigator ratings of success for each treatment area at each follow-up time**

Time (months)	Treatment Area	Artecoll					Control				
		N	Mean	Std. Dev.	Std. Err.	Mean Rank	N	Mean	Std. Dev.	Std. Err.	Mean Rank
1	Glabellar Folds	68	1.93	0.94	0.11	74.82	79	1.91	1.00	0.11	73.30
	Nasolabial Folds	93	1.99	0.89	0.09	92.89	93	2.06	1.03	0.11	94.11
	Upper Lip Lines	61	1.88	0.82	0.11	55.49	54	2.02	0.88	0.12	60.83
	Mouth Corners	74	2.00	0.97	0.11	66.91	77	2.55	1.28	0.15	84.73
3	Glabellar Folds	67	2.02	1.00	0.12	61.51	74	2.68	1.40	0.16	79.59
	Nasolabial Folds	89	1.90	0.87	0.09	68.08	89	3.07	1.41	0.15	110.92
	Upper Lip Lines	58	2.04	0.90	0.12	43.58	51	3.11	1.39	0.20	67.99
	Mouth Corners	68	2.08	0.94	0.11	51.85	76	3.38	1.34	0.15	90.97
6	Glabellar Folds	74	2.06	1.07	0.12	57.91	82	3.43	1.51	0.17	97.09
	Nasolabial Folds	97	1.73	0.69	0.07	58.87	96	4.05	1.32	0.13	135.53
	Upper Lip Lines	60	1.98	0.93	0.12	36.76	54	4.13	1.28	0.17	80.55
	Mouth Corners	73	2.19	0.98	0.12	48.95	81	4.09	1.32	0.15	103.23

Figure 1. Mean investigator success ratings



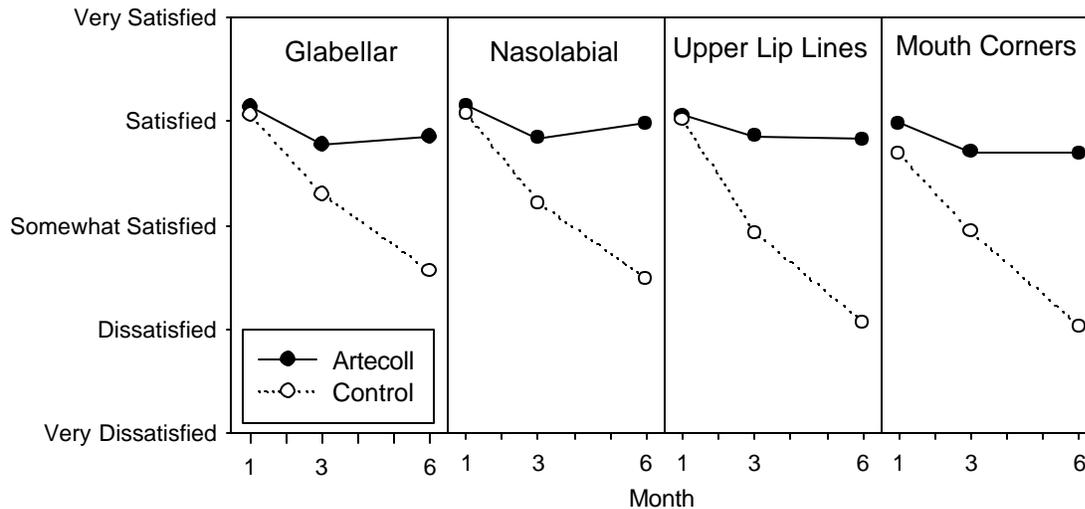
To determine subject assessment of satisfaction with respect to the subject's personal expectations, the subject's assessment (masked) of satisfaction was rated using a five-point scale, with 1 corresponding to "very satisfied" and 5 to "very dissatisfied," at one, three and six months post-treatment. Descriptive statistics were used to characterize the satisfaction ratings. Table 9 summarizes the findings and the means are illustrated in Figure 2. By month three, more "satisfied" ratings were obtained for Artecoll than for the established Control implants in each treatment area. Mean satisfaction ratings for Artecoll were roughly at the "satisfied" level at all follow-up points while subjects showed lower satisfaction with Control at months three and six.

Table 9.

Subject ratings of satisfaction for each treatment area at each follow-up point

Time (months)	Treatment Area	Artecoll					Control				
		N	Mean	Std. Dev.	Std. Err.	Mean Rank	N	Mean	Std. Dev.	Std. Err.	Mean Rank
1	Glabellar Folds	70	1.92	0.99	0.12	73.75	82	2.02	0.98	0.11	78.85
	Nasolabial Folds	95	1.88	1.04	0.11	91.85	98	2.02	0.96	0.10	101.99
	Upper Lip Lines	64	1.96	1.07	0.13	59.34	57	2.07	1.09	0.14	62.86
	Mouth Corners	77	2.08	0.98	0.11	72.71	83	2.44	1.12	0.12	87.72
3	Glabellar Folds	64	2.20	1.15	0.14	61.30	73	2.72	1.38	0.16	75.75
	Nasolabial Folds	88	2.14	1.08	0.12	76.16	89	2.81	1.34	0.14	101.70
	Upper Lip Lines	55	2.13	1.07	0.14	42.64	50	3.09	1.34	0.19	64.40
	Mouth Corners	66	2.24	1.06	0.13	57.53	75	3.05	1.31	0.15	82.85
6	Glabellar Folds	73	2.15	1.19	0.14	57.00	83	3.45	1.34	0.15	97.41
	Nasolabial Folds	97	2.03	0.95	0.10	68.96	99	3.50	1.33	0.13	127.44
	Upper Lip Lines	59	2.16	1.13	0.15	39.42	57	3.91	1.25	0.17	78.25
	Mouth Corners	74	2.32	1.04	0.12	50.82	84	3.98	1.18	0.13	104.77

Figure 2. Mean subject satisfaction ratings



5. 12-month Efficacy Data

Although the study design did not afford a controlled comparison at twelve months, the Artecoll efficacy (improvement over pre-treatment values) at twelve months was compared to the Control group efficacy at six months. Non-parametric Mann-Whitney U tests were utilized for these comparisons. The results for masked observer FFA scale ratings are summarized in Table 10. The Nasolabial fold area showed significantly greater improvement for Artecoll at twelve months than for Control at six months. No differences were significant for the other treatment areas. These results concur with the comparison of the treatments at six months.

Table 10.**Comparison of improvement in masked observer FFA Scale ratings twelve months following Artecoll treatment with improvement six months following Control treatment**

Treatment Area	Artecoll 12-Month Improvement				Control 6-Month Improvement				U	p
	N	Mean	Std. Dev.	Std. Err.	N	Mean	Std. Dev.	Std. Err.		
Glabellar Folds	59	0.27	0.85	0.11	79	0.32	0.68	0.08	2303	.906
Nasolabial Folds	79	0.98	0.93	0.10	91	-0.00	0.90	0.09	1459	<.001
Upper Lip Lines	46	0.19	0.71	0.10	50	0.22	0.48	0.07	1070.5	.559
Mouth Corners	58	-0.01	0.87	0.11	79	0.09	0.74	0.08	2078	.353

Investigator FFA Scale ratings were used for similar comparisons. Improvement in the Artecoll group after twelve months was significantly greater than improvement in the established Control group after six months for all fold sites, as summarized in Table 11.

Table 11.**Comparison of improvement in investigator FFA Scale ratings twelve months following Artecoll treatment with improvement six months following Control treatment**

Treatment Area	Artecoll 12-Month Improvement				Control 6-Month Improvement				U	p
	N	Mean	Std. Dev.	Std. Err.	N	Mean	Std. Dev.	Std. Err.		
Glabellar Folds	69	1.29	1.01	0.12	82	0.46	1.04	0.12	1505	<.001
Nasolabial Folds	91	2.07	1.06	0.11	96	0.01	0.86	0.09	566.5	<.001
Upper Lip Lines	58	1.41	1.02	0.13	54	0.05	0.98	0.13	507.5	<.001
Mouth Corners	72	1.51	1.23	1.14	80	0.02	0.83	0.09	766.5	<.001

Investigator success ratings and subject satisfaction ratings for the Artecoll group at twelve months were compared to the ratings for the Control group at six months. Lower means indicate greater success in investigator ratings and greater satisfaction in patient ratings. The results are summarized in Tables 12 and 13. For all fold sites, investigators rated the Artecoll treatment at twelve months as significantly more successful than the control treatment at six months. Likewise, patients ratings indicated greater satisfaction with the Artecoll treatment at twelve months than with the Control treatment at six months.

Table 12.**Comparison of investigator success ratings twelve months following Artecoll treatment with success ratings six months following Control treatment**

Treatment Area	Artecoll 12-Months				Control 6-Months				U	p
	N	Mean	Std. Dev.	Std. Err.	N	Mean	Std. Dev.	Std. Err.		
Glabellar Folds	70	2.03	1.13	0.13	82	3.43	1.51	0.17	1403.5	<.001
Nasolabial Folds	92	1.64	0.74	0.08	96	4.05	1.32	0.13	853	<.001
Upper Lip Lines	58	2.15	0.98	0.13	54	4.13	1.28	0.17	449	<.001
Mouth Corners	73	2.08	1.01	0.12	81	4.09	1.32	0.15	842.5	<.001

Table 13.**Comparison of subject satisfaction ratings twelve months following Artecoll treatment with satisfaction six months following Control treatment**

Treatment Area	Artecoll 12-Months				Control 6-Months				U	p
	N	Mean	Std. Dev.	Std. Err.	N	Mean	Std. Dev.	Std. Err.		
Glabellar Folds	70	2.11	1.14	0.14	82	3.44	1.35	0.15	1346.5	<.001
Nasolabial Folds	92	2.00	1.08	0.11	96	3.52	1.37	0.14	1813.5	<.001
Upper Lip Lines	58	2.17	1.12	0.15	54	3.94	1.28	0.17	516	<.001
Mouth Corners	73	2.25	1.15	0.13	81	3.97	1.19	0.13	967.5	<.001

6. Device failures and replacements

One device failure, defined as an adverse event requiring removal of the implant was recorded for Artecoll in the controlled, randomized trial. Two such events were recorded for Control implant in the controlled, randomized trial.

B. Open Label Trial

1. Study design

The study was an open label multi-center clinical trial conducted under conditional IDE approval. No Control group was included. 157 subjects were treated and 1-year safety information was obtained for 126 subjects. Results are shown in Table 2, above.

2. Device failures and replacements

Two device failures, defined as an adverse event requiring removal of the implant were recorded for Artecoll in the open label trial.

C. Additional Studies

Two previous clinical studies on effectiveness and adverse events had been conducted in Frankfurt, Germany and published in 1995 (5) and 1998 (6). In the first prospective study, 118 subjects with 200 implantation sites were followed for up to two years and the results evaluated clinically and with the help of an anonymous questionnaire. Overall, 89.5 % of the subjects were pleased or satisfied with the result; 10.5 % did not see a difference or had experienced a side effect.

The second clinical study contained the evaluation of 515 questionnaires sent out to patients 2 years after the implantation of Artecoll. Satisfaction with the treatment was rated "very good" in 29%, "good" in 38%, "satisfactory" in 23%, and "no difference" in 8% of the patients. The question, "would you repeat the treatment again?" was answered by 91% of the patients with "yes". The overall complication rate was 3%.

X. Conclusions Drawn from the Studies

A. Risk/benefit analysis

The risk of treatment with Artecoll, as defined by number of adverse events, has been shown to be equivalent to or less than that of currently marketed Control implants. The benefit of treatment with Artecoll, as defined by degree of improvement, has been shown to be equivalent to or better than Control implants. Therefore, the risk/benefit ratio for Artecoll is equivalent to or better than that of the established Control implants.

B. Safety

The number of adverse events was lower for the Artecoll group than for the Control group. Additionally, the number of adverse events classified as severe was also lower. When comparing total number of subject with adverse events, there was no significant difference in adverse events rates between Artecoll and the Control. The pre-clinical and clinical data provide a reasonable assurance that Artecoll is safe when used in accordance with labeling.

C. Effectiveness

Artecoll has been shown to provide statistically better improvement than Control when used for the correction of Nasolabial Folds. Artecoll has also been shown to provide improvement that is not significantly different than that provided by the Control implants when used for the correction of Glabellar Folds, Upper Lip Lines, and Mouth Corners. Improvement in investigator FFA Scale ratings with Artecoll treatment was superior to Control treatment for all treatment areas. Investigator success ratings and subject satisfaction ratings for Artecoll treatment were superior to Control treatment for all treatment areas. Analyses of potential confounds and other factors were supportive of study validity.

The overall conclusion from the studies is that Artecoll is a safe treatment that is equivalent to or better than the established Control treatment in efficacy.

XI. References

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XII. Panel Recommendations (To be completed by FDA)

XIII. CDRH Decision (To be completed by FDA)

XIV. Approval Specifications (To be completed by FDA)