Executive Clinical Summary
P020012
Artecoll
Artes Medical, Inc.

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PART I

I. Product Description

Artecoll is a suspension of polymethylmethacrylate (PMMA) microspheres in a 3.5% collagen solution.

No changes were made in the final product composition or formulation between or during the Rofil and Artes Medical studies that are described below.

II. Proposed Indications for Use

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

PART II

I. Artes Medical Clinical Study

a. Design

- ?? Prospective, randomized, double-blind, controlled clinical trial
- ?? Compares Artecoll to Zyplast® Implant for correction of:
    1. Nasolabial Folds
    2. Radial Upper Lip Lines
    3. Depressed Mouth Corners
- ?? Compares Artecoll to Zyderm® Implant for correction of Glabellar Folds

b. Inclusion/Exclusion Criteria

Inclusion	Exclusion
?? Subjects 18 years of age or older, of either sex ?? Subjects having realistic expectations of the benefit and limitation of the augmentation procedure, as determined by a willingness to sign the informed consent form after it has been carefully explained. The informed consent form includes the statement that the subjects will not look younger after the treatment, and that treatment with Artecoll does not replace a facelift or eyelid surgery, nor	?? Subjects who were pregnant ?? Subjects who had been treated with collagen, Botulinum toxin, or other wrinkle/fold therapies within the last six months at any intended implant area ?? Subjects considering additional cosmetic treatments to the treatment area at any later time during the study ?? Subjects who had received chemotherapy agents or corticosteroids within the last 3 months ?? Subjects receiving UV light

does it replace the effect of laser treatment, chemical peel or dermabrasion on fine wrinkling. ?? Subjects able and willing to give informed consent ?? Subjects presenting for correction of any of the following four types of dermal contour deformities of the face: - Glabellar Folds (right and/or left side and/or center) - Nasolabial Folds (right and/or left side) - Radial Upper Lip Lines (right and/or left side) - Depressed Corners of the Mouth (right and/or left side) ?? Subjects willing and able to comply with the requirements of the study (e.g. study duration, number of visits, completion of questionnaires)	therapy ?? Subjects who were planning to use substances which reduce coagulation, such as aspirin, non-steroidal anti-inflammatory drugs or Coumadin, within the 4 weeks preceding treatment (this was changed to 72 hours as of January 10th, 2000 per Protocol Revision 1) ?? Subjects presenting with history of autoimmune disorder ?? Subjects presenting with atrophic skin diseases at any intended treatment area ?? Subjects with very thin and flaccid skin at any intended treatment area ?? Subjects with known susceptibility to keloids ?? Subjects with known lidocaine hypersensitivity ?? Subjects with dietary beef allergy, or undergoing or planning to undergo desensitization to meat products ?? Subjects with known allergy to collagen ?? Subjects with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies ?? Subjects with cellulitis or infection at the treatment area ?? Subjects demonstrating anti-bovine collagen serum IgG levels outside the normal range at baseline (after randomization) ?? Subjects demonstrating a positive skin test or two equivocal skin tests (after randomization)

c. Treatment Protocol

1. Patient screened

2. Patients randomized to receive either Artecoll or Zyplast/Zyderm treatment in one or more of the eight treatment areas (four for each side). Subjects were masked regarding the randomization assignment.
3. Blood was then drawn for a test of serum IgG level and the subject received the collagen skin test that correlated with the randomization assignment
4. Subject underwent a 30-day observation period following the collagen skin test.
5. In the case of equivocal test results, the subject underwent a second skin test with a subsequent 30-day observation period.
6. Upon a negative skin test and a serum IgG level within normal range, the subject received treatment with Artecoll or Zyplast/Zyderm according to the randomization assignment.
    i. Among subjects treated with the Control, Zyplast was used for Nasolabial folds, Upper lip lines and Mouth Corners
    ii. Zyderm was used for Glabellar Folds on the basis of labeling for Zyderm/Zyplast.
7. Before treatment, a topical or deep dermal anesthetic was applied to areas selected for treatment as necessary.
8. During each treatment session, the appropriate implant was injected deep dermally, immediately above the subcutaneous tissue, using a tunneling technique.
9. To even distribution, the implant was spread and modeled with the fingertips.
10. Post-procedure, subjects were encouraged to minimize facial movement for several days following the treatment session.
11. The treatment course lasted up to one month and included a total of up to 3 treatment sessions.

d. Follow-up Protocol

1. Follow-up intervals

?? All subjects in both treatment groups were scheduled to follow-up at 1, 3, and 6 months post-treatment.
?? Only the Artecoll treatment group patients were seen again at 12 months post-treatment to assess the occurrence of late adverse events

2. Follow-up Assessments included

?? Adverse event assessment, documentation and additional treatments required
?? Photographic documentation using a standardized process

3. Assessment Tools

Assessment	**Assessment Tool**	**Details Regarding Assessment Tool**

made by:		
Masked Observer	Facial Fold Assessment (FFA) Scale (Validated Scale)	A scale created and validated for this study for: ?? Glabellar Folds ?? Nasolabial Folds ?? Radial Upper Lip Lines ?? Marionette Lines And not for mouth corners. Each fold/line is graded on a 0 – 5 point scale based on reference photos where 0 is considered the least severe, optimal condition. _____ Reference photographs used by the masked observers were the same size as the photographs being evaluated. (Reference photographs appear in Volume 3 p. 12-096) _____ Although the scale was not validated for this, non-integral values for Masked Observer FFA scale ratings occurred under 2 circumstances: 1) For any facial location at any time point ratings were averaged across raters and sides 2) MO used ½ point steps for FFA ratings between 2 FFA scale anchor points Then the pre-treatment severity was determined by rounding the FFA scale score to the nearest integer. _____ Interclass correlations for rater reliability of masked observer FFA ratings were acceptable being greater than 0.8 for each treatment area.
Unblinded Investigator	Rating of Treatment Success *(Scale not validated)*	1) During each follow-up visit, the unblinded investigator rated the success of the implant at each treatment area using the following five point rating scale. These

		evaluations were based on seeing the patient in person. 1 = Completely Successful (Defined as Optimal Desired Outcome) 2 = Very Successful 3 = Moderately Successful 4 = Somewhat Successful 5 = Not at all Successful 2) During each follow-up visit, the unblinded investigator rated the success of the implant based on seeing the patient in person and using reduced size FFA reference photographs.
Blinded Patient	Subject satisfaction of treatment *(Scale Not Validated)*	During each follow-up visit, subject satisfaction with the result of each treatment area was assessed using a questionnaire at each follow-up period. Subjects rated their personal opinion of each treatment area using the following 5-point rating scale: 1 = Very Satisfied 2 = Satisfied 3 = Somewhat Satisfied 4 = Dissatisfied 5 = Very Dissatisfied

e. Study Endpoints

1. Primary Endpoints

?? Objective 1: The cosmetic correction will be assessed using the FFA Scale, related to the Fitzpatrick scale, but adapted to the deep folds that are the subject of this study, rather than the fine wrinkles for which the Fitzpatrick scale was developed. A comparison will be made between Artecoll and Zyplast/Zyderm by measuring the correction that remains at the evaluation 6 months after completion of the treatment course. The null hypothesis will be that there is no difference between Artecoll and Zyplast/Zyderm 6 months after completion of the treatment course. A clinically significant difference will be defined as a difference of at least one FFA Scale classification.

?? Objective 2: The assessment of safety will be based on the incidence of serious unanticipated adverse events. Unanticipated adverse

events will be characterized by the severity and relation to the implant product.

In addition, the occurrence of all anticipated adverse events will be assessed at each follow-up period and compared between treatment groups.

The level of serum IgG will be monitored pre-treatment and at 1 month post-treatment. If the IgG level is elevated at the 1 month post-treatment visit, an additional sample will be taken at the 3 month visit. If the 3 month sample is elevated, a final sample will be taken at the 6 month post-treatment visit. The occurrence of levels falling outside the normal range will be compared between treatment groups.

2. Secondary Endpoints

?? Objective 3: The quality of the initial treatment result will be characterized using the FFA Scale and will be used to characterize the cosmetic correction during the early period up to 3 months post-treatment. The percent of folds/lines that exhibit a decrease of at least one classification (improvement) between the pre-implant assessment and the 1 and 3 month post-treatment assessments will be calculated for each treatment group.

?? Objective 4: The physician's assessment of success will be characterized using a non-parametric 5-point scale, measured at 1, 3, and 6 months post-treatment.

?? Objective 5: The patient's assessment of satisfaction will be characterized using a non-parametric 5-point scale, measured at 1, 3, and 6 months post-treatment.

II. Artes Medical Study Conduct

a. Enrollment

1. Included 285 subjects (141 Artecoll, 144 Control)
2. 111 subjects being available for 1-year safety evaluation

b. Demographics

	Artecoll	**Control**	**p-value**
Gender			
Male	11 (8.6%)	11 (8.9%)	1.000
Female	117 (91.4%)	112 (91.1%)	
Mean Age (Std. dev.)	53.2 (10.3)	51.2 (11.3)	0.157

Ethnicity			
Caucasian	102(76.7%)	107 (82.3%)	0.277
Hispanic	24 (18.0%)	21 (16.2%)	
Asian	1 (0.8%)	1 (0.8%)	
Other	6 (4.5%)	1 (0.8%)	
Smoking Rate			
?? None	122 (91.0%)	108 (83.1%)	0.061
?? Low	8 (6.0%)	18 (13.8%)	
?? Medium	4 (3.0%)	3 (2.3%)	
?? High	0 (0.0%)	1 (0.8%)	
Sun Exposure			
?? Low	69 (51.9%)	84 (64.6%)	**0.043**
?? Medium	49 (36.8%)	35 (26.9%)	
?? High	15 (11.3%)	11 (8.5%)	
Mean pretreatment masked observer FFA Scale Ratings (Std. dev.)			
Glabellar Folds	1.42 (0.90)	1.40 (0.86)	0.934
Nasolabial Folds	**1.74 (1.06)**	**1.45 (1.02)**	**0.039**
Upper Lip Lines	1.17 (0.82)	1.18 (0.86)	0.886
Mouth Corners	1.91 (1.15)	1.87 (1.10)	0.891

Using the Spearman Rank Order Correlation, the sponsor determined that the smoking rates were not associated with treatment effects and thus not a source of bias in the clinical trial.

Using the Spearman Rank Order Correlation, the sponsor found only one correlation significant for sun exposure. In the Control group, Nasolabial fold improvement was found to be negatively correlated with sun exposure. Lower sun exposure was associated with greater improvement in this group.

Please note that the mean pretreatment masked observer FFA scale ratings for nasolabial folds indicate that the fold severity is more severe for the Artecoll treatment group versus the control group severity. This statistically significant difference between groups allows the Artecoll treatment group more room for improvement than the control.

	Artecoll	**Control**	**p-value**
Treated folds (treated subjects)			
Glabellar Folds	155 (81)	165 (86)	0.153 (0.327)
Nasolabial Folds	214 (108)	206 (104)	0.939 (1.00)
Upper lip lines	137 (69)	116 (59)	0.182 (0.415)
Mouth corners	86	87	0.210 (0.638)
Number of facial fold areas treated			
1 area	20	22	0.412
2 areas	36	24	
3 areas	36	42	
4 areas	36	35	
Bilateral treatment to:			
Glabellar Folds	74	79	0.312
Nasolabial Folds	106	102	0.886
Upper Lip Lines	68	57	0.621

Mouth Corners	85	83	0.963
Unilateral treatment to:			
Glabellar Folds	7	7	0.578
Nasolabial Folds	2	2	0.674
Upper Lip Lines	1	2	0.485
Mouth Corners	1	4	0.173

c. Accountability

Patient Accounting - Artes medical study – Artecoll patients						
	Preop	Intraop	1 month	3 months	6 months	12 months
Theoretical[1]	141					
Device removals, (cumulative)	0	0	0	1*	1*	1*
Expected[2]	141	141	141	140	140	140
Lost to follow-up (cumulative)	0	0	2	4	6	10
Aborted study (includes not treated and voluntary withdrawal) (cumulative)	13	13	14	15	15	16
Evaluated[3]	128	128	125	121	119	114
% Expected Follow-up	100% 141/141	100% 141/141	100% 141/141	99.3% 140/141	99.3% 140/141	99.3% 140/141
Actual % Follow-up[4]	90% 128/141	90% 128/141	89% 125/141	86% 121/140	85% 119/140	81% 114/140

***** Subject with device removal (due to lumpiness) was seen at all follow-up visits

1 Theoretical = Patients enrolled in the study

2 Expected = Theoretical – Device removals

3 Evaluated = Theoretical – (Failures+ Lost to Follow-Up + Aborted)

4 As per evaluated[3]

Patient Accounting – Artes Medical Study - Control Patients					
	Preop	Intraop	1 month	3 months	6 months
Theoretical[1]	144				
Device removals, (cumulative)	0	0	0	0	0
Expected[2]	144	144	144	144	144
Lost to follow-up (cumulative)	0	0	0	2	2
Aborted study (includes not treated and voluntary withdrawal) (cumulative)	21	21	21	22	23

Evaluated[3]	123	123	123	120	119
% Expected Follow-up	100% 144/144	100% 144/144	100% 144/144	100% 144/144	100% 144/144
Actual % Follow-up[4]	85% 123/144	85% 123/144	85% 123/144	83% 123/144	83% 123/144

1. Theoretical = Patients enrolled in the study
2. Expected = Theoretical – Device removals
3. Evaluated = Theoretical – (Failures+ Lost to Follow-Up + Aborted)
4. As per evaluated[3]

d. Adequacy of Blinding

1) Patient Satisfaction
1 month – guess rates were not different than chance
3 months – guess rates were 61.3% ($p = 0.001$) accurate
6 months – guess rates were 73.6% ($p < 0.001$) accurate
Additional analysis (table 57 p. 12-053) demonstrates that treatment guesses at 6 months were not related to outcome on the masked observer FFA scale ratings.

2) Masked Observer - The observers were not asked questions regarding their guesses about treatment assignment or follow-up time for the photos. No conclusions can be drawn regarding the efficacy of the blinding of the masked observers.

III. Artes Medical Study Results

The sponsor has performed a number of post-hoc supplemental analyses of various subsets of patients. These subset analyses have not been included in this review memo as they do not provide any additional information that are not already addressed in the prospectively defined data analysis.

a. Safety

Onset of Adverse Events – Artecoll patients in the Artes Medical Study

	24-48 hours	**1 week**	**1 month**	**3 months**	**6 months**	**12 months**
Number of patients evaluated	128	128	112	106	113	111
Total number of patients with adverse events	12	3	2	3	2	0
Total number of adverse	14	4*	2	4	2	0

events						
Lumpiness at injection area more than one month after injection	3	0	0	3	2	0
Persistent swelling or redness	6	1*	0	0	0	0
Increased sensitivity	2	0	2	0	0	0
Rash, itching more than 48 hours after injection	0	1	0	1	0	0
Blurred vision	0	1	0	0	0	0
Flu-like symptoms	0	1	0	0	0	0
Recurrence of existing herpes labialis	1	0	0	0	0	0
Sensitization reactions[1]	0	0	0	0	0	0
Abscess	0	0	0	0	0	0
Visibility of the puncture area	0	0	0	0	0	0
Granuloma or enlargement of the implant	0	0	0	0	0	0
Infection	0	0	0	0	0	0
Other local complications	1 –dry skin	0	0	0	0	0
Other systemic complications	1 – vasovagal episode, patient briefly lost consciousness during injection	0	0	0	0	0
Severe illness, trauma, death	0	0	0	0	0	0

* Subject reported that event occurred 3 additional times – no dates for onset of 2nd and 4th times

1. As defined per each investigator.

Onset of Adverse Events – Control subjects in the Artes Medical Study

	24-48 hours	**1 week**	**1 month**	**3 months**	**6 months**
Number of patients evaluated	123	123	111	109	116

Total number of patients with adverse events	10	1	3	2	4
Total number of adverse events	21	3	4	2	6
Lumpiness at injection area more than one month after injection	2	0	1	0	1
Persistent swelling or redness	9	1	1	2	0
Increased sensitivity	1	0	0	0	0
Rash, itching more than 48 hours after injection	1	1	0	0	0
Blurred vision	0	0	0	0	0
Flu-like symptoms	0	0	0	0	1
Recurrence of existing herpes labialis	0	0	0	0	0
Sensitization reactions [1]	3	1	2	0	0
Abscess	2	0	0	0	1
Visibility of the puncture area	2	0	0	0	0
Granuloma or enlargement of the implant	1	0	0	0	0
Infection	0	0	0	0	1
Other local complications	0	0	0	0	1 – acneform
Other systemic complications	0	0	0	0	0
Severe	0	0	0	0	1 -

illness, trauma, death					carjacking

1. As defined per each investigator.

Duration of Adverse Events:

Please see Attachment 2a and 2b for the Duration of adverse events in Artecoll treated patients and Control group patients.

Summary of incidence of adverse events:

	Artecoll	**Control**
Number of adverse events	26	36
Number of patients experiencing adverse events	21	16
Total number of subjects treated	128	123
% of subjects with adverse events	16.4%	13.0%

The top 3 adverse events occurring in the Artecoll treatment group were lumpiness more than 1 month post-injection, persistent swelling or redness, and increased sensitivity.

For Artecoll treated patients, these events lasted over 3 months in

- ?? *5/7 patients found to have lumpiness more than 1 month post injection*
- ?? *3/7 patients found to have persistent swelling or redness*
- ?? *¼ patients found to have increased sensitivity*

For control treated patients, these events lasted over 3 months in:

- ?? *2/4 patients found to have lumpiness more than 1 month post injection*
- ?? *9/12 patients found to have persistent swelling or redness*
- ?? *1/1 patient found to have increased sensitivity*

b. Effectiveness

The results of the Masked Observer Assessments are shown in the following table:

Follow-up	**Treatment Area**	**Treatment**	**N**	**Mean change in FFA**	**P-Value**
1-month	Glabellar Folds	Artecoll	64	0.17	**0.004**
		Control	**77**	**0.49**	
	Nasolabial Folds	Artecoll	91	0.75	0.713
		Control	91	0.74	

	Upper Lip Lines	Artecoll	58	0.31	0.205
		Control	53	0.48	
	Mouth Corners	Artecoll	71	0.46	0.179
		Control	76	0.30	
3-months	Glabellar Folds	Artecoll	65	0.25	0.348
		Control	75	0.35	
	Nasolabial Folds	**Artecoll**	**87**	**0.81**	**<0.001**
		Control	88	0.15	
	Upper Lip Lines	Artecoll	53	0.18	0.454
		Control	51	0.25	
	Mouth Corners	**Artecoll**	**64**	**0.45**	**0.001**
		Control	77	0.01	
6-months	Glabellar Folds	Artecoll	71	0.34	0.971
		Control	79	0.32	
	Nasolabial Folds	**Artecoll**	**92**	**0.77**	**<0.001**
		Control	91	0.00	
	Upper Lip Lines	Artecoll	55	0.08	0.176
		Control	50	0.22	
	Mouth Corners	Artecoll	69	0.26	0.316
		Control	79	0.09	

The un-blinded investigator assessments of success (ranging from not at all successful to completely successful; 1 – 5 scale) are shown in the following table:

Follow-up	**Treatment Area**	**Treatment**	**N**	**Mean**	**Standard Deviation**
1-month	Glabellar Folds	Artecoll	68	1.93	0.94
		Control	79	1.91	1.00
	Nasolabial Folds	Artecoll	93	1.99	0.89
		Control	93	2.06	1.03
	Upper Lip Lines	Artecoll	61	1.88	0.82
		Control	54	2.02	0.88
	Mouth Corners	Artecoll	74	2.00	0.97
		Control	77	2.55	1.28
3-months	Glabellar Folds	Artecoll	67	2.02	1.00
		Control	74	2.68	1.40
	Nasolabial Folds	Artecoll	89	1.90	0.87
		Control	89	3.07	1.41
	Upper Lip Lines	Artecoll	58	2.04	0.90
		Control	51	3.11	1.39
	Mouth Corners	Artecoll	68	2.08	0.94
		Control	76	3.38	1.34
6-months	Glabellar Folds	Artecoll	74	2.06	1.07
		Control	82	3.43	1.51

	Nasolabial Folds	Artecoll	97	1.73	0.69
		Control	96	4.05	1.32
	Upper Lip Lines	Artecoll	60	1.98	0.93
		Control	54	4.13	1.28
	Mouth Corners	Artecoll	73	2.19	0.98
		Control	81	4.09	1.32

Patient Satisfaction

Time (months)	Treatment area	Artecoll			Control		
		N	Mean	Std. Dev.	N	Mean	Std. Dev.
1	Glabellar Folds	66	1.86	0.97	78	1.94	0.94
1	Nasolabial Folds	92	1.85	1.03	93	1.92	0.89
1	Upper Lip Lines	61	1.94	1.09	54	1.98	1.04
1	Mouth Corners	74	2.01	0.94	77	2.32	1.07
3	Glabellar Folds	67	2.22	1.13	74	2.70	1.34
3	Nasolabial Folds	89	2.16	1.08	89	2.78	1.30
3	Upper Lip Lines	58	2.14	1.05	51	3.07	1.30
3	Mouth Corners	68	2.29	1.08	77	3.06	1.29
6	Glabellar Folds	74	2.14	1.19	82	3.44	1.35
6	Nasolabial Folds	97	2.02	0.95	96	3.52	1.37
6	Upper Lip Lines	60	2.17	1.12	54	3.94	1.28
6	Mouth Corners	73	2.31	1.04	81	3.97	1.19

Both the unmasked investigator assessment of patient success and the blinded patient satisfaction rating demonstrated higher success in the Artecoll treated group versus the control. However, the potential for bias is present as the investigator was not blinded to treatment group and the assessment of patient blinding demonstrated that over 73.6% of patients accurately guessed their randomization assignment at 6 months.

IV. Did the Study Meet Its Objectives?

Objective 1 (a primary objective) was to explore whether the cosmetic correction provided by Artecoll at the end of a six-month period following injection is superior to

that provided by Zyplast/Zyderm at the same time period.

Although a statistically significant difference was noted at six months for patients in the Artecoll treatment arm versus the control in the area of the NL fold, it is unknown whether this represents a clinically detectable difference as the FFA scale only recognizes full point differences. The findings may be skewed by the statistically significant difference of the pre-treatment severity score with the Artecoll group that was greater (more severe at baseline) than the control group. The sponsor states that this issue was addressed by using a non-parametric Mann-Whitney U tests for these comparisons since the severity ratings were positively skewed. The ability of this test to adequately compensate for this difference should be considered.

The results show that Artecoll efficacy in other 3 treatment areas versus the control has not been demonstrated as per objective 1.

The sponsor states that Artecoll efficacy from the perspective of the unblinded investigator and blinded patient demonstrated higher success and better patient satisfaction than the control. This is useful information however is biased due to unblinding of the investigator and lack of effective blinding of the patient as demonstrated by the blinding assessment.

Objective 2 (primary objective) To explore whether the safety of Artecoll as an injectable implant for correction of contour deformities of the dermis of the face

Based on the information provided in this executive summary, the panel should address:

- ?? *The level of safety required for a cosmetic device*
- ?? *Whether this objective was met for Artecoll based on the information presented*

Objective 3 (a secondary objective) To characterize the initial quality of the cosmetic correction provided by Artecoll and Zyplast/Zyderm.

The study attempted to characterize the initial quality of cosmetic correction by the devices as per the patients' satisfaction, investigator assessment and masked observer FFA scale rating. Each of these assessment tools has associated flaws whether it be bias, differences in observation from photos versus in-person assessment, baseline severity, use of the FFA scale in methods that have not been validated, or level of expectation.

Objective 4 (a secondary objective) of the study is to characterize the investigator assessment of success with respect to how closely the treatment met the investigator's initial expectations for correction.

This is a vague objective as the investigators assessment of success was based on the investigator's initial expectations for correction. The investigator's initial expectations for correction were never defined in the protocol.

Objective 5 (a secondary objective) is to characterize the subject's assessment of

satisfaction with respect to the subject's personal expectations.

This is a vague objective as the subjects' assessment of success was based on their initial expectations for correction. The subjects' initial expectations for correction were never defined in the protocol.

PART III

I. Rofil Clinical Study

a. Background – This study was intended to evaluate the safety and effectiveness of Artecoll when used for cosmetic correction. However, the originally approved protocol did not involve a control group, and the ratings made by the investigators were based on improvement rather than objective measurement. The protocol changed significantly during the process of obtaining unconditional approval. Also, the method of capturing efficacy data was too subjective to be adequate, and the number of subjects and areas treated were not sufficient to be considered statistically significant.

For all of these reasons, the primary focus of the analysis of the Rofil study has been to obtain the safety of Artecoll when used for cosmetic correction.

b. Design -

?? Open label study
?? Uncontrolled

c. Inclusion/Exclusion

Inclusion	Exclusion
?? Subjects 18 years of age or older ?? In the opinion of the investigator, the subjects has realistic expectations of the benefit and limitation of the augmentation procedure ?? Subjects presenting for correction of dermal contour deformities of the face: - Glabellar Frowns/Folds - Nasolabial Folds - Perioral Lines) - Depressed Corners of the Mouth	?? Subjects who had been treated with collagen, Botulinum toxin, or other wrinkle/fold therapies within the last six months at any intended implant area ?? Subjects who were receiving current treatment with corticosteroids subdermally, intradermally or epiperiostally ?? Subjects receiving UV light therapy ?? Subjects presenting with a personal or family history of autoimmune disorder ?? Subjects presenting with atrophic skin diseases ?? Subjects with thin and flaccid skin ?? Subjects with known susceptibility to keloids ?? Subjects with known allergy to collagen ?? Subjects requiring correction of atrophy or defects in the subcutaneous fat ?? Subjects requiring correction of crow's feet

d. Treatment Protocol

1. Treatment areas included:
   Glabellar Folds
   Nasolabial folds
   Perioral lines
   Depressed mouth corners
2. Each subject received as many as 6 facial treatment areas (3 of the 4 per side) as deemed appropriate by the investigators

e. Follow-up Protocol - Subjects had follow-up assessments at 3, 6, and 12 months following the last treatment session.

II. Rofil Medical Study Conduct

?? 157 patients were treated with Artecoll
?? One year safety data was obtained for 126 of the 157 patients treated

Patient Accounting - Rofil Study					
	Preop	Intraop	3 months	6 months	12 months
Theoretical[1]	167				
Device removals, (cumulative)	0	0	0	0	0*
Expected[2]	167	167	167	167	167
Lost to follow-up (cumulative)	5	0	24	6	2
Aborted study (includes not treated and voluntary withdrawal) (cumulative)	5	0	0	0	0
Evaluated[3]	157	157	133	127	125
% Expected Follow-up	100% 167/167	100% 167/167	100% 167/167	100% 167/167	100% 167/167
Actual % Follow-up[4]	94% 157/167	94% 157/167	80% 133/167	76% 127/167	75% 125/167

*2 excisions after 12 month time period

1. Theoretical = Patients enrolled in the study
2. Expected = Theoretical – Device removals
3. Evaluated = Theoretical – (Failures+ Lost to Follow-Up + Aborted)
4. As per evaluated[3]

III. Rofil Medical Study Results

Onset of Adverse Events – Rofil Study

	24-48 hours	**1 week**	**1 month**	**3 months**	**6 months**	**12 months**
Number of patients evaluated	NA	NA	NA	133	127	125
Total number of patients with adverse events	6	2	1	3	5	3
Total number of adverse events	7	2	1	3	6	6
Lumpiness at injection area more than one month after injection	2 (2 estimated?)	2	0	0	1	0
Persistent swelling or redness	1 (1 estimated?)	0	0	0	2	0
Increased sensitivity[2]	1 (1 estimated?)	0	0	0	0	0
Rash, itching	0	0	0	2	1 (1	1 (1

more than 48 hours after injection					estimated?)	estimated?)
Blurred vision	0	0	0	0	0	0
Flu-like symptoms	0	0	0	0	0	0
Recurrence of existing herpes labialis	0	0	0	0	0	0
Sensitization reactions [1]	1 (1 estimated?)	0	0	0	1	0
Abscess	0	0	0	0	0	0
Visibility of the puncture area	0	0	0	0	0	0
Granuloma or enlargement of the implant	0	0	0	1	0	2 (1 after 12 months)
Infection	0	0	0	0	0	0
Other local complications [2]	0	0	0	0	1	3 (2 estimated after 12 months)
Other systemic complications [2]	2	0	0	0	0	0
Severe illness, trauma, death	0	0	1 – breast cancer	0	0	0

1. As defined per each investigator.
2 Local complications - "redness and visible capillaries in NF" and "patchy complete alopecia areata on head at 3 mos".
3 Systemic complications - "mild chest congestion after both treatment sessions."

Duration of Adverse Events:

See Attachment 2c: Duration of Adverse Events – Rofil Study

Based on the Duration of Adverse events attachment 2c, the top 3 specific adverse events occurring on a per incident basis in the Rofil treated patients were lumpiness more than 1 month post-injection, persistent swelling or redness, and granuloma or enlargement of the implant.

For Rofil treated patients, these events lasted over 3 months in:

- ?? *4/5 patients found to have lumpiness more than 1 month post injection*
- ?? *1/3 patients found to have persistent swelling or redness*
- ?? *1/1 patient granulomas or enlargement of the implant*

PART IV

I. Product Description

The test material is a 3.5% purified bovine collagen manufactured by European Medical Contract Manufacturing. The specific formulation is 3.5% collagen, 2.7% phosphate buffer, 0.3% sodium chloride, and 0.3% lidocaine hydrochloride and 93.2% WFI. Test material is provided sterile and nonpyrogenic in a prefilled 1.0 cc syringe with 0.1cc of collagen solution.

II. Bovine Collagen Immunogenicity Study

a. Design

?? Single investigator, prospective, open-label non-controlled clinical trial
?? To determine the safety and immunogenicity of the bovine collagen in Artecoll because collagen source for the proposed commercial product differs from the collagen component used in the large scale clinical study (i.e., the Artes Study).

b. Inclusion/Exclusion Criteria

Inclusion	Exclusion
?? Subjects 35 years of age of older, of either sex ?? Subjects wiling and able to comply with study requirements ?? Subjects willing and able to comply study follow-up requirements ?? Subjects willing and able to give informed consent	?? Subjects who are pregnant ?? Subjects who have had collagen treatment within the last 3 months ?? Subjects who were treated with chemotherapy agents or corticosteroids within the past 3 months ?? Subjects with a history of autoimmune disorder ?? Subjects with known lidocaine hypersensitivity ?? Subjects with known sensitivity to bovine collagen ?? Subjects who have a history of dietary beef, undergoing desensitization to beef products or planning to undergo desensitization within the study evaluation period. ?? Subjects with severe allergies manifested by a history of anaphylaxis ?? Subjects with a current disease state that can effect the ?? immunoresponse (e.g., flu, cancer, HIV) ?? Subjects who are currently treated with

c. Treatment Protocol

1. Subjects screened
2. If entry criteria met then patient had a pre-injection serum sample drawn
3. The physician then injected 0.1 ml of a collagen solution intra-dermally in the volar forearm
4. The physician then assessed the test site for an acute reaction for 15-30 minutes after the injection
5. The subject was permitted to go home and was instructed to observe the test site daily for 30 days and notified the investigator if any effects indicative of a positive response were observed or systemic effects were experienced. The subject received both written instructions for assessing the test site and a "Patient Skin Response Sheet"
6. 30 days after the first injection the subjects returned to the clinic. If the investigator determined that the subject displayed a positive response, the subject's participation in the study was completed and a final blood drawn was taken.
7. If the subject did not display a positive response to the first collagen injection, they received a second 0.1 ml injection intradermally in the contra lateral volar forearm.
8. The physician then assessed the test site for an acute reaction for 15-30 minutes after the injection after which the subject went home and observed the test site daily for 30 days. The subjects were instructed to notify the investigator if any effects indicative of a positive skin test response or systemic effects were experienced. The subjects also recorded observations in a "Patient Skin Response Sheet"

d. Follow-up Protocol

- ?? Visit 2 30 days following initial skin test
- ?? Visit 3 following 2nd skin test
- ?? Daily evaluations by patient

e. Follow-up Assessment Method

1) Skin test results - The injection site was evaluated to determine negative, positive or equivocal response:

- ?? Negative = No localized skin reaction and the patient has no systemic reaction
- ?? Positive = Erythema of any degree, induration, tenderness, rash and swelling with or without pruritis, which can appear immediately following implantation and persists for more than 24 hours or appears more than 24 hours following implantation

?? Equivocal =No localized skin reaction but the patient does elicit a possible systemic reaction such as rash, arthralgia, or myalgia which occurs at any time during the 30 (+/- 5) day observation period.

2) Abnormal Serum IgG Test Results - the number of patients exhibiting a normal serum IgG level before administration of the skin test and the an abnormally high serum IgG at the time of the second blood draw

3) Adverse events

f. Study Purpose and Objective

Purpose To determine the frequency of positive collagen skin test results for a new Artecoll collagen source.

Objective To provide information that can be used in labeling to be submitted to the US Food and Drug Administration and other regulatory bodies in connection with applications for marketing approval.

III. Bovine Collagen Study Conduct

a. Enrollment

?? 235 subjects were injected with bovine collagen.
?? 225 subjects completed the study per protocol.

b. Demographics

N = 235	
Gender	
Male	78 (32.8%)
Female	157 (67.2%)
Mean Age	48.2 years
Ethnicity	
Caucasian	188 (80.0 %)
Hispanic	32 (13.6 %)
Black	11 (4.7 %)
Asian	2 (0.085%)
Black & Hispanic	1 (0.042%)
Native American	1 (0.042%)

c. Accountability

Patient Accounting

Time of:		Injection 1		Injection 2	
	Screened	Enrolled	Visit 1	Visit 2	Visit 3
Expected[1]	244	235			
Lost to follow-up (cumulative)[3]	0	0	0	7	2
Aborted study (includes not treated and voluntary withdrawal) (cumulative)[4]	0	0	0	0	1
Evaluated[5]	244	235	235	228	225
Experienced skin reaction but were not discontinued (cumulative)	0	0	0	5	8
Actual % Follow-up[6]	100% 244/244	100% 235/235	100% 235/235	97% 228/235	97.5% 225/235

1. Expected = Patients enrolled in the study
2. Of the patients lost to follow-up, 5/9 were contacted and reported no local skin reaction
3. Patient violated the exclusion criteria, but had no skin test reaction or abnormal elevation in serum IgG levels.
4. Evaluated = Theoretical – (skin reactions+ Lost to Follow-Up + Aborted)
5. As per evaluated

IV. Study Results

a. Positive Skin Tests Responses –

	Within 15-30 minutes Post Injection 1	Within 30 days Post Injection 1	Within 15-30 minutes Post Injection 2	Within 30 days Post Injection 2
Number of patients with positive skin test (8 patients of 235 studied = 3.4%)	0	4	1	3

b. Adverse Events

Time to onset of Adverse Events

Category	**24-48 hours**	**1 week**	**1 month**
Number of subjects evaluated	235		
Total number of			

adverse events	5	22	31
Total number of patients with adverse events	5	18	26
Arm tingling, warmth, clammy	1	0	0
Broken toe	0	1	0
Broken wrist	0	0	1
Cataract surgery	0	0	1
Cellulitis	0	1	0
Cough	0	1	3
Dental extraction	0	0	1
Diarrhea	0	3	0
Facial and Hand Edema	0	1	0
Flu Symptom	0	0	1
Headache	1	0	1
Increased perspiration	1	0	0
Irritant dermatitis	1	0	0
Lymphadenopathy	1	0	0
Migraine Headache	0	0	1
Muscle Ache	0	1	0
Recurrent Herpes simplex virus	0	1	0
Recurrent oral herpes simplex virus	0	0	1
Rhinitis	0	0	1
Sinus congestion	0	1	1
Sore throat	0	0	2
Stomach Ache	0	0	1
Swollen glands right neck	0	1	0
Tooth infection	0	0	1
Torn ligament right foot	0	0	1
Upper respiratory infection	0	8	13
Urinary tract infection	0	0	1
Vomiting	0	3	0

Duration of Adverse Events

See attachment 2d: Bovine Collagen Immunogenicity Study – Duration of Adverse Events

c. Serum Levels of Bovine Collagen Antibodies

The Center testing laboratory defined the normal serum IgG range as a titer between 700 and 1,600. No subjects transitioned from the normal serum IgG level before administration to an abnormally high serum IgG level in the post-treatment blood sample.

V. Did the Study Meet Its Purpose and Objective?

Purpose To determine the frequency of positive collagen skin test results for a new Artecoll collagen source.

The incidence of a positive skin response was found to be 3.4%. The incidence of equivocal skin test results as prospectively defined is not well characterized and should be assessed by examination of adverse events.

Objective To provide information that can be used in labeling to be submitted to the US Food and Drug Administration and other regulatory bodies in connection with applications for marketing approval.

The information provided can be used in device labeling.

Of note, the labeling of ZYDERM collagen implant states that the incidence of positive test site response or similar systemic responses as described here has been approximately 3.0%.