SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. General Information

DEVICE GENERIC NAME:	Dermal implant for aesthetic use
DEVICE TRADE NAME:	ArteFill
APPLICANT:	ARTES MEDICAL, INC. 5870 Pacific Center Blvd. San Diego, CA. 92121 USA
PREMARKET APPROVAL APPLICATION (PMA):	P020012
DATE OF PANEL RECOMMENDATION:	February 28, 2003
DATE OF NOTICE OF APPROVAL TO THE APPLICANT:	October 27, 2006

II. INTENDED USE / INDICATIONS FOR USE

ArteFill is indicated for the correction of nasolabial folds.

III. CONTRAINDICATIONS

- ArteFill is contraindicated for patients displaying a positive response to the required ArteFill Skin Test. Refer to ArteFill Skin Test Instructions for Use for complete instructions for administration and evaluation of the skin test.

- ArteFill is contraindicated for patients with severe allergies manifested by a history of anaphylaxis, or history or presence of multiple severe allergies.

- ArteFill contains lidocaine and is contraindicated for patients with known lidocaine hypersensitivity.

- ArteFill contains bovine collagen and is contraindicated for 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 ArteFill.

- ArteFill is contraindicated for patients undergoing or planning to undergo desensitization injections to meat products, as these injections can contain bovine collagen.

- ArteFill is contraindicated for use in lip augmentation and injection into the vermilion or the wet mucosa of the lip

- ArteFill should not be used in patients with known susceptibility to keloid formation or hypertrophic scarring.

IV. WARNINGS AND PRECAUTIONS

Warnings and precautions can be found in the ArteFill physician's labeling.

V. DEVICE DESCRIPTION

ArteFill is an implant composed of non-resorbable polymethylmethacrylate (PMMA) microspheres, 30 to 50 microns in diameter, suspended in a water-based carrier gel composed of 3.5% bovine collagen, 92.6% buffered, isotonic water for injection, 0.3% lidocaine hydrochloride, 2.7% phosphate buffer, and 0.9% sodium chloride.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternatives to ArteFill treatment include injection of dermal fillers composed of bovine or human collagens and hyaluronic acid as well as treatment with botulinum toxin or laser resurfacing.

VII. MARKETING HISTORY

ArteFill is not marketed outside of the United States.

VIII. ADVERSE EFFECTS

All adverse events (AEs), including those attributed and not attributed to treatment, reported in ArteFill or Control subjects at an incidence of 1% or greater in US studies are presented Table 1 in descending order according to frequency in the ArteFill group.

Table 1 - Adverse Events Reported at an Incidence of 1% or Greater in US Clinical Trials of ArteFill

Event	Number of Events (Events/subjects treated, %)		
	ArteFill[1] n = 285	ArteFill[2] n = 106	Control[3,4] n = 123
Lumpiness at injection area more than one month after injection	13 (4.6)		4 (3.3)
Persistent swelling or redness	10 (3.5)	3 (2.8)	13 (10.6)
Increased sensitivity	5 (1.8)	2 (1.9)	
Rash, itching more than 48 hours after injection	4 (1.4)		2 (1.6)
Sensitization reactions			6 (4.9)
Abscess			3 (2.4)
Visibility of puncture area			2 (1.6)

[1]128 ArteFill subjects in the controlled study and 157 subjects in an open label study, who were followed for 1 year after implantation.

[2]106 Control subjects who received ArteFill in the cross-over arm of the controlled study and were followed for 6 months after implantation.

[3] A commercially available collagen implant

[4]123 subjects who received the Control treatment in the controlled study and were followed for 6 months after implantation.

No systemic adverse events were reported at an incidence of 1% or greater. One severe adverse event (granuloma or enlargement of the implant) and 14 moderate adverse events (persistent swelling or redness, lumpiness at injection site more than 1 month after injection, blurred vision, flu-like symptoms, abscess, granuloma or enlargement of the implant, alopecia areata) were reported for ArteFill subjects. Nine severe adverse events (lumpiness at injection site more than 1 month after injection, abscess, infection, granuloma or enlargement of the implant, sensitization reactions, increased sensitivity, persistent swelling or redness), and 12 moderate adverse events (persistent swelling or redness, rash, itching more than 48 hours after injection, sensitization reactions, lumpiness at injection site more than 1 month after injection, visibility of the puncture area, abscess) were reported for Control subjects.

Local adverse events reported in ArteFill subjects at an incidence of less than 1% in US studies, whether or not they were determined to be related to the implant, were sensitization reactions, abscess, visibility of the puncture area, blurred vision, flu-like symptoms, recurrence of existing herpes labialis, granuloma or enlargement of the implant, acneiform lesions, occasional tenderness, redness and visible capillaries, alopecia areata, and dry skin. Systemic adverse events reported at an incidence of less than 1% were mild chest congestion and fainting. One subject was diagnosed with breast cancer, determined by the investigator not to be related to the implant.

For Control subjects, local adverse events reported at an incidence of less than 1%, whether or not they were determined to be related to the implant, were increased

sensitivity, flu-like symptoms, granuloma or enlargement of the implant, infection, and acneiform reaction. One subject died of trauma unrelated to the implant.

The following is a summary of the reported duration of adverse events lasting longer than 2 weeks in ArteFill subjects (n=391 subjects) in US studies: lumpiness at injection site more than 1 month after injection (n=12 events), duration varied from 4 weeks to unresolved at 26 weeks; persistent swelling or redness (n=8 events), duration varied from 5 weeks to unresolved at 26 weeks; increased sensitivity (n=7 events), duration varied from 4 weeks to unresolved at 26 weeks; rash and itching (n=2 events), duration varied from 3 weeks to 6 weeks; sensitization reactions (n=2 events), duration varied from 19 weeks to unresolved at 26 weeks; visibility of the puncture site (n=1 event), duration was 13 weeks; granuloma or enlargement of the implant (n=4 events), duration varied from 10 weeks to unresolved at 26 weeks; other local complications (n=5 events), duration was unresolved at 26 weeks. One subject suffered from breast cancer unrelated to the implant.

Reported duration of adverse events lasting longer than 2 weeks in Control subjects (n=123 subjects): lumpiness at injection site more than 1 month after injection (n=2 events), duration varied from 13 weeks to unresolved at 26 weeks; persistent swelling or redness (n=12 events), duration varied from 7 weeks to unresolved at 26 weeks; increased sensitivity (n=1 event), duration was unresolved at 26 weeks; rash and itching (n=2 events), duration was unresolved at 26 weeks; sensitization reactions (n=4 events), duration varied from 7 weeks to unresolved at 26 weeks; abscess (n=2 events), durations were unresolved at 26 weeks; visibility of the puncture site (n=1 event), duration was unresolved at 26 weeks; granuloma or enlargement of the implant (n=1 event), duration was unresolved at 26 weeks; flu-like symptoms (n=1 event), duration was unresolved at 26 weeks. One subject died from an accident unrelated to the implant.

Among the 391 subjects treated with ArteFill, adverse events with reported onset dates 3 months or more after treatment were lumpiness at the injection site (6), rash and itching (3), sensitization reaction (2), increased sensitivity (2), persistent swelling and redness (1), granuloma or granulomatous inflammation (1), alopecia areata (1), visibility of the puncture site (1), and redness and visible capillaries near the area of injection (1).

Among the 123 Control subjects, adverse events with reported onset dates 3 months or more after treatment were abscess (1), infection (1), lumpiness (1), acneiform reaction (1), flu-like symptoms (1), persistent swelling or redness (1), and trauma fatality not related to the implant (1).

- *Potential Adverse Events*

Clinical experience with similar products used outside United States suggests that the following adverse events that did not occur in US clinical trials might occur: hypersensitivity to bovine collagen, severe anaphylaxis reaction, nodule formation requiring excision or drug treatment and leakage of the device or fluid from the injection site.

IX. SUMMARY OF PRECLINICAL STUDIES

In support of the safety and biocompatibility of ArteFill, the sponsor submitted the following preclinical studies of: 1) the biocompatibility of the collagen / lidocaine carrier and 2) the comparability testing of the commercial and investigational collagens and 3) the ArteFill final product (Table 3).

Table 2 – Summary of Non-clinical Studies:
ISO 10993 Biocompatibility Studies with Collagen/Lidocaine Carrier

Test	Results/Conclusions
Cytotoxicity Agarose Overlay Method (Liquid) – L-929	There were no signs of cytotoxicity or lysis
Hemocompatibility In Vitro – Direct Contact Method	There were no signs of hemolysis
Systemic Toxicity (Acute) Intraperitoneal – Direct dosing mice – 3 - 7 days	There were no signs of acute systemic toxicity. There was no weight loss, no mortality or abnormal appearance in relation to the controls
Irritation (Intracutaneous toxicity) Intracutaneous – rabbit 24-72 hrs	The Primary Irritation Index for the test sample was 0.5 (slight)
Implantation (Local Tolerance) ISO muscle Implantation – rabbits – 7 days with histology	Gross and microscopic observations of the test article were equivalent to the non-irritant controls
Genotoxicity Bacterial Reverse Mutation Assay Chromosomal Aberration Assay Mouse Micronucleus Assay	There was no evidence of gene mutation in the three genotoxicity studies conducted
Sensitization Dermal – Maximization in Guinea Pigs	There were no signs of sensitization and the sample was considered to be a non-irritant in this assay
Pyrogenicity (LAL method)	The LAL test was less than 5 EU/mL

Table 3 - Comparability Tests of
Commercial and Investigational Collagens

Test	Results/Conclusions
Hydroxyproline Content (Collagen Content)	Hydroxyproline content of both collagens (0.40% – 0.48%) is comparable and consistent with the published literature
Amino Acid Composition	The amino acid composition of both collagens (i.e., (Gly~34%, Pro~13%, Hypro~9%, Tyr ~0.1%, Cys<0.1%) is comparable and consistent with the published literature
Pepsin Determination	At a detection level of 0.1%, no pepsin was detected in either collagen material
Bovine Serum Album Determination	At a detection level of 1 μg/mL, no BSA was detected in either collagen material
USP Heavy Metals	The results were comparable for both collagen formulations
pH Measurement	The pH values measured (i.e., 6.9 – 7.0) for both

	collagen formulations were comparable
Carbohydrate Content	Analyses demonstrated that the carbohydrate content of both collagen formulations (i.e., 0.35% – 0.45%) were similar
Lidocaine Content	Analyses demonstrated that the lidocaine content of both collagen formulations were similar (i.e., 0.25 - 0.35%)
Opacity @ OD^{405nm}	The results obtained with both collagen formulations were comparable
Residue on Ignition	The results observed with both collagen formulations (i.e., 4.07% – 4.39%) were comparable
Extrusion Test	The results observed with both collagen formulations (i.e., 24.1 – 26.6N) were comparable
SDS-PAGE Analysis	The banding patterns were comparable with greater than 95% of the intensity being the α, β, γ bands of collagen
Lipid Content (crude fat)	The lipid content of both collagen formulations (i.e., 0.05% - 0.08%) were similar
Determination of the Percent Soluble and Denatured Protein	Results were comparable for both collagen formulations
Type I, II, III, and IV Collagen (ELISA)	At a detection limit of 1 ug/ml, no Types II, III and IV collagen were observed in either formulations
Type Collagen – Interrupted Electrophoresis	No Type III collagen was detected in either collagen formulation

Table 4 – Summary of Preclinical Studies with ArteFill

Test	Results/Conclusions
Cytotoxicity Agarose Overlay Method – L929 fibroblast	Non-cytotoxic (no signs of cytotoxicity or lysis)
Genotoxicity Bacterial Reverse Mutation Assay	There was no evidence of gene mutation in the genotoxicity study conducted
Sensitization Dermal – Maximization in Guinea Pigs	There were no signs of delayed dermal contact sensitization in this assay
Implantation (Local Tolerance) ISO muscle Implantation – rabbits – 7 days with histology	Gross and microscopic observations of the test article were equivalent to non-irritant controls
Implantation Subdermal and intramuscular injections of cross-linked collagen, hyaluronic acid (HA), silicone oil, PMMA microspheres (4-40 microns), PMMA microspheres in hyaluronic acid (40 microns), polylactic acid (PLA) microspheres (40 microns), dextran microspheres (40 microns), Trisacryl-gelatin microspheres, silicone particles, pyrrolytic carbon coated with ZrO beads (212 – 500 microns) suspended in 3% beta glucan and polyacrylamide (PAA) – mice - 1, 3, 6 and 9 months	No migration or transportation of any of injected particular filler substance to lymph nodes or filter organs detected. Collagen and HA were phagocytosized at 6 and 9 months, respectively. PLA microspheres caused a mild inflammatory response and disappeared by 4 months. Dextran microspheres caused a pronounced foreign body response and disappeared at 8 months. Silicone caused the most pronounced foreign body reaction with a considerable amount of giant cell-persistence. PAA was well tolerated, but disappeared at 5 months. Trisacryl-gelatin microspheres caused little foreign body reaction, but were absorbed from the skin by 6 months. Polyvinylhydroxide and PMMA microspheres were well tolerated and stable over 9 months
In vitro phagocytosis – PLA and PMMA microspheres (4.3 – 72 microns) were incubated with U-937 macrophages, XS 106 and XS 52 Langerhans cells, and HaCaT keratinocytes	U-937 macrophages, keratinocytes and Langerhans cells phagocytosized PMMA microspheres smaller than 20 microns. Microspheres greater in size than 20 microns were not ingested by cells
Syringe leak – Tests of the seal between the syringe tip and the syringe cap	Pre-filled syringes (n=12) held a pressure of 20 pounds / in^2 for more than 5 minutes without a decrease greater than 1 PSI
Extrusion force – The plunger force required to expel 0.5 ml of ArteFill through a 27 gauge needle from a standard 1.0 ml syringe	The average force of 3.1 lbs (n= 3 lots) was measured
Shelf-life testing at 4C and 20C	The sterility, visual appearance and homogeneity of ArteFill indicated that an expiration date of 18 months is appropriate

X. SUMMARY OF CLINICAL STUDIES

The following is a summary of the pivotal study i.e., "Evaluation of ArteFill PMMA Microspheres in 3.5% Collagen for Soft Tissue Augmentation". At the conclusion of this description is a brief summary of the preliminary study (i.e., "Open Label Evaluation of ArteFill PMMA Microspheres in 3.5% Collagen for Soft Tissue Augmentation").

Study Design:
The clinical trial was a prospective, multi-center, randomized, double-masked trial. Subjects were randomized (1:1) to either ArteFill or a commercially available collagen implant. Patients were implanted into 1 or more of 4 facial areas (i.e., Glabellar Folds, Nasolabial Folds, Upper Lip lines and/or Mouth Corners) as required. Blood samples were drawn prior to treatment and at 4 and 12 weeks to evaluate immune response against ArteFill. At 2 week intervals touch-up treatments were allowed. Effectiveness was studied at 1, 3 and 6 months after the last ArteFill or control injection. Safety evaluations were performed at each study visit, including the 12-month follow-up visit for the ArteFill group.

- *Cross-over study arm:*

Patients who received the control treatment were offered 6 months after the last injection, the opportunity to receive ArteFill treatment. These patients were followed for 6 months after the last ArteFill injection.

Primary Endpoints

- *Effectiveness*

The primary effectiveness endpoint was a comparison of the cosmetic correction provided by ArteFill and Control treatments at the end of a 6 month period after injection, evaluated by means of a validated facial fold assessment scale (FFA Scale) using standardized photographs as reference. The numerical values for FFA Scale were: zero – no folds; one – folds just perceptible (i.e., ~0.1 mm); two – shallow folds with some defined edges (i.e., ~0.2 mm); three – moderately deep folds with some well-defined edges (i.e., ~0.5 mm); four – deep folds with most edges well-defined and some redundant folds (i.e., ~1.0 mm) and five – very deep folds with most edges well-defined and some redundant folds (i.e., ~2.0 mm). Comparisons to the reference photos were made at pre-treatment and at each follow-up visit.

- *Safety*

Adverse outcomes were evaluated by comparing the incidence and severity of clinical events during 1, 3, 6 and 12 month study visits after treatment completion.

Secondary Endpoints:

The secondary objectives of the study were:

- *Determination of product effectiveness at 1 and 3 months after treatment via a masked assessment of patient photographs* via the validated facial fold assessment scale.

- *Determination of product effectiveness at 1, 3 and 6 months after treatment by the treating (unmasked) investigator.* The treating investigators' assessments of success were rated using a five-point scale with 1 corresponding to "completely successful" and 5 "not to all successful".

- *Determination of product effectiveness at 1, 3 and 6 months after treatment by the patient self-assessment.* The subject's assessment was rated using a 5 point scale with 1 corresponding to "very satisfied" and 5 to "very dissatisfied"

Patient Enrollment

- *Selected Study Population Criteria*
  - Men or women 18 years of age or older
  - Negative skin test to collagen test implant
  - One or more of the following anatomical sites requiring correction: a) glabellar folds (right and/or left side), b) nasolabial folds (right and/or left side), c) perioral lines (right and/or left side) and d) depressed corners of the mouth (right or left side)
  - If female and of childbearing age, had a negative pregnancy test
  - The absence of a history of autoimmune disorders
  - The absence of atrophic skin disease
  - The absence of any allergy to collagen
  - The lack of susceptibility to keloid formation
  - Patients not receiving UV therapy
  - No treatment with other wrinkle therapies within the past 6 months at any implantation site
  - Skin not determined to be thin or flaccid skin
  - The absence of cellulitis or infection at the implant site
  - Patients who did not use or intend to use products containing a-hydroxy acids or Retin A at any later time during the study
  - Patients who were not considering additional cosmetic treatments to the injection site at any later time during the study
  - The absence of lidocaine hypersensitivity
  - The absence of a history of dietary beef allergy or undergoing or planning to undergo desensitization to meat products
  - The absence of severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies
  - No use of substances which reduce coagulation (e.g., aspirin and non-steroidal anti-inflammatory drugs) within the last 4 weeks before treatment

- No patients who received cancer chemotherapy agents or corticosteroids within the last 3 months
- The absence of an anti-bovine collagen serum IgG outside the normal range at baseline screening
- The absence of a positive or two equivocal skin tests

- *Patient Accounting*

369 subjects were screened for the study. 84 were ineligible and 285 were enrolled in the study. After blood and skin tests, an additional 30 subjects were removed or withdrew from the study. 9/30 subjects (5 ArteFill and 4 control) had an abnormal baseline serum, IgG level, six (0 ArteFill, 6 control) had positive skin tests, 7 withdrew voluntarily, 6 did not return for treatment and 2 were withdrawn because of screening errors.

A total of 251 subjects were treated (128 ArteFill, 123 controls). Of the 251 subjects treated, 223 returned for the 1 month follow-up, 4 subjects were lost to follow-up at this point and 24 missed the 1 month follow-up evaluation. Of the remaining 247 subjects, 215 returned for the 3 month follow.

Table 5 – Patient Accounting

Visit	ArteFill No. (%)	Control No.(%)	Total
Enrolled & randomized	141	144	285
Serum IgG	141	140	281
Other screening issues	128	123	251
Treated	**128**	**123**	**251**
1-month evaluation	112/128 (87.5%)	111/123 (90.0%)	223
3-month evaluation	106/128 (82.8%)	109/123 (88.6%)	215
6-month evaluation	113/128 (88.3%)	116/123 (94.3%)	229
12 month evaluation	111/128 (86.7%)	N/A	N/A

- *Listing of Study Centers and Patient Treatment Group Assignment:*

The study enrolled and treated subjects at eight centers.

Table 6 - Patient Enrollment by Study Site

Center	Investigator	Address	ArteFill Pts.	Control Pts.	Total
1	Peter Rullan Cole B. Willoughby	Dermatology Inst. Chula Vista, CA	13	15	**28**
2	Matthew Gleason Thomas Vecchione	Plast Surg Med Clin. San Diego, CA	14	14	**28**
3	Carl Berner	Bellevue, WA	21	18	**39**
4	Mariano Busso	Miami, FL	20	20	**40**
5	Millard Thaler Zeena Ubogy	Papillon Cos. Der. Cent. Mesa, AZ	21	17	**38**

6	Ralph Holmes Steven Cohen	FACES San Diego, CA	17	18	**35**
7	James Romano	San Francisco, CA	8	9	**17**
8	Douglas Hamilton	Woodland Hills, CA	14	12	**26**
Total			**128**	**123**	**251**

- *Baseline Demographics:*

The study population was composed of twenty-two men and 229 women between the ages of 28 and 82 with an overall mean age was 52.2 years.

Table 7 - Subjects and Baseline Characteristics

Demographic Characteristic	ArteFill (n = 128)	Control (n = 123)
Gender		
Male	11 (8.6%)	11 (8.9%)
Female	117 (91.4%)	112 (91.1%)
Age, years		
Mean	53.2	51.2
Range	28-82	29-78
Ethnicity		
(i) Caucasian	100 (78.1%)	101 (82.1%)
(ii) Hispanic	21 (16.4%)	20 (16.3%)
Asian	1 (0.8%)	1 (0.8%)
Other[1]	6 (4.7%)	1 (0.8%)
Facial Area Treated		
Nasolabial Folds	108 (84.4%)	104 (84.6%)
Wrinkle Severity	**Mean Value**	**Mean Value**
Nasolabial Folds[2]	1.74	1.45

1. "Other" ethnicities, as reported by ArteFill subjects, were Mexican/Greek/English, Italian, Hispanic/Irish, American Indian, Native American, and Middle Eastern. "Other" ethnicity, as reported by a control subject, was Persian.

2. Subjects in the ArteFill treated group had a higher baseline fold severity than those in the control group. The difference was statistically significant (p=0.039).

The majority of the demographic factors were the same for both treatment arms (e.g., gender, race, and age). The only demographic factor approaching a statistically significant

difference was pretreatment nasolabial fold severity as determined by the masked evaluators of photographs. The study population was largely patients with mild/moderate wrinkles as illustrated by the masked pre-treatment FFA scale ratings for wrinkle severity shown above. The numerical values for FFA Scale were: zero – no folds; one – folds just perceptible (i.e., ~0.1 mm); two – shallow folds with some defined edges (i.e., ~0.2 mm); three – moderately deep folds with some well-defined edges (i.e., ~0.5 mm); four – deep folds with most edges well-defined and some redundant folds (i.e., ~1.0 mm) and five – very deep folds with most edges well-defined and some redundant folds (i.e., ~2.0 mm).

- *Number of Treatment Sessions* – are displayed below. No statistically significant differences were observed.

Table 8 – Number of Treatment Sessions

Area	Treatment	N	Mean (sessions)
Nasolabial Folds	ArteFill	108	2.28
	Control	104	2.18

- *Quantity of Product Used* - is displayed below.

Table 9 – Quantity of Product Used

Area	Treatment	N	Mean (cc)
Nasolabial Folds	ArteFill	108	0.82
	Control	104	1.46

Effectiveness Analysis:

The changes in masked observer FFA Scale ratings from pre-treatment to six months are presented below by treatment group. The outcome was statistically significant.

Table 10 – Primary Effectiveness Outcomes

Treatment Area	Treatment	N	Mean	Std.Dev.	Std. Err.	Mean Rank	Mann-Whitney U Test	
							U	P
Nasolabial Folds	ArteFill	92	0.77	0.87	0.09	113.8	2176.5	<.001
	Control	91	0.00	0.90	0.09	69.9		

Secondary Effectiveness Analyses

- *Masked Photograph Assessments at 1 and 3 Months After Treatment*
    - The mean difference in pre-treatment to 1 month post treatment scores not show a statistically significant difference between Control and ArteFill treatments of nasolabial folds.
    - The mean difference between pretreatment and 3 months post implant scores was statistically significant improvement for ArteFill (0.81 points) treatment

when compared to Control (0.15 points) in the treatment of nasolabial folds (p-value < 0.001).

- *Treating (Unmasked) Investigator Ratings of Treatment Success*

The mean nasolabial folds ratings for ArteFill treatment (by the treating investigator) were "very successful" at 1, 3 and 6 months after treatment. Ratings for Control Treatments were "very successful" at 1 month, "moderately successful" at 3 months and "somewhat successful" at 6 months.

- *FFA Scale Assessments by the Treating (unmasked) Investigator*

    - At 1 month after treatment the mean improvement for nasolabial fold wrinkle severity was not statistically significantly different.

    - The assessed difference between pretreatment and three months post-treatment on the FFA scale for treating investigators was statistically significant (p-value < 0.001) for ArteFill treatment of nasolabial folds when compared to Control treatment.

    - At 6 months after device implantation the mean improvement in the FFA scale assessments of nasolabial folds by treating investigators was statistically significantly (p-value < 0.001) when comparing ArteFill and Control treatments.

- *Subject Ratings*

Similar to the treating investigator ratings, the mean ratings for ArteFill treatment of nasolabial folds were "satisfied" at 1, 3 and 6 months after treatment. Ratings for Control Treatment of nasolabial folds were "satisfied" at 1 month. By month 3 numerically superior, but not statistically significant increases in "satisfactory" ratings were observed for ArteFill treatment compared to Control.

Other analyses -

- *Correlation between patient demographics to Patient Treatment*

The following categories were examined to determine if a correlation existed between demographic parameters and treatment outcome: age (i.e., < 65 or > 65 y.o.), gender, and pretreatment wrinkle severity (i.e., greater than or less then two on the FFA scale). Tests for differences in improvement on masked observer FFA ratings were made using 3-way main effects analyses of variance (ANOVA). In this analysis only pre-treatment severity of nasolabial folds was found to be a statistically significant contributor. A series of supplemental analyses were conducted to determine whether or not treatment effects differed between the two study arms once this difference in initial wrinkle severity was accounted for. An analysis of covariance (ANCOVA) of nasolabial fold improvement

was conducted using pretreatment nasolabial fold severity as the covariate. The results demonstrate that ArteFill maintained its treatment superiority after adjustment for inequalities in baseline wrinkle severity.

- *Effectiveness of masking*

Subjects were asked to guess which treatment group they were assigned to at each follow-up visit. At 1 month after treatment the guess rates did not differ from those predicted by chance. At 3 and 6 months after treatment, 75% of the subjects correctly guessed their treatment assignment.

- *FFA Scale Masked Observer Rater reliability*

FFA scale ratings were pooled among the 3 masked observers and were computed using intraclass correlation. A correlation greater than 0.8 was obtained in each case.

- *Correlation between Masked observer and investigator ratings*

The masked observer FFA ratings correlated about 0.5 with the investigator FFA ratings (via Spearman's rank-order correlation), about 0.3 with investigator success ratings and about 0.2 with subject satisfaction ratings. Investigator's FFA ratings were generally more severe than the masked observer ratings. This was also observed on the pretreatment ratings.

Device Safety

- *Adverse Events*

The reported adverse events are presented in Section VIII.

- *Collagen Immunoreactivity*

The immunogenicity of the collagen component was evaluated in the randomized study. All patients were required to have a skin test prior to being considered for injection with ArteFill. In the randomized trial, 128 patients received ArteFill Skin Test as their first injection. The 123 patients in the control group received skin tests for the control collagen. Of the 123 patients in the control group, 106 patients received the ArteFill skin test after 6 months when they elected ArteFill treatment in the cross over study.

- *Results of the skin tests*

In the randomized study there were no positive skin tests in the 128 patients first randomized to ArteFill or the 106 control patients who received ArteFill injections in the cross-over cohort. Of the 141 patents that underwent a control collagen skin test, 6 had a positive skin test and were excluded from the study.

- *Serum IgG*

In the randomized study, 4 ArteFill and 2 control patients were not treated because they displayed abnormal baseline serum IgG levels against bovine collagen during screening. One subject in the ArteFill group transitioned from a normal IgG level before administration of the skin test to a value above the normal range at 1 month after treatment. This patient's IgG levels decreased to the normal range by 3 months after the last treatment. One patient in the control group transition from a normal IgG level before administration of the skin test to a value above the normal range at 1, 3 and 6 months after treatment.

Other Clinical Studies with ArteFill:

- *Open Label Clinical Study with ArteFill*

Prior to initiating the controlled clinical study in the United States, the sponsor performed an open label study of 157 subjects. Patients received ArteFill injections for correction of soft tissue contours of the face. Patients were monitored at 3, 6 and 12 months post implant. FDA reviewed the study results for device safety, but not effectiveness because the study was not controlled. All of the adverse events (treatment-related and non-treatment-related) reported are presented in Section VIII.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

The submitted clinical data provide a reasonable assurance of the safety and effectiveness of ArteFill for the correction of nasolabial folds. The studies demonstrated that:

In the controlled clinical study ArteFill injection provided a statistically significant advantage over control treatment in reducing the severity of nasolabial fold wrinkles at 6 months after completion of treatment. ArteFill is indicated for correction of nasolabial folds, because significant improvement over control treatment at other studied facial locations (i.e., glabellar folds, upper lip lines and mouth corners) was not observed. Improvement over an active control was important in determining ArteFill's intended use because the device is a non-resorbable implant and the effectiveness of the control device at six months post implantation was unknown.

The Panel stated that the proposed indication was too broad. Specific Contraindications should include lip augmentation or treatment of large volume tissue defects.

In the controlled clinical study the incidence of all adverse clinical outcomes was not statistically significantly different for ArteFill and Control patients.

The incidence, severity and types of adverse events observed in an open-label ArteFill study were similar to those reported in the Controlled Clinical Study.

XII. PANEL RECOMMENDATION

On February 28, 2003, the General and Plastic Surgery Devices Panel recommended approval with conditions for Artes Medical's PMA for ArteFill. The conditions of approval included a post approval study for safety of not less than 5 years, a contraindication for lip augmentation, physician training, and a patient educational brochure.

XIII. CDRH ACTION

Inspection of the sponsor's manufacturing facilities was performed from March 29 – April 7, 2006. The facility was found to be in compliance with the device Good Manufacturing Practice regulations on August 3, 2006

After the Panel meeting, FDA completed review of preclinical testing, product manufacturing, additional clinical data and product labeling. In specific:

1) It was determined that a long term Post-Market Approval safety study should be performed. This study will examine the incidence, severity and medical interventions necessary to treat patients who develop granulomas for up to 5 years after implantation.

2) The limited clinical data available for ArteFill use in persons of color was also considered. Through FDA review it was determined that the racial composition of the potential target population for ArteFill treatment may - by its design – practically exclude the vast majority of African American patients that encounter plastic surgery or dermatology consultation. This statement is based on the belief that there is a low probability for nasolabial folds or wrinkles in these patients due to the inherent nature of the African American skin. Because there is also fairly high probability that the use of a transdermally injected material in these patients could lead to an unacceptable incidence of hypertrophic scarring and/or keloid formation (as a direct result of the treatment), FDA determined that a specific clinical study in such patients would not be appropriate. Consequently, the product was contraindicated for patients with a known susceptibility to keloid formation or hypertrophic scarring. In addition, FDA would continue to collect specific adverse event information on this patient population through both the above cited Post Approval Safety Study and voluntary adverse event reporting.

FDA issued an approval order on October 27, 2006.

XIV. Approval Specifications

Directions for Use: See the labeling

Hazard to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Reactions in the labeling

Post Approval Requirements and Restrictions: see the Approval Order.