

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: SCULPTRA Aesthetic

Applicant's Name and Address: sanofi-aventis U.S. LLC
9 Great Valley Parkway
Malvern, PA 19355

Premarket Approval Application (PMA) Number: P030050/S2

Date of Panel Recommendation: None.

Date of FDA Notice of Approval: July 28, 2009

Expedited: Not Applicable

The original PMA (P030050) was approved on August 3, 2004 and is indicated for restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus. The SSED to support the indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication for SCULPTRA Aesthetic.

II. INDICATIONS FOR USE

SCULPTRA Aesthetic is indicated for use in immune-competent subjects as a single regimen for correction of shallow to deep nasolabial fold contour deficiencies and other facial wrinkles in which deep dermal grid pattern (cross-hatch) injection technique is appropriate.

III. CONTRAINDICATIONS

- SCULPTRA Aesthetic should not be used in any person who has hypersensitivity to any of the components of SCULPTRA Aesthetic (see DEVICE DESCRIPTION).
- SCULPTRA Aesthetic should not be used in patients with known history of or susceptibility for keloid formation or hypertrophic scarring.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the SCULPTRA Aesthetic physician's Labeling.

V. DEVICE DESCRIPTION

SCULPTRA Aesthetic is an injectable implant containing microparticles of poly-L-lactic acid (PLLA), carboxymethylcellulose (USP), non-pyrogenic mannitol (USP) and sterile water for injection (USP). SCULPTRA Aesthetic is available in 367.5mg dose vials and is to be reconstituted prior to use by the addition of 5 ml of Sterile Water for Injection, USP (SWFI) to form a sterile non-pyrogenic suspension.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative therapies for treating mild to severe nasolabial folds include bovine collagen dermal fillers, human collagen dermal fillers, hyaluronic acid-based dermal fillers and autologous fat transfer. Other methods for treatment of facial rhytids include injection of botulinum toxin, topical creams, chemical peels, laser skin resurfacing, dermabrasion and surgical intervention.

VII. MARKETING HISTORY

SCULPTRA[®] was approved by the FDA in August 2004 for restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus (HIV).

This device under the tradenames of NEW-FILL and SCULPTRA is marketed in the following countries: Australia, Belgium, Brazil, Bulgaria, Canada, Cyprus, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Netherlands, Norway, Poland, Portugal, Romania, Spain, Switzerland, and United Kingdom.

SCULPTRA has not been withdrawn from any marketplace for any reason.

VIII. POTENTIAL ADVERSE EVENTS

A prospective, randomized clinical study was conducted at 10 centers in the US. Two hundred and thirty three (233), immune-competent and non-pregnant and non-breast feeding subjects with previously untreated nasolabial fold wrinkles and Wrinkle Assessment Scores (WAS) of 2 through 4 received bilateral injections of either SCULPTRA Aesthetic or Control in both nasolabial fold wrinkles during a maximum of 4 sessions over 9 weeks. Study treatment was planned to be stopped when the right and left nasolabial fold wrinkle reached WAS of 1 or 0, or the maximum of 4 treatment sessions were completed. Adverse events reported in subject diaries after initial treatment are summarized in Tables 1 (intensity) and 2 (duration) below. Adverse events described in the physician case reports are summarized in Table 3 below.

TABLE 1
INTENSITY OF ADVERSE EVENTS AFTER THE INITIAL TREATMENT SESSION,
RECORDED IN THE 14 DAY SUBJECT DIARY
 (Controlled Phase, 0-13 months)
 All-Treated Population: Per subject

Injection Procedure Related Event	SCULPTRA Aesthetic (First Treatment Session: N = 116)					Control (First Treatment Session: N = 117)				
	Total subjects reporting symptoms ^a n (%)	Severity of Adverse Event ^a				Total subjects reporting symptoms ^a n (%)	Severity of Adverse Event ^a			
		Mild n	Moderate n	Severe n	Missing n		Mild n	Moderate n	Severe n	Missing n
Localized Swelling	94 (81.0)	64	24	5	1	76 (65.0)	60	13	1	2
Localized Tenderness	94 (81.0)	63	24	2	5	83 (70.9)	62	16	1	4
Localized Redness	90 (77.6)	63	23	1	3	88 (75.2)	63	23	1	1
Post-Injection Site Pain	82 (70.7)	58	16	1	7	65 (55.6)	50	7	1	7
Localized Bruising	75 (64.7)	44	22	6	3	50 (42.7)	26	18	1	5
Bleeding from Site(s)	39 (33.6)	29	3	0	7	43 (36.8)	33	5	0	5
Localized Itching	23 (19.8)	14	1	0	8	34 (29.1)	24	6	1	3
Nodules / papules / lumps	4 (3.4)	2	1	0	1	14 (12.0)	4	7	1	2
Other ^b	19 (16.4)	7	8	1	3	22 (18.8)	11	6	3	2
Total	113 (97.4)	48	54	11	0	110 (94.0)	61	42	5	2

^a Subjects experiencing multiple episodes of a given adverse event are counted once for that event within the most severe category.

^b Subjects who reported multiple events in the "Other" category are counted only once within the most severe category. Adverse Events reported as "Others" are headache, dry skin, skin peeling, rash at injection, pimples, improvement of allergy symptoms, needle marks, sinus pressure, bruising, mouth sores, tenderness and twitching of nostril.

TABLE 2
DURATION OF ADVERSE EVENTS AFTER THE INITIAL TREATMENT SESSION,
RECORDED IN THE 14 DAY SUBJECT DIARY
(Controlled Phase, 0-13 months)
All-Treated Population: Per subject

Injection Procedure Related Event	SCULPTRA Aesthetic (First Treatment Session: N = 116)							Cosmoplast (First Treatment Session: N = 117)						
	Total subjects reporting symptoms n (%)	Duration of Adverse Event ^a						Total subjects reporting symptoms ^a n (%)	Duration of Adverse Event ^a					
		< 1 hour	1-24 hrs	2-7 days	8-14 days	≥15 days	Missing		< 1 hour	1-24 hrs	2-7 days	8-14 days	≥15 days	Missing
Localized Swelling	94 (81.0)	4	48	35	2	0	5	76 (65.0)	6	34	29	2	2	3
Localized Tenderness	94 (81.0)	7	45	32	1	4	5	83 (70.9)	6	33	29	2	10	3
Localized Redness	90 (77.6)	13	50	24	0	0	3	88 (75.2)	11	25	33	3	13	3
Post-Injection Site Pain	82 (70.7)	21	44	14	0	1	2	65 (55.6)	16	35	8	0	4	2
Localized Bruising	75 (64.7)	6	11	44	7	2	5	50 (42.7)	3	12	25	9	0	1
Bleeding from Site(s)	39 (33.6)	28	6	1	0	0	4	43 (36.8)	35	6	0	0	0	2
Localized Itching	23 (19.8)	9	5	6	0	0	3	34 (29.1)	5	8	13	2	4	2
Nodules / papules / lumps	4 (3.4)	0	0	2	0	1	1	14 (12.0)	0	0	3	0	9	2
Other ^b	19 (16.4)	0	3	10	2	3	1	22 (18.8)	1	2	7	2	8	2
Total	113 (97.4)	2	24	67	10	9	1	110 (94.0)	5	18	54	5	27	1

^a Subjects experiencing multiple episodes of a given adverse event are counted once for that event within the longest duration category.
^b Subjects who reported multiple events in "Other" category are counted only once within the longest duration category. For list of adverse events categorized as "other", see table 1.

TABLE 3
PHYSICIAN REPORTED* ADVERSE EVENTS
AFTER ALL TREATMENTS REGARDLESS OF RELATIONSHIP TO THE DEVICE OCCURRING
IN > 1% OF SUBJECTS
(Controlled Phase, 0-13 months)
All-Treated Population: Per subject

ADVERSE EVENTS	SCULPTRA Aesthetic N = 116 N (%)	Control N = 117 N (%)
injection site pain	11 (9.5)	12 (10.3)
application site nodule**	10 (8.6)	11 (9.4)
application site papule***	10 (8.6)	4 (3.4)
nasopharyngitis	7 (6.0)	9 (7.7)
headache	5 (4.3)	4 (3.4)
injection site erythema	4 (3.4)	38 (32.5)
acne	3 (2.6)	4 (3.4)
pain	3 (2.6)	2 (1.7)
injection site dermatitis	3 (2.6)	1 (0.9)
hypertension	3 (2.6)	0 (0.0)
injection site haemorrhage	2 (1.7)	6 (5.1)
swelling	2 (1.7)	2 (1.7)
fracture	2 (1.7)	2 (1.7)
urinary tract infection	2 (1.7)	2 (1.7)
streptococcal infection	2 (1.7)	0 (0.0)
tooth abscess	2 (1.7)	0 (0.0)
syncope vasovagal	2 (1.7)	0 (0.0)
cough	2 (1.7)	0 (0.0)
injection site pruritus	1 (0.9)	12 (10.3)
sinusitis	1 (0.9)	6 (5.1)
application site dryness	1 (0.9)	5 (4.3)
influenza	1 (0.9)	5 (4.3)
injection site swelling	1 (0.9)	4 (3.4)
bronchitis	1 (0.9)	2 (1.7)
upper respiratory tract infection	1 (0.9)	2 (1.7)
injection site discoloration	0 (0.0)	2 (1.7)
injection site eczema	0 (0.0)	2 (1.7)
skin tightness	0 (0.0)	2 (1.7)

* includes all subjects with nodules and papules regardless of duration

** Application site nodule is a lesion equal to or greater than to 5 mm, typically palpable, asymptomatic and non-visible

*** Application site papule is a lesions less than 5 mm, typically palpable, asymptomatic and non-visible

Adverse events that occurred with SCULPTRA Aesthetic at an incidence of <1%:
 Acrochordon, anxiety, colitis, contusion, corneal abrasion, cyst, depression, dermatitis, eczema, gastritis, herpes simplex, hypercholesterolemia, hypersensitivity, hypothyroidism, injection site desquamation, injection site rash, lower respiratory infection, lymphadenopathy, migraine, muscle injury, muscle twitching, myalgia, osteoarthritis, osteopenia, pruritus, rheumatoid arthritis, gastroenteritis, skin burning sensation, spider vein, staphylococcal infection, stress symptoms, tooth infection, toothache, vaginal infection.

Extension Phase Study (13 to 25 months)

A total of 106 subjects treated with SCULPTRA Aesthetic in the initial 13 month study were followed for an additional 12 months (25 months total) after their last treatment. Only SCULPTRA Aesthetic related adverse events were collected on the physician case report forms. Five new device related adverse events were reported in three subjects: 2 subcutaneous papules (1.9%), 1 nodule (0.9%) and 2 injection site pain (0.9%).

Nodules and Papules

In the controlled clinical study the percentage of subjects with nodules and/or papules was greater after SCULPTRA Aesthetic [(17.2%(20/116)] than after the Control treatment [(12.8%) (15/117)]. This reflects 8 Sculptra Aesthetic subjects who experienced nodules, 10 Sculptra Aesthetic subjects who experienced papules and 2 Sculptra Aesthetic subjects who experienced both nodules and papules.

After the first SCULPTRA Aesthetic injection session, time to onset for nodules was 160 days (median) and 209 days (mean) and for papules 55 days (median) and 159 days (mean). After the first SCULPTRA Aesthetic injection, the duration of nodules was 100 days (median) and 180 (mean) days, for papules was 110 days (median) and 176 days (mean).

One subject with a papule required a single intralesional corticosteroid injection and the event resolved. For three subjects with nodules/papules, no information on outcome was available at the end of the 25 month extension phase study. For all remaining subjects, nodules/papules resolved spontaneously. None of these events were reported as a serious adverse event by the investigator.

Table 4 contains, for the SCULPTRA Aesthetic (0-25 months) and Control (0-13 months) groups, summaries of the number of nodules and papules per baseline skin type, age group, and race stratified by baseline WAS. Summaries of the time to onset and duration of nodules and papules, stratified by baseline WAS are also presented.

TABLE 4
SUMMARY OF NODULES AND PAPULES,
SCULPTRA AESTHETIC (SA) AND CONTROL (CON)

Baseline (Pre-Injection, before first treatment) WAS	1		2		3		4		ALL	
	SA	CON	SA	CON	SA	CON	SA	CON	SA	CON
Treatment										
Number of pt injected (N)	6	4	55	41	41	55	14	17	116	117
Patients with nodule	0 0%	0 0%	4 7.3%	4 9.8%	4 9.8%	6 10.9%	2 14.3%	1 5.9%	10 8.6%	11 9.4%
Patients with papule	0 0%	0 0%	7 12.7%	1 2.4%	5 12.2%	1 1.8%	0 0%	2 11.8%	12 10.3%	4 3.4%
Demographics										
Patients Nodules or Papules per Fitzpatrick Skin Type										
Fitzpatrick Skin Type = 1	0	0	1	0	1	0	0	1	2	1
Fitzpatrick Skin Type = 2	0	0	4	2	3	2	0	1	7	5
Fitzpatrick Skin Type = 3	0	0	4	2	2	4	2	1	8	7
Fitzpatrick Skin Type = 4	0	0	2	1	1	1	0	0	3	2
Fitzpatrick Skin Type = 5	0	0	0	0	0	0	0	0	0	0
Fitzpatrick Skin Type = 6	0	0	0	0	0	0	0	0	0	0
Patients Nodules or Papules per age group										
Patients <35 y.o.	0	0	0	0	0	0	0	0	0	0
Patients 35-55 y.o.	0	0	7	5	4	4	1	1	12	10
Patients >55 y.o.	0	0	4	0	3	3	1	2	8	5
Patients Nodules or Papules per race										
Caucasian	0	0	10	4	5	6	2	3	17	13
Hispanic	0	0	0	1	2	1	0	0	2	2
Black / Asian /Other	0	0	1	0	0	0	0	0	1	0
Time (days) from first device injection to start of event [median, mean, min, max]										
Nodules - median days to event onset	0	0	261	4.5	66	2	48.5	1	160	1
Nodules - mean days to event onset	0	0	255.4	5.0	221.1	11	48.5	1	208.7	7.9
Nodules - time to onset minimum days	0	0	1	1	1	1	1	1	1	1
Nodules - time to onset maximum days			447	10	669	43	96	1	669	43
Papule - median days to event onset	0	0	49	1	64	25	0	22	54.5	22
Papules - mean days to event onset	0	0	130.7	1	197.8	25	0	17.7	158.7	15.8
Papules - time to onset minimum days	0	0	4	1	1	25	0	1	1	1
Papules - time to onset maximum days			500	1	586	25		30	586	30
Event Duration, days [median, mean, min, max]										
Nodule - median duration days	0	0	357	158.5	50	26	56.5	97	99.5	41
Nodule - mean duration days	0	0	315.4	196.8	118.9	31	56.5	97	180.1	97.3
Nodule duration minimum days	0	0	22	8	4	3	18	97	4	3
Nodule duration maximum days			543	462	489	68	95	97	543	462

Papule - median duration days	0	0	157	45	62	6	0	16	109.5	16
Papule - mean duration days	0	0	186.1	45	161.6	6	0	17.7	175.9	20.8
Papules – duration minimum days	0	0	9	45	8	6	0	15	8	6
maximum days			407	45	512	6		22	512	45

No significant associations were found between incidence of nodule/papules and geographic site, volume injected, number of treatment sessions, subject characteristics at baseline (Fitzpatrick skin type, age and race), or baseline WAS (pre-injection, before first treatment).

Post Marketing Surveillance

The following adverse events were received from post-marketing surveillance for SCULPTRA and SCULPTRA Aesthetic in the U.S. and outside the U.S., that were not observed in the clinical trials with SCULPTRA Aesthetic: allergic reaction, angioedema (Quincke's edema), application site discharge, fatigue, hypersensitivity reaction, hypertrophy of skin, injection site abscess, injection site atrophy, injection site fat atrophy, injection site granuloma (including ectropion), injection site induration, lack of effectiveness, malaise, periorbital nodules, photosensitive reaction, scar and skin discoloration, skin infection (including cellulitis (facial) and staphylococcal infection), skin rash, skin roughness, skin sarcoidosis, telangiectasias, urticaria, visible nodules with or without inflammation or discoloration.

Scarring, mostly a non-serious event, has been reported in association with skin discoloration, nodules, lumps, indurations, granulomas, hyperpigmentation, hypertrophic scars, and suspicion of keloid formation. Time to onset ranged from 1 month to 24 months post-Sculptra injection and outcome ranged from 'improved' to 'on-going' at last contact.

Skin discoloration has been reported as a non-serious event, typically reported in association with lumps and nodules. It has also been reported with blanching and telangiectasias. Time to onset usually ranged from 1 month to 12 months post-injection. Outcome ranged from 'improved' to 'on-going' at last contact.

Serious adverse events have infrequently been reported. The most commonly reported serious adverse events were injection site nodule, granuloma, nodule, erythema, pain, inflammation, edema, hypersensitivity and pruritus. Regarding these infrequently reported adverse events the following describes serious adverse events with a frequency greater than 5 reported events:

- Injection site nodules mostly occurred several months post-injection, with time to onset ranging from 1-2 months to 14 months post-last injection. In some cases, the nodules were reported to resolve spontaneously or following treatment with intralesional corticosteroids; others have been described with a prolonged duration of up to 2 years. For those nodules that were larger in size, occurring in difficult anatomical regions

(e.g. lower eyelid) or persisted after other treatments such as intralesional corticosteroids failed, surgical excision of the device was required.

- Serious granulomas usually occur several months after injection, in few cases onset was more than 1 year post-injection. While events were reported as granuloma, biopsy confirmation was made on few cases. Treatment ranged from subcision or intralesional corticosteroid with subsequent improvement, to surgical extraction. Of the few granuloma cases that required hospitalization, these were associated with infraorbital use or injection in the lip vermilion. For cases where information was available the patients were recovering following treatment.
- Serious erythema, serious pain, and serious pruritus reported with bruising and heat sensation, were reported within 24 hours post-injection. Treatment included corticosteroids, anti-histamines and/or anti-inflammatories. Events resolved within 7-10 days post-injection without sequelae and with no significant impact on daily life.
- Serious edema has been reported in association with erythema, pain, and heat sensation. The symptoms were mostly temporary, and with no significant impact on the quality of daily life reported. Treatment included corticosteroids, anti-histamines and/or anti-inflammatories. Recovery occurred within 7-10 days without sequelae.
- Serious hypersensitivity reactions have been reported mainly in association with facial swelling and Quincke's edema, with symptoms appearing from 1 day to 1 week post-injection. Patients recovered without sequelae after treatment with intravenous corticosteroids and anti-histamines.
- Serious infections such as subcutaneous abscesses, cellulitis, folliculitis, and methicillin-resistant *Staphylococcus aureus* at the injection site, have been reported. Time to onset of event ranged from 1 day to one week. Of these cases a few required hospitalization with administration of intravenous antibiotics. All patients recovered or were recovering at the last contact.

IX. SUMMARY OF PRE-CLINICAL STUDIES

The testing performed in the original application was adequate to support the safety and effectiveness of the device for the treatment of patients with signs of facial fat loss (lipoatrophy) and receiving treatment for human immunodeficiency virus.

Table 5 summarizes the new preclinical study submitted in Supplement 2 in support of the device use in immunocompetent patients requiring correction of contour deficiencies of Wrinkle Assessment Score (WAS) 2 (shallow) to 4 (deep) facial wrinkles such as nasolabial fold wrinkles.

Table 5: Preclinical Toxicity Study of the Device

Test Category	Study Results
Implantation - Rabbit (Local Tolerance)	Intradermal implantation revealed that all animals had 'several relatively large remnants' of PLLA visible at 64 weeks after implantation. The tissue response to PLLA was a mild-moderate inflammation described as a chronic, granulomatous reaction characterized by foreign body giant cells and macrophages. The tissue reaction was confined to the area between particles, did not involve the surrounding tissue and was not unexpected, because it was consistent with the persistent and particle nature of SCULPTRA Aesthetic.

X. SUMMARY OF PRIMARY CLINICAL STUDY

A. Study Design

Controlled Phase Study (0-13 Months):

The safety and effectiveness of SCULPTRA Aesthetic use to correct WAS 2 (shallow) to 4 (deep) nasolabial fold wrinkles was evaluated in a randomized, multicenter, evaluator blinded, controlled study of otherwise healthy and immune-competent, as well as not pregnant or breast-feeding subjects with previously untreated nasolabial fold wrinkles and WAS of 2 through 4.

The subjects received bilateral injections of either SCULPTRA Aesthetic or Control in both nasolabial fold wrinkles during a maximum of 4 sessions over 9 weeks. Study treatment was planned to be stopped when both nasolabial fold wrinkle reached optimal correction of WAS equal to 1 or 0, or until the maximum of 4 treatment sessions were completed.

The study subjects recorded adverse events in a subject diary after each treatment visit, and were followed by investigators at Week 3 and Months 3, 6, 9, and 13, after the last injection session. Standardized photographs were taken at screening, before each injection session and at each follow up visit.

Extension Phase Study (13-25 Months):

Study subjects who had received SCULPTRA Aesthetic were followed for safety and efficacy at months 19 and 25 after the last injection session. Standardized photographs were taken at each follow-up visit.

B. Study Endpoints

Controlled Phase Study (0-13 Months):

The primary efficacy endpoint was defined as the difference between SCULPTRA Aesthetic and Control cohorts on the mean change from baseline in the WAS of the nasolabial folds at the 13 month follow-up time point as determined by the Blinded Evaluation Committee (BEC). Evaluation was based on the 6-point photo-numeric Wrinkle Assessment Scale (see INSTRUCTIONS FOR USE)

Optimal correction was defined as a WAS of 0 or 1.

Secondary effectiveness endpoints were: 1) Mean change from pre-treatment baseline in the WAS as determined by the BEC at the non-primary follow-up time points (Week 3 and Months 3, 6, 9, following the last treatment); 2) Treatment success rate defined as the proportion of patients with a photographic WAS of <2 as defined by the BEC at each follow-up time point; 3) Investigator/Subject Global Assessments (4= Excellent Improvement, 3= Much Improved, 2= Improved, 1= No Change, 0= Worse) and the Subject Satisfaction Scores (4= Excellent, 3= Very Good, 2= Good, 1= Satisfactory, 0= Not Satisfied) at each follow-up time point compared between treatments; and 4) Time to peak correction, defined as the length of time between pre-treatment baseline and the first time point at which the best score assessed by the BEC was obtained over the length of the follow up period. Degree of peak correction was also assessed.

Extension Phase Study (13-25 Months):

All secondary effectiveness endpoints described above were evaluated for the long-term extension study time points at 19 and 25 months.

C. Study Population

Controlled Phase Study (0-13 Months):

A total of 233 subjects (age 26 to 73 years) were randomized and treated. At the conclusion of 13 months 106 out of 116 SCULPTRA Aesthetic subjects and 111 out of 117 control subjects completed the controlled phase of the study. Demographics are outlined in Table 6.

Extension Phase Study (13-25 Months):

One hundred and six subjects, who had received SCULPTRA Aesthetic and completed the controlled phase study, entered the extension phase. The demographic and background characteristics of all subjects were similar to the overall population randomized in the controlled phase study. At the end of the 25 month follow-up phase, 95 out of 106 of the subjects completed (see Table 6).

TABLE 6
STUDY POPULATION DEMOGRAPHICS

Demographic	Controlled Phase Study		Extension Phase Study
	SCULPTRA Aesthetic	Control	SCULPTRA Aesthetic
	N (%)	N (%)	N (%)
Total enrollment (randomized)	116	117	106
Age			
Mean (SD)	51.2 (7.8)	51.6 (8.4)	51.5 (7.9)
Gender			
Male	3 (2.6)	10 (8.5)	3 (2.8)
Female	113 (97.4)	107 (91.5)	103 (97.2)
Race			
Caucasian	96 (92.8)	89 (76.1)	86 (81.1)
Black	1 (0.9)	5 (4.3)	1 (0.9)
Asian	0	1 (0.9)	0
Hispanic	19 (16.4)	21 (17.9)	19 (17.9)
Other	0	1 (0.9)	0
Fitzpatrick skin type			
Type I	11 (9.5)	5 (4.3)	10 (9.4)
Type II	39 (33.6)	43 (36.8)	34 (32.1)
Type III	44 (37.9)	48 (41.0)	41 (38.7)
Type IV	16 (13.8)	15 (12.8)	16 (15.1)
Type V	5 (4.3)	4 (3.4)	4 (3.8)
Type VI	1 (0.9)	2 (1.7)	1 (0.9)
Nasolabial fold WAS before injection			
1	6 (5.2)	4 (3.4)	4 (3.8)
2	55 (47.6)	41 (35.3)	50 (47.2)
3	41 (35.3)	55 (47.6)	39 (36.8)
4	14 (12.1)	17 (14.7)	13 (12.3)
Total completed	106	111	95

D. Treatments Delivered

Controlled Phase Study (0-13 Months):

Treatment was planned for one to four sessions at 3 week intervals until optimal correction (was = 1 or 0) was achieved or four sessions were completed. At each treatment with SCULPTRA Aesthetic, multiple deep dermal injections in cross hatch grid pattern (see figures 3 – 7 in the instructions for use) of 0.1-0.2 ml SCULPTRA Aesthetic (up to a maximum of 2.5 ml per nasolabial fold per session) were performed into the left and right nasolabial folds according to product instructions for use. At each treatment session with Control multiple mid to deep dermal injections of an average of 1.0 ml per nasolabial fold per session were performed into the left and right nasolabial folds according to product instructions for use. Table 7 presents the amount of SCULPTRA Aesthetic and Control injected as a function of baseline wrinkle severity.

TABLE 7
SUMMARY SCULPTRA AESTHETIC AND CONTROL INJECTIONS

Baseline (Pre-Injection before first treatment) WAS	1		2		3		4		ALL	
	SCULPTRA Aesthetic	Control	SCULPTRA Aesthetic	Control	SCULPTRA Aesthetic	Control	SCULPTRA Aesthetic	Control	SCULPTRA Aesthetic	Control
Number of pt injected (N)	6	4	55	41	41	55	14	17	116	117
Injection volume, mL										
Session 1										
n	6	4	55	41	41	55	14	17	116	117
Mean	4.4	2.7	4.0	2.8	4.2	3.3	4.0	3.5	4.1	3.1
Median	5.0	2.5	4.4	2.9	4.8	3.8	4.0	3.6	4.5	3.0
Range	2.0,5.0	2.0,4.0	1.5,5.0	1.4,4.0	1.7,5.0	0.9,6.0	2.6,5.0	1.0,6.0	1.5,5.0	0.9,6.0
Session 2										
n	5	3	52	28	39	47	14	16	110	94
Mean	3.7	1.9	3.3	1.8	3.8	2.2	3.9	2.2	3.5	2.1
Median	4.0	2.0	3.5	1.8	4.0	2.0	4.0	1.9	3.8	2.0
Range	2.0,5.0	1.6,2.0	1.4,5.0	0.9,4.0	0.4,5.0	0.9,4.0	2.7,5.0	0.6,5.0	0.4,5.0	0.6,5.0
Session 3										
n	4	1	32	18	35	30	14	11	85	60
Mean	3.4	3.0	3.0	1.6	3.4	2.0	4.0	2.0	3.3	1.9
Median	3.8	3.0	3.0	1.4	3.5	2.0	4.2	1.9	3.5	2.0
Range	1.6,4.5	3.0,3.0	0.8,5.0	0.8,4.0	0.9,5.0	0.5,5.0	2.0,4.6	0.6,4.0	0.8,5.0	0.5,5.0
Session 4										
n	3	1	18	8	25	17	13	6	59	32
Mean	3.5	2.0	3.4	1.3	3.3	2.0	4.1	1.2	3.5	1.7
Median	3.4	2.0	3.7	1.0	3.3	2.0	4.0	1.0	3.7	2.0
Range	3.0,4.0	2.0,2.0	1.5,5.0	0.5,2.6	1.0,5.0	0.4,4.0	3.0,5.0	0.5,2.0	1.0,5.0	0.4,4.0
Total Volume Injected, mL										
Mean	11.5	5.4	9.9	5.0	12.7	6.9	15.7	7.3	11.7	6.2
Median	11.9	4.3	8.8	4.5	13.3	5.5	15.9	5.8	11.5	5.0
Range	4.7,17.9	4.0,9.0	4.5,18.2	1.6,14.0	2.8,20.0	1.8,16.0	11.7,19.0	2.7,16.0	2.8,20.0	1.6,16.0
Number of sessions										
Total Number of Sessions	18	9	157	95	140	149	55	50	370	303
Mean Number of Sessions	3	2.3	2.9	2.3	3.4	2.7	3.9	2.9	3.2	2.6
Range	1.0,4.0	1.0,4.0	1.0,4.0	1.0,4.0	1.0,4.0	1.0,4.0	3.0,4.0	1.0,4.0	1.0,4.0	1.0,4.0

The mean total volume injected per subject was 11.7 and 6.2 mL for SCULPTRA Aesthetic and Control treatments, respectively. The mean total volume injected per session, for both nasolabial folds, for SCULPTRA Aesthetic was 3.7 mL and 2.4 mL for Control. A mean number of 3.2 and 2.6 injection sessions were required for SCULPTRA Aesthetic and

Control subjects, respectively to achieve WAS of 1 or 0, or until the maximum of 4 treatment sessions with 3 week interval was reached in the study population.

Extension Phase Study (13-25 Months):

Of the 106 subjects who entered the extension phase study, 105 (99%) did not receive any additional SCULPTRA Aesthetic treatments after optimal correction was achieved in the controlled study. One subject in the extension phase study received one treatment session of SCULPTRA Aesthetic at month 19.

EFFECTIVENESS RESULTS:

Controlled Phase (0-13 month) and Extension Phase (13-25 Months) Study Results:

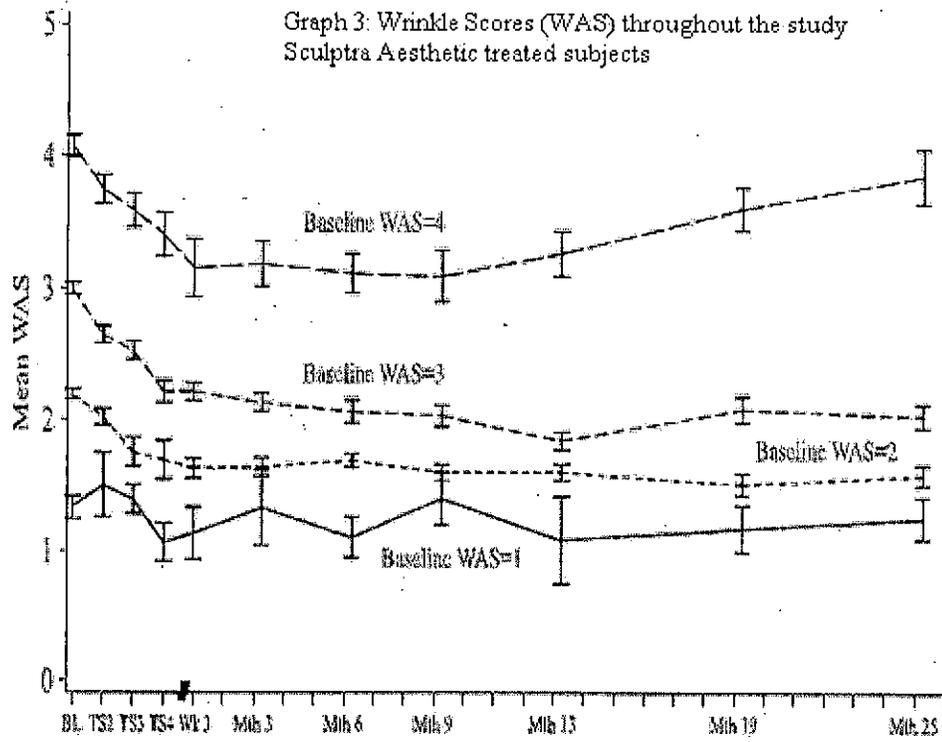
Primary Effectiveness Endpoint -

The difference between SCULPTRA Aesthetic and Control cohorts on the mean change from baseline in the WAS of the nasolabial folds at the 13 month follow up time point as determined by the Blinded Evaluation Committee was predicted to be 1.0 unit.

For the intended use population, Figure 1 demonstrates the observed WAS change from pre-treatment baseline through each treatment and follow-up point, individually for pre-treatment WAS = 2, 3, and 4. Table 8 presents the WAS change from pre-treatment baseline at each time point stratified by pre-treatment baseline score.

SCULPTRA Aesthetic (N=116) demonstrated improved WAS as compared to control (N=117) in correcting the contour deficiency of shallow (W=2) to deep (W=4) nasolabial folds at 13 months follow up after a single treatment regimen of up to four sessions of 2.5 mL maximum injections to the deep dermis with 3 week intervals. During the extension phase study (19 and 25 months follow up) SCULPTRA Aesthetic (N=106) continued to demonstrate improvements in WAS.

Figure 1



N of Subjects

WAS=4:	14	14	13	13	11	12	11	11	13	10	9
WAS=3:	41	38	33	21	39	34	35	36	37	36	36
WAS=2:	55	50	27	16	48	48	48	46	48	43	44
WAS=1:	6	4	3	3	5	3	5	3	4	4	4

BL = Baseline (Pre-injection)

TS2 = Pre-treatment session 2 (3 weeks after initial treatment)

TS3 = Pre-treatment session 3 (6 weeks after initial treatment)

TS4 = Pre-treatment session 4 (9 weeks after initial treatment)

Wk3 = 3 weeks after last treatment session

Mth 3, 6, 9, 13, 19, 25 = 3, 6, 9, 13, 19, 25 months after last treatment session

TABLE 8
WAS SUMMARY AT EACH TIME POINT STRATIFIED BY BASELINE SCORE
 (Controlled and Extension Phase Study, 0-25 months)
 Intent-to-treat Population, SCULPTRA Aesthetic Subjects only

Baseline WAS		Baseline (Pre-Injection)	Trt Session 2	Trt Session 3	Trt Session 4	Wk 3	Month 3	Month 6	Month 9	Month 13	Month 19	Month 25
1	N	6	4	3	3	5	3	5	5	4	4	4
	Mean (SE)	1.33 (0.086)	1.50 (0.245)	1.39 (0.111)	1.06 (0.147)	1.13 (0.200)	1.33 (0.289)	1.10 (0.155)	1.40 (0.201)	1.08 (0.337)	1.17 (0.180)	1.25 (0.160)
	Median	1.42	1.58	1.50	1.00	1.33	1.33	1.17	1.50	1.25	1.25	1.33
	Mean Change from Baseline (SE)	N/A	0.17 (0.236)	-0.06 (0.056)	-0.22 (0.056)	-0.17 (0.190)	-0.11 (0.242)	-0.27 (0.113)	0.03 (0.111)	-0.25 (0.220)	-0.17 (0.068)	-0.08 (0.048)
	P-Value for Change from Baseline	N/A	0.530	0.423	0.057	0.430	0.691	0.078	0.778	0.339	0.092	0.182
2	N	55	50	27	16	48	48	48	46	48	42	44
	Mean (SE)	2.19 (0.037)	2.02 (0.060)	1.75 (0.112)	1.69 (0.147)	1.63 (0.073)	1.64 (0.070)	1.69 (0.051)	1.60 (0.063)	1.60 (0.063)	1.51 (0.082)	1.58 (0.076)
	Median	2.17	2.00	1.83	1.92	1.67	1.67	1.83	1.50	1.67	1.50	1.58
	Mean Change from Baseline (SE)	N/A	-0.17 (0.057)	-0.46 (0.107)	-0.57 (0.145)	-0.53 (0.077)	-0.53 (0.071)	-0.50 (0.054)	-0.59 (0.062)	-0.59 (0.067)	-0.69 (0.084)	-0.61 (0.079)
	P-Value for Change from Baseline	N/A	0.005	<0.001	0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Baseline WAS		Baseline (Pre-Injection)	Trt Session 2	Trt Session 3	Trt Session 4	Wk 3	Month 3	Month 6	Month 9	Month 13	Month 19	Month 25
3	N	41	38	33	21	39	34	35	36	37	36	36
	Mean (SE)	2.99 (0.043)	2.64 (0.065)	2.52 (0.067)	2.21 (0.084)	2.21 (0.068)	2.13 (0.066)	2.06 (0.088)	2.03 (0.084)	1.84 (0.068)	2.08 (0.098)	2.03 (0.090)
	Median	2.83	2.67	2.33	2.17	2.17	2.08	2.00	2.08	1.83	2.08	2.00
	Mean Change from Baseline (SE)	N/A	-0.37 (0.066)	-0.52 (0.053)	-0.83 (0.085)	-0.77 (0.069)	-0.83 (0.068)	-0.94 (0.083)	-0.97 (0.078)	-1.15 (0.065)	-0.94 (0.097)	-0.96 (0.089)
	P-Value for Change from Baseline	N/A	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
4	N	14	14	13	13	11	12	11	11	13	10	9
	Mean (SE)	4.07 (0.078)	3.74 (0.107)	3.58 (0.129)	3.40 (0.166)	3.15 (0.220)	3.18 (0.168)	3.11 (0.151)	3.09 (0.196)	3.26 (0.169)	3.60 (0.161)	3.85 (0.207)
	Median	4.08	3.67	3.67	3.33	3.17	3.17	3.17	3.00	3.17	3.75	3.83
	Mean Change from Baseline (SE)	N/A	-0.33 (0.103)	-0.49 (0.112)	-0.71 (0.145)	-0.92 (0.232)	-0.94 (0.167)	-1.02 (0.138)	-0.97 (0.194)	-0.85 (0.164)	-0.53 (0.108)	-0.31 (0.168)
	P-Value for Change from Baseline	N/A	0.007	<0.001	<0.001	0.003	<0.001	<0.001	<0.001	<0.001	<0.001	0.097

2. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

Because the data submitted in this PMA supplement substantially duplicates information previously reviewed by the General and Plastic Surgery Devices Panel, this supplement was not referred to the Advisory Panel for review and recommendation.

3. CONCLUSIONS DRAWN FROM THE STUDIES

Based on the preclinical and clinical data in the PMA, CDRH determined the data provide a reasonable assurance that the device is safe and effective when used in accordance with the labeling.

4. CDRH DECISION

CDRH issued an approval order on July 28, 2009. The final conditions of approval cited in the approval order are described below.

In addition to the periodic post-market report (often referred to as annual report) requirements outlined in the enclosure, the sponsor agreed to the following Conditions of Approval:

- A Post Approval Study to determine the visibility of SCULPTRA Aesthetic via different standard facial imaging methods. Because the microparticles of SCULPTRA Aesthetic may be visible on computer tomography (CT) scans, magnetic resonance imaging (MRI), ultrasound (US) or standard, plain radiography, the sponsor will evaluate in animals the ability of these imaging techniques to detect the product and potential inflammation resulting from the foreign body response associated with device resorption.
- A 5-year post approval study (PAS) to assess the postmarket safety of Sculptra Aesthetic in immune-competent subjects when used as a single regimen for correction of shallow to deep nasolabial fold contour deficiencies and other facial wrinkles in which deep dermal grid pattern (cross-hatch) injection technique is appropriate. This corresponds to Wrinkle Assessment Scores (WAS) of 2 to 4. A single regimen consists of up to 4 sessions with 3 week intervals.

Specific objectives of this study are: (1) to determine the incidence, severity, duration, and time to onset of hypertrophic scarring, keloid formation and other changes in skin pigmentation in persons of color (Fitzpatrick skin types IV-VI), and to (2) determine the long term safety of SCULPTRA Aesthetic with regard to device-induced long term chronic inflammation (e.g., nodules, papules, granulomas, skin necrosis, hypersensitivity, and other injection site reactions).

This post-approval study will be a prospective, open-label, multi-center study conducted in the United States. The study will enroll 863 SCULPTRA Aesthetic naïve subjects (including at least 22 with Fitzpatrick skin type IV and 122 with Fitzpatrick skin type V-VI) who meet the eligibility criteria described in the labeling and follow them for 5 years in order to have a total of 604 evaluable subjects with 5 year follow-up data (including at least 15 with Fitzpatrick skin type IV and 85 with Fitzpatrick skin type V-VI). Following the initial treatment regimen of the nasolabial folds, subjects' safety will be evaluated at Week 3; Months 3, 6, 9, 13 and then at Years 2, 3, 4, and 5. Subject assessment of effectiveness will be evaluated at Months 6, 13 and then at Years 2, 3, 4 and 5.

The co-primary endpoints of the PAS are: (1) The 5-year incidence rate of any nodule and/or papule at SCULPTRA Aesthetic injection site (defined as nasolabial fold injection site and/or other facial wrinkles for which grid pattern (cross-hatch) injection technique is appropriate); and (2) The 5-year incidence rate of chronic inflammation

adverse events (AEs) other than nodule or papule at SCULPTRA Aesthetic injection site (as defined above). Chronic inflammation includes granulomas, skin necrosis, hypersensitivity reactions, hypertrophic scarring, keloid formation, changes in the skin pigmentation, and unexpected change in wrinkle contour. The secondary endpoints are the 2-year incidence rate of nodules, papules, any of the above chronic inflammation AE at SCULPTRA Aesthetic injection site (as defined above).

The primary hypothesis to be evaluated is that by the end of the 5 years of study follow-up the upper bound of the one-sided 95% confidence interval for the percentage of subjects (with Fitzpatrick skin types I-VI) with any injection site nodule or papule AE is less than 21%; and the upper bound of the one-sided 95% confidence interval for the percentage of subjects with Fitzpatrick skin types I-VI) with any injection site chronic inflammation AE other than nodule or papule is less than 3%. In addition, the study will include formal hypothesis testing for the year 2 endpoint (i.e., upper bound of the one-sided 95% confidence interval for the percentage of subjects with any injection site nodule or papule AE is less than 21%, and the upper bound of the one-sided 95% confidence interval for the percentage of subjects with any injection site chronic inflammation AE other than nodule or papule is less than 3%). The primary and secondary hypotheses will be tested for significance at the one-sided significance level of 5%, using an exact test.

Data will be collected on baseline (pre-treatment) patient demographic characteristics and device use for treatment (e.g., volume of device, number of injections), all AEs, will be collected and summarized by the number of subjects reporting adverse events, system organ class, preferred term, time of onset, severity of event, duration of event (timing relative to last injection), medical interventions required to resolve / treat such adverse outcomes, relationship to device or procedure, and different anatomic sites that the device was injected.

The assessment of other WAS 2-4 facial wrinkles for which grid pattern (cross-hatch) technique is considered appropriate will be conducted at baseline using a validated photo-numeric scale.

The study will include every reasonable effort to limit the cumulative loss-to-follow-up to less than 30% at the 5 year follow-up (with an average yearly loss <7%). If the follow-up rate is unacceptably low during the 5 year follow-up, FDA will consider other regulatory options to limit loss-to-follow-up, including requiring you to recruit more subjects.

Descriptive statistics showing the incidence of any injection site nodule or papule AEs, other chronic inflammations AEs and acute inflammatory AEs will be evaluated with the exact 95% confidence intervals for all subjects, for subjects with Fitzpatrick skin types I-III, for subjects with Fitzpatrick skin types IV-VI, for subjects with concomitant facial fillers, and for subjects without concomitant facial fillers, respectively. The percentages of subjects with each individual injection site chronic inflammation AE will be evaluated.

Every six months for the first two years and then annually until the study is completed a progress report will be submitted to the FDA that includes, but is not limited to, the status of site enrollment, the status of patient enrollment, the status of patient follow-up, and other milestones and an explanation for a delay, if any in meeting these goals, and the safety and effectiveness data collected during that reporting period.

Finally, the patient and physician labeling will be updated via PMA supplement to reflect the results of the post-approval study 2-year and 5-year findings, as soon as these data are available, as well as any other time point deemed necessary by FDA if significant new information from the study becomes available.

5. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.