Sculptra®

The *Sculptra* implant package (i.e., lyophilized vials) is provided sterile.

Caution: Federal (USA) law restricts this device to sale by or on the order of a licensed physician or properly licensed healthcare professional.

BEFORE USING SCULPTRA, PLEASE READ THE FOLLOWING INFORMATION THOROUGHLY.

Please direct any questions to Galderma Laboratories, L.P. Dallas, TX 75201 USA 1-855-425-8722.

DEVICE DESCRIPTION

Sculptra is an injectable implant containing microparticles of poly-L-lactic acid (PLLA), sodium carboxymethylcellulose (USP), non-pyrogenic mannitol (USP) and sterile water for injection (SWFI) (USP). Sculptra is available in 367.5 mg dose vials and is to be reconstituted prior to use to form a sterile, non-pyrogenic suspension (see INSTRUCTIONS FOR USE – Reconstitution).

INTENDED USE / INDICATIONS

Sculptra is indicated for correction of shallow to deep nasolabial fold contour deficiencies and other facial wrinkles for use in immune-competent subjects *.

Sculptra is indicated for correction of fine lines and wrinkles in the cheek region for use in immune-competent subjects *.

Sculptra is intended for restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus**.

* For nasolabial fold contour and other facial wrinkles indication, including correction of fine lines and wrinkles in the cheek region, please go to page 2.
** For HIV-associated lipoatrophy indication, please go to page 68

SCULPTRA FOR CORRECTION OF SHALLOW TO DEEP NASOLABIAL FOLD CONTOUR DEFICIENCES AND OTHER FACIAL WRINKLES

SCULPTRA FOR CORRECTION OF FINE LINES AND WRINKLES IN THE CHEEK REGION FOR USE IN IMMUNE-COMPETENT SUBJECTS

CONTRAINDICATIONS

Sculptra should not be used in any person who has hypersensitivity to any of the components of *Sculptra* (see DEVICE DESCRIPTION).

Sculptra should not be used in patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.

Sculptra should not be used in patients with known history of or susceptibility to keloid formation or hypertrophic scarring.

Sculptra reconstituted with lidocaine hydrochloride (lidocaine) should not be used in patients with a history of allergies to lidocaine or other amide type local anesthetics.

WARNINGS

- Do not overcorrect (overfill) the volume deficiencies or contour defects, because the depression is expected to gradually improve during several weeks after injection as the treatment effect of *Sculptra* occurs (see INSTRUCTION FOR USE – Patient Treatment).

- *Sculptra* must not be injected intramuscularly or intravascularly. Localised superficial necrosis and scarring may occur after injection in or near vessels. It is thought to result from the injury, obstruction, or compromise of blood vessels. Areas with limited collateral blood flow has an increased risk of ischaemia. Special caution should be taken if the patient has undergone a prior surgical procedure in the planned treatment area. Aspiration prior to injection is recommended.

- Introduction of product into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Take extra care when injecting soft tissue fillers, for example inject the product slowly and apply the least amount of pressure necessary. Rare but serious adverse events associated with the intravascular injection of soft tissue fillers in the face have been reported and include temporary or permanent vision impairment, blindness, cerebral ischemia or cerebral hemorrhage, leading to stroke, skin necrosis, and damage to underlying facial structures. Immediately stop the injection if a patient exhibits any of the following symptoms, including changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist should an intravascular injection

occur.

- *Sculptra* use at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes or hives) or infection is present should be deferred until the inflammatory process has resolved and is controlled.

- *Sculptra* post-treatment reactions have included delayed occurrence of subcutaneous papules and nodules. The subcutaneous papules and nodules were often confined to the injection site, typically palpable, asymptomatic and non-visible, occurring days to months after injection and had a prolonged time course to resolution. See ADVERSE EVENTS section for details.

- The kinetics of *Sculptra* resorption in humans has not been determined. In an intradermal implantation study in rabbits all animals had "several relatively large remnants" of injectable PLLA visible at 64 weeks after implantation. The tissue response to injectable PLLA was generally greater than the vehicle or negative plastic controls and was 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 injectable PLLA.

PRECAUTIONS

- *Sculptra* vials are for single patient and single session use only in order to avoid contamination. Do not reuse the vial and do not re-sterilize the vial. Discard immediately after use. Do not use if the package or vial is opened or damaged.

- *Sculptra* should only be used by healthcare professionals trained in the approved indication. See INSTRUCTION FOR USE section for details.

- In order to minimize the risks of potential complications (such as formation of papules/nodules, perforation of vessels, or trauma to nerves and other vulnerable structures), *Sculptra* should only be used by healthcare professional who have appropriate training, experience, and who are knowledgeable about the anatomy at and around the site of injection and who are fully familiar with the product, product educational materials, and the entire package insert and patient labeling.

- Healthcare professionals are encouraged to discuss all potential risks of soft tissue injection with their patients prior to treatment and ensure that patients are aware of signs and symptoms of potential complications.

- The safety and effectiveness of injecting *Sculptra*: 1) in larger amounts, 2) at different frequencies, 3) at anatomic sites different than specified for the intended use of the product, or 4) at anatomic sites that have had other dermal filler injections, have not been evaluated.

- The safety and effectiveness of *Sculptra* for use in the lips has not been evaluated. *Sculptra* should not be injected into the red area (vermillion) of the lips.

- Avoid superficial injections as this may be associated with increased local adverse events such as nodules and papules. Take special care when using *Sculptra* in patients with thin skin. Please refer to PATIENT TREATMENT for injection technique instruction.

- *Sculptra* injection in the periorbital area has not been studied. An increased risk of papules and nodules has been reported in published literature after injections in the periorbital area.

- Results from the completed 5-year post approval study, in which *Sculptra* was reconstituted with 5 mL, indicates an increased risk of papules and nodules, which may be associated with a larger injection volume and higher baseline wrinkle severity scores, particularly in the treatment of marionette lines, see ADVERSE EVENTS, Clinical Trial, Post Approval Study.

- Safety and effectiveness of *Sculptra* has not been evaluated in patients who are pregnant, lactating, breast feeding, or under 18 years of age.

- Safety and effectiveness of *Sculptra* has not been evaluated in patients with the following: connective tissue disease, bleeding disorders, active hepatitis, serious abnormalities in laboratory findings other than CD4 cell count, HIV viral load and lactic acid, disease such as cancer, stroke and/or myocardial infarction and on any immunosuppressive therapy.

- Safety and effectiveness of *Sculptra* has not been systematically evaluated with other drugs (other than lidocaine) or substances, filler products, implants or devices used prior or during the same treatment session.

- Other filler products should not be directly mixed with *Sculptra*. No studies of interactions of *Sculptra* mixed with drugs (other than lidocaine) or other substances or implants have been made.

- It is not known whether *Sculptra* is radiopaque in humans. The microparticles of *Sculptra* may be visible on computer tomography (CT) scans, magnetic resonance imaging (MRI), ultrasound or standard, plain radiography. Patients should be informed that the device may be radiopaque, so that they can inform their health care professionals, including radiologists. In an animal study, *Sculptra* implants were observed in 10/10 rats via MRI and ultrasound imaging 24 hours after subcutaneous injection. Ninety (90) days after injection, *Sculptra* was observed in 3/10 rats via ultrasound and no animals via MRI. *Sculptra* was not observed at either time point via CT scan or standard, plain radiography.

- Injections into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.

- Patients with bleeding disorders or patients using substances that affect platelet function, thrombolytics or anticoagulants may, as with any injection, experience increased bruising, haematoma or localized bleeding at injection site.

- Injection procedures are associated with a risk of infection. Aseptic technique and standard practice to prevent cross-infections are to be followed.

- After use, treatment syringes and needles are considered contaminated biohazards. Handle and dispose contaminated syringes and needles in accordance with accepted medical practice and applicable local, state and federal requirements.

- The patient should be informed that he or she should minimize exposure of the treatment area to sun and avoid UV lamp exposure and extreme temperatures until any initial swelling and redness has resolved.

- If laser treatment, chemical peeling or any other procedure based on active dermal response is considered after treatment with *Sculptra*, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if *Sculptra* is administered before the skin has healed completely after such a procedure.

In addition, the following precautions should be observed if lidocaine is added to the reconstituted *Sculptra* suspension:

- Only a sterile lidocaine solution should be added to the reconstituted *Sculptra* suspension just before the injection procedure and this should then be used immediately. Please refer to INSTRUCTIONS FOR USE section for additional information.

- Consider safety risks associated with the use of lidocaine, including possible toxic effects in patients with increased sensitivity and accumulating levels of lidocaine if used concurrently with other administration. For specific safety information, please refer to the product labeling for the lidocaine solution used.

ADVERSE EVENTS

SCULPTRA FOR CORRECTION OF SHALLOW TO DEEP NASOLABIAL FOLD CONTOUR DEFICIENCES AND OTHER FACIAL WRINKLES (RECONSTITUTED WITH 5 ML SWFI)

Clinical Studies 5 mL reconstitution

Controlled phase study (0-13 months)

A prospective, randomized clinical study was conducted at 10 centers in the US. Two hundred thirty-three (233), immune-competent and non-pregnant and non-breastfeeding subjects with previously untreated nasolabial fold wrinkles with wrinkle assessment scale (WAS) of 2 through 4 received bilateral injections of either *Sculptra Aesthetic* or *Cosmoplast* 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. AES reported in subject diaries after initial treatment are summarized in Tables 1 (intensity) and 2 (duration) below. AEs 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)					*Cosmoplast* (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 Tendernes	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[a] 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 the "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 OCCURING IN >1% OF SUBJECTS
(Controlled Phase, 0-13 months)
All-Treated Population: Per Subject

Adverse Events (MedDRA Preferred Term)	***Sculptra Aesthetic*** N=116 N (%)	***Cosmoplast*** 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 (26)	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 lesion 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 AEs were collected on the physician case report forms. Five new device-related AEs 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 *Sculptra Aesthetic* injection, the duration of nodules was 100 days (median) and 180 days (mean), 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 3 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 (SAE) by the investigator.

Table 4 contains, for the *Sculptra Aesthetic* (0-25 months) and *Cosmoplast* (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 COSMOPLAST (COS)

Baseline (Pre-Injection, before first treatment) WAS	**1**		**2**		**3**		**4**		**ALL**	
Treatment	**SA**	**COS**	**SA**	**COS**	**SA**	**COS**	**SA**	**COS**	**SA**	**COS**
Number of pt injected (N)	6	4	55	41	41	55	14	17	116	117
Patients with nodule	0	0	4	4	4	6	2	1	10	11
	0%	0%	7.3%	9.8%	9.8%	10.9%	14.3%	5.9%	8.6%	9.4%
Patients with papule	0	0	7	1	5	1	0	2	12	4
	0%	0%	12.7%	2.4%	12.2%	1.8%	0%	11.8%	10.3%	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 < 35y.o	0	0	0	0	0	0	0	0	0	0
Patients 35-55y.o	0	0	7	5	4	4	1	1	12	10
Patients > 55y.o	0	0	4	0	3	3	1	2	8	5
Patients Nodules or Papules per age 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
maximum days			447	10	669	43	96	1	669	43
Papules-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
maximum days			500	1	586	25		30	586	30
Event Duration, days (median, mean, min, max)										
Nodules-median duration days	0	0	357	158.5	50	26	56.5	97	99.5	41
Nodules-mean duration days	0	0	315.4	196.8	118.9	31	56.5	97	180.1	97.3
Nodules- duration minimum days	0	0	22	8	4	3	18	97	4	3
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
Papule- 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 Approval Study

A 5-year post approval study was conducted in a total of 867 subjects enrolled and treated at 20 investigational sites in the US. Treated subjects received a single regimen of *Sculptra Aesthetic* to correct shallow to deep NLF contour deficiencies and, if present, other facial wrinkles for which grid pattern (cross-hatch) injection technique was appropriate. Subjects received up to four treatments spaced 3 weeks apart through Study Week 9 and were followed for up to 5 years.

A total of 465 of 867 subjects (53.6%) reported AEs through the Year 5 visit; 29.1% of reported AEs were found to be related to treatment. One SAE related to treatment was reported (foreign body granuloma).

Nodules and Papules

The overall incidence rate of injection site nodules and/or papules (NPs) occurred in 28.5% of subjects treated with *Sculptra Aesthetic* in all treated facial areas (i.e. nasolabial folds (NLFs), marionette lines (MLs), cheek folds, and chin crease). The incidence rates of NPs in each anatomic area varied (27.2% in the MLs, 19.0% in the NLFs, 5.4% in the cheek folds, and 3.6% in the chin creases). See Tables 5-7 below. While the overall NPs incident rate exceeded the pre-specified 21% threshold for the 5-year endpoint, it is important to note that the rate of NPs in the NLFs was 19% (165/867, ITT Population) and 21% (139/661) for the population that completed the Year 5 visit.

The overall mean total treatment volume was similar in anatomic sides with a NP (3.92± 1.92mL) as compared to anatomic sides without a NP (3.65 ± 2.15 mL). However, increased injection volumes may be associated with higher frequencies of NPs, particularly in the MLs (treatment volume in the MLs with a NP [3.13 ± 1.49 mL] as compared to treatment volume in MLs without a NP [2.67 ± 1.44 mL]). When comparing treatment volumes, the reported incidence rates for NPs at the MLs was higher when compared to other treated facial areas (i.e. NLF, cheek folds, chin crease). Further, for treatment volumes greater than 2 mL per ML, the incidence rate of NPs exceeded the pre-specified 21% protocol threshold.

Overall, there was a slight increase in the overall rate of NPs with increasing wrinkle severity: Baseline WAS 2 (9.9%); baseline WAS 3 (12.1%); baseline WAS 4 (17.5%).

Treatment of nodules and/or papules in this study included injections of: Sodium chloride, triamcinolone, 5-Fluorouracil/triamcinolone/lidocaine; and/or oral: Diphenhydramine, doxycycline, ibuprofen; and/or topical: Benzocaine, mometasone cream.

TABLE 5
SUMMARY OF TOTAL TREATMENT VOLUME (ML) BY ANATOMIC AREA, NODULE/PAPULE PER ANATOMIC SIDES, AND FITZPATRICK SKIN TYPE

Anatomic Area Nodule/Papule[a] Anatomic Sides[b]	Fitzpatrick Skin Type I-III (N=557)	Fitzpatrick Skin Type IV-VI (N=310)	Overall (N=867)
All Anatomic Areas **All Anatomic Sides**			
Number of Anatomic Sides	2273	1006	3279
Mean (SD)	3.676 (2.1429)	3.716 (2.0889)	3.688 (2.1262)
Median	3.400	3.500	3.430
Min, Max	0.14, 13.00	0.10, 10.00	0.10, 13.00
Anatomic Sides with Any Nodule and/or Papules			
Number of Anatomic Sides	320	124	444
Mean (SD)	3.968 (1.9230)	3.788 (1.9115)	3.918 (1.9193)
Median	3.600	3.500	3.505
Min, Max	0.30, 10.00	0.50, 9.50	0.30, 10.00
Anatomic Sides without Any Nodule and/or Papules			
Number of Anatomic Sides	1953	882	2835
Mean (SD)	3.628 (2.1735)	3.705 (2.1134)	3.652 (2.1549)
Median	3.300	3.500	3.400
Min, Max	0.14, 13.00	0.10, 10.00	0.10, 13.00
Nasolabial Folds **All Anatomic Sides**			
Number of Anatomic Sides	1114	620	1734
Mean (SD)	4.596 (2.1660)	4.425 (2.0762)	4.535 (2.1353)
Median	4.270	4.000	4.200
Min, Max	0.50, 10.00	0.60, 10.00	0.50, 10.00
Anatomic Sides with Any Nodule and/or Papules			
Number of Anatomic Sides	158	77	235
Mean (SD)	4.759 (1.9473)	4.308 (1.9864)	4.611 (1.9675)
Median	4.400	4.000	4.200
Min, Max	0.90, 10.00	1.40, 9.50	0.90, 10.00
Anatomic Sides without Any Nodule and/or Papules			
Number of Anatomic Sides	956	543	1499
Mean (SD)	4.569 (2.1998)	4.442 (2.0899)	4.523 (2.1608)
Median	4.250	4.000	4.200
Min, Max	0.50, 10.00	0.60, 10.00	0.50, 10.00

a: For purposes of this study, a nodule or papule is conservatively defined to include investigator-confirmed lumps, bumps, etc. (by visual examination or palpation), regardless of onset time or duration, including induration (not generalized swelling) occurring in the injection area, as well as non-uniform distribution of study product.

b: This table summarizes the relationship between nodules/papules and injection frequency by anatomic sides (left or right), as every anatomic side may not have been treated at each injection session. Anatomic sides include the chin crease and the left and right sides for nasolabial folds, cheek folds, and marionette lines.

Source: Table 14.3.1.3

TABLE 6
SUMMARY OF INCIDENCE OF INJECTION SITE NODULE AND/OR PAPULE[a,b] BY NUMBER OF INJECTION SESSIONS, ANATOMIC SIDES AND FITZPATRICK SKIN TYPE (ITT POPULATION; DATA THROUGH YEAR 5 VISIT)

Number of Injection Sessions Anatomic Sides[b]	Fitzpatrick Skin Type I-III (N=557)		Fitzpatrick Skin Type IV-VI (N=310)		Overall (N=867)	
	Anatomic Sides[c] n / N (%)	Events n	Anatomic Sides[c] n / N (%)	Events n	Anatomic Sides[c] n / N (%)	Events n
Number of Injection Sessions = 1						
All Anatomic Sides with Injection Site Nodule and/or Papule	20 / 209 (9.6)	20	12 / 78 (15.4)	15	32 / 287 (11.1)	35
NLF Sides with Injection Site Nodule and/or Papule	8 / 80 (10.0)	8	9 / 47 (19.1)	12	17 / 127 (13.4)	20
Number of Injection Sessions = 2						
All Anatomic Sides with Injection Site Nodule and/or Papule	47 / 290 (16.2)	51	19 / 151 (12.6)	20	66 / 441 (15.0)	71
NLF Sides with Injection Site Nodule and/or Papule	20 / 117 (17.1)	22	8 / 76 (10.5)	9	28 / 193 (14.5)	31
Number of Injection Sessions = 3						
All Anatomic Sides with Injection Site Nodule and/or Papule	62 / 461 (13.4)	67	38 / 247 (15.4)	42	100 / 708 (14.1)	109
NLF Sides with Injection Site Nodule and/or Papule	27 / 221 (12.2)	30	21 / 138 (15.2)	24	48 / 359 (13.4)	54
Number of Injection Sessions = 4						
All Anatomic Sides with Injection Site Nodule and/or Papule	191 / 1313 (14.5)	203	55 / 530 (10.4)	60	246 / 1843 (13.3)	263
NLF Sides with Injection Site Nodule and/or Papule	103 / 696 (14.8)	108	39 / 359 (10.9)	41	142 / 1055 (13.5)	149

a: For purposes of this study, a nodule or papule is conservatively defined to include investigator-confirmed lumps, bumps, etc (by visual examination or palpation), regardless of onset time or duration, including induration (not generalized swelling) occurring in the injection area, as well as non-uniform distribution of study product.

b: This table summarizes incidence of nodules/papules by injection frequency and anatomic sides (left or right), as the injection frequency may vary by side. Anatomic sides include the chin crease and the left and right sides for NLFs, cheek folds and marionette lines.

c: Anatomic sides experiencing multiple episodes of event are counted once within each event category.

Source: CSR, Table 14.3.3.9.

TABLE 7
SUMMARY OF INCIDENCE OF INJECTION SITE NODULE AND/OR PAPULE [a,b] BY BASELINE WRINKLE ASSESSMENTS (WAS), ANATOMIC SIDES, AND FITZPATRICK SKIN TYPE

Baseline Wrinkle Assessments Anatomic Sides[b]	Fitzpatrick Skin Type I-III (N=557)		Fitzpatrick Skin Type IV-VI (N=310)		Overall (N=867)	
	Anatomic Sides[c] n / N (%)	Events n	Anatomic Sides[c] n / N (%)	Events n	Anatomic Sides[c] n / N (%)	Events n
Baseline Wrinkle Assessments: 2						
All Anatomic Sides with Injection Site Nodule and/or Papule	53 / 574(9.2)	54	32 / 281 (11.4)	35	85 / 855 (9.9)	89
NLF Sides with Injection Site Nodule and/or Papule	19 / 210(9.0)	19	20 / 143 (14.0)	23	39 / 353 (11.0)	42
Anatomic Sides other than NLF with Injection Site Nodule and/or Papule	34 / 364(9.3)	35	12 / 138 (8.7)	12	46 / 502 (9.2)	47
Cheek Fold Sides with Injection Site Nodule and/or Papule	7 / 114(6.1)	7	0 / 21	0	7 / 135 (5.2)	7
Marionette Line Sides with Injection Site Nodule and/or Papule	26 / 190 (13.7)	27	12 / 77 (15.6)	12	38 / 267 (14.2)	39
Chin Crease Sides with Injection Site Nodule and/or Papule	1 / 60 (1.7)	1	0 / 40	0	1 / 100 (1.0)	1
Baseline Wrinkle Assessments: 3						
All Anatomic Sides with Injection Site Nodule and/or Papule	108 / 854 (12.6)	115	36 / 341 (10.6)	39	144 / 1195 (12.1)	154
NLF Sides with Injection Site Nodule and/or Papule	55 / 429 (12.8)	59	23 / 208 (11.1)	24	78 / 637 (12.2)	83
Anatomic Sides other than NLF with Injection Site Nodule and/or Papule	53 / 425 (12.5)	56	13 / 133 (9.8)	15	66 / 558 (11.8)	71
Cheek Fold Sides with Injection Site Nodule and/or Papule	2 / 104(1.9)	2	2 / 28 (7.1)	2	4 / 132 (3.0)	4
Marionette Line Sides with Injection Site Nodule and/or Papule	49 / 231 (21.2)	52	10 / 76 (13.2)	12	59 / 307 (19.2)	64
Chin Crease Sides with Injection Site Nodule and/or Papule	2 / 90 (2.2)	2	1 / 29 (3.4)	1	3 / 119 (2.5)	3
Baseline Wrinkle Assessments: 4						
All Anatomic Sides with Injection Site Nodule and/or Papule	159 / 845 (18.8)	172	56 / 384 (14.6)	63	215 / 1229 (17.5)	235
NLF Sides with Injection Site Nodule and/or Papule	84 / 475 (17.7)	90	34 / 269 (12.6)	39	118 / 744 (15.9)	129
Anatomic Sides other than NLF with Injection Site Nodule and/or Papule	75 / 370 (20.3)	82	22 / 115 (19.1)	24	97 / 485 (20.0)	106
Cheek Fold Sides with Injection Site Nodule and/or Papule	0 / 43	0	0 / 8	0	0 / 51	0

a: For purposes of this study, a nodule or papule is conservatively defined to include investigator-confirmed lumps, bumps, etc (by visual examination or palpation), regardless of onset time or duration, including induration (not generalized swelling) occurring in the injection area, as well as non-uniform distribution of study product.

b: This table summarizes incidence of nodules/papules by injection frequency and anatomic sides (left or right), as the injection frequency may vary by side. Anatomic sides include the chin crease and the left and right sides for NLFs, cheek folds and marionette lines.

c: Anatomic sides experiencing multiple episodes of event are counted once within each event category.

Source: Listings 16.2.6.1.1 and 16.2.7.5.1

Across the investigational sites, there was substantial site-to-site variability in the incidence of overall NPs ranging from 0 – 79.1%. The site-to-site variability should be interpreted with an understanding that sub-analyses by individual study site show the nodule/papule incidence to be highly variable. Similar sub-analyses of treatment volume by surface area (TVSA) data show site-to-site variability in both the magnitude and relationship to nodules/papules, in context of overall TVSA results (i.e., higher mean TVSA is not always associated with nodules/papules). Sub-analyses by individual study site are suggestive of other possible contributing factors associated with nodules/papules, than product alone. These data reinforce the importance of proper training and product use to avoid concentrated product deposits.

Other Adverse Events of Interest
Adverse Events of Interest (AEIs) other than NPs were defined as hypertrophic scarring, keloid formation, changes in the skin pigmentation at the site of injection, biopsy-confirmed granuloma, skin necrosis, hypersensitivity reactions, and unexpected change in wrinkle contour. The overall incidence of AEIs other than NPs occurred in 1.0% of subjects treated with *Sculptra Aesthetic* in all treated facial areas (i.e. NLFs, MLs, cheek folds, and chin crease), which is well within the pre-specified threshold of 3%.

There was no reported incidence of hypertrophic scarring, keloid formation, skin necrosis, or hypersensitivity reactions in individuals of Fitzpatrick Skin types I-VI.

A total of six subjects (0.7%) reported changes in skin pigmentation at the site of injection compared to adjacent skin. These events occurred in 1/557 (0.2%) subjects of FST I-III and in 5/310 (1.6%) subjects of FST IV-VI with onset 6 to 399 days post-injection. Post-inflammatory hyperpigmentation (PIH) is a common skin disorder that develops due to injury or inflammation and can manifest as tan, brown, dark brown, or even blue-gray patches and spots on the skin. People with higher FST are known to be more susceptible to PIH. All events of changes in skin pigmentation were considered mild in severity with a duration of 24 to 152 days (unresolved at study end in one FST V subject).

SCULPTRA FOR CORRECTION OF SHALLOW TO DEEP NASOLABIAL FOLD CONTOUR DEFICIENCIES (RECONSTITUTED WITH 8 ML SWFI WITH THE ADDITION OF 1 ML 2% LIDOCAINE)

Clinical Studies 8 mL reconstitution

Base study (0-48 weeks)

Eighty subjects were enrolled in a randomized, treatment-controlled, evaluator-blinded, multicenter study to evaluate the safety and effectiveness of *Sculptra Aesthetic* reconstituted in 8 mL SWFI with the addition of 1 mL 2% lidocaine for treatment of nasolabial folds. Subjects were treated to optimal correction at four-week intervals, with a maximum of four treatment sessions. Out of the 80 subjects enrolled, 59 subjects received *Sculptra Aesthetic* reconstituted in 8 mL SWFI with the addition of 1 mL 2% lidocaine (treatment group) and 21 subjects received *Sculptra Aesthetic* reconstituted in 5 mL SWFI (control group).

Pre-printed diary forms were used by subjects to record the presence of pre-defined expected post-treatment events in the treated area, i.e. bruising, redness, swelling, pain, tenderness, itching,

lumps/bumps, and “other” for 28 days following each treatment. Subjects rated each treatment site response as “None”, “Mild”, “Moderate” or “Severe”.

Vision function assessments: Snellen Visual Acuity Test, Extraocular Muscle Function Test and Confrontation Visual Field Test, was performed both prior to and post injection of the study product at baseline, before and after treatments, and all physical scheduled follow-up visits.

Subjects assessed their pain, for each treatment area individually, before (prior to application of any anesthetic) and immediately after (before any post-injection therapy was provided, e.g., ice packs) each treatment session. Subjects rated their pain using an 11-point NPS where 0 was no pain and 10 was the worst pain imaginable.

AEs were also reported by the Treating Investigator at all follow-up visits when applicable.

Out of the 59 subjects in the 8 mL treatment group, the Investigator reported a total of 18 treatment-related events for 7 subjects (11.9%), all categorized as mild in severity. In the control group, 7 out of 21 (33.3%) had a total of 12 treatment-related events reported, most were mild, but three of these were considered moderate in severity (one event of rhinorrhea and two events of headache). The Investigator-reported AEs by percentage of treated population in the 8 mL treatment group were injection site hypoaesthesia, oral disorder, injection site paresthesia, injection site induration, herpes simplex, oral herpes, headache, dry skin, skin mass – all reported at a frequency of 1.7%, i.e. these events occurred in one subject out of the 59 in the treatment group respectively. In the 5 mL treatment group, rhinorrhea was reported for two subjects (9.5%), and the following: hypoaesthesia, injection site nodule, injection site pain, injection site swelling, contusion, headache, nasal congestion and papule were reported for one subject respectively.

Two subjects reported one serious adverse event each, retinal detachment and anxiety requiring hospitalization. None of these events were considered related to study treatment.

The frequency, intensity and duration of pre-defined events reported by the subject in the daily diary are presented in Tables 8 and 9. Pain, tenderness and swelling were the three events most commonly reported in all subjects, both from the 8 mL and 5 mL group. The majority were mild in intensity and resolved within two weeks.

TABLE 8
FREQUENCY AND INTENSITY OF PRE-DEFINED EVENTS REPORTED IN THE DAILY DIARY

Summary of Subject Diary Symptoms by Session and Maximum Severity
Safety Population

	All 5 mL (N=21)				All 8 mL (N=59)			
	Any n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Any n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Overall, NLF Any Symptom	21 (100.0)	9 (42.9)	11 (52.4)	1 (4.8)	56 (94.9)	27 (45.8)	26 (44.1)	3 (5.1)
Pain (including burning)	20 (95.2)	13 (61.9)	6 (28.6)	1 (4.8)	38 (64.4)	33 (55.9)	5 (8.5)	0
Tenderness	21 (100.0)	14 (66.7)	7 (33.3)	0	49 (83.1)	39 (66.1)	9 (15.3)	1 (1.7)
Redness	15 (71.4)	13 (61.9)	2 (9.5)	0	37 (62.7)	28 (47.5)	9 (15.3)	0
Bruising	15 (71.4)	9 (42.9)	5 (23.8)	1 (4.8)	36 (61.0)	21 (35.6)	13 (22.0)	2 (3.4)
Swelling	16 (76.2)	8 (38.1)	8 (38.1)	0	48 (81.4)	29 (49.2)	18 (30.5)	1 (1.7)
Itching	3 (14.3)	3 (14.3)	0	0	13 (22.0)	13 (22.0)	0	0
Lumps/Bumps	10 (47.6)	7 (33.3)	3 (14.3)	0	21 (35.6)	18 (30.5)	2 (3.4)	1 (1.7)

Note: N = Number of subjects, n = Number of subjects in specific category. Percentages calculated as 100 x (n/number of subjects with response at visit for applicable question).
Subjects reporting multiple events of the same symptom are counted once for that event within the most severe category. For the Overall, the maximum severity from each session was determined for each subject and summarized.

TABLE 9
FREQUENCY AND DURATION OF PRE-DEFINED EVENTS
REPORTED IN THE DAILY DIARY

Summary of Subject Diary Symptoms by Session and Number of Days with Symptoms
Safety Population

	All 5 mL (N=21)				All 8 mL (N=59)			
	1 Day n (%)	2-7 Days n (%)	8-14 Days n (%)	15-28 Days n (%)	1 Day n (%)	2-7 Days n (%)	8-14 Days n (%)	15-28 Days n (%)
Overall, NLF Any Symptom	3 (14.3)	8 (38.1)	7 (33.3)	3 (14.3)	4 (7.1)	41 (73.2)	8 (14.3)	3 (5.4)
Pain (including burning)	8 (38.1)	12 (57.1)	0	0	21 (37.5)	17 (30.4)	0	0
Tenderness	5 (23.8)	15 (71.4)	1 (4.8)	0	11 (19.6)	36 (64.3)	2 (3.6)	0
Redness	9 (42.9)	5 (23.8)	1 (4.8)	0	24 (42.9)	13 (23.2)	0	0
Bruising	2 (9.5)	7 (33.3)	6 (28.6)	0	5 (8.9)	24 (42.9)	6 (10.7)	1 (1.8)
Swelling	2 (9.5)	12 (57.1)	2 (9.5)	0	14 (25.0)	31 (55.4)	2 (3.6)	1 (1.8)
Itching	1 (4.8)	1 (4.8)	1 (4.8)	0	6 (10.7)	7 (12.5)	0	0
Lumps/Bumps	1 (4.8)	5 (23.8)	1 (4.8)	3 (14.3)	9 (16.1)	11 (19.6)	1 (1.8)	0

Note: N = Number of subjects, n = Number of subjects in specific category. Percentages calculated as 100 x (n/number of subjects with response at visit for applicable question).
For the Overall, the maximum of the durations from each session was determined for each subject and summarized.

No clinically meaningful changes from baseline were observed in any visual function test for the 5-mL or 8-mL groups.

The mean pain score difference (after treatment score minus before treatment score) was lower after all treatments in the 8-mL group (range: 0.4 to 1.3) compared with the 5-mL group (range: 2.1 to 3.0) based on the 11-point NPS. These results reflect that the addition of 1 mL of 2% lidocaine HCl in the 8-mL group was effective to manage pain during injection.

Extension study (48-96 weeks)

Study subjects randomized and treated with *Sculptra Aesthetic* reconstituted with 8 mL of SWFI in the base study were followed for an additional 48 weeks in this extension study. Out of the 58 eligible subjects that completed the base study, 38 subjects were enrolled in this extension study. 20 subjects were not enrolled, the most common reason for non-enrollment was the subject intended to have facial cosmetic procedures/treatments that were prohibited in the extension study (9 [45.0%] subjects). 35 subjects completed the study.

Safety evaluations for this extension study included an interview of the subjects at each visit to obtain information about any medical occurrence that met the definition of an AE. Information on AEs was also obtained from signs and symptoms detected during each examination by the Investigator or designee, which included visual inspection of the treatment area.
No subjects experienced a related AE during this extension study and no SAEs were reported. One subject experienced an AE of skin mass during the base study; the event was considered related to study product and injection procedure, mild in intensity, and had not recovered during the base study but was considered chronic and/or stable during this extension study.

SCULPTRA FOR CORRECTION OF FINE LINES AND WRINKLES IN THE CHEEK REGION FOR USE IN IMMUNE-COMPETENT SUBJECTS

Base study (0 to 12 months)
One hundred forty-nine (149) subjects were enrolled in a randomized, treatment-controlled, evaluator-blinded, multicenter study to evaluate the safety and effectiveness of Sculptra Aesthetic reconstituted in 8 mL SWFI with the addition of 1 mL 2% lidocaine for correction of cheek wrinkles. Subjects were treated to optimal correction at four-week intervals, with a maximum of four treatment sessions. Out of the 149 subjects enrolled, 97 were randomized to receive *Sculptra Aesthetic* reconstituted in 8 mL SWFI with the addition of 1 mL 2% lidocaine (treatment group) and 52 subjects were randomized to the no-treatment control group.

Pre-printed diary forms were used by subjects to record the presence of pre-defined expected post-treatment events in the treated area, i.e. bruising, redness, swelling, pain, tenderness, itching, lumps/bumps, and "other" for 28 days following each treatment. Subjects rated each treatment site response as "None", "Mild", "Moderate" or "Severe".

Vision function assessments: Snellen Visual Acuity Test, Extraocular Muscle Function Test and Confrontation Visual Field Test, were performed both prior to and post injection of the study product at baseline, before and after treatments, and all physical scheduled follow-up visits.

At all physical visits, a study staff member who was qualified by training and experience to perform safety assessments assessed each subject's cheek sensation; firmness and symmetry; and mass formation. After treatment with the study product, product palpability was performed at each physical visit.

AEs were also reported by the Treating Investigator at all follow-up visits when applicable.

Out of the 97 subjects randomized to treatment, a total of 20 subjects (20.6%) experienced an AE considered related to study treatment. A summary of reported related AEs is presented below in Table 10.

21.3% (20/94) of females experienced a related adverse event, while no male subjects (0/5) had a related adverse event. Due to the small number of male subjects, conclusions cannot be drawn.

Three subjects in the treatment group experienced SAEs. None of these were considered related to study product or injection procedure.

One (1.0%) subject in the treatment group experienced an adverse event of special interest (AESI), an AE of hypermetropia with late onset (>21 days after the most recent treatment) related to study product or injection procedure, mild in intensity. The duration of the event was 37 days and was resolved without action taken.

One subject experienced multiple small, palpable skin nodules in the treatment area on both her left and right cheeks (PT: injection site nodule) on Day 332, 180 days after her most recent injection. The

AEs (for both the left and right cheeks) were considered mild in intensity and were ongoing at study completion. No action was taken with regard to the AEs.

One subject experienced a 5-6 mm small, oblong lump that was palpable on her lower left cheek, near the corner of their mouth (PT: skin mass [small lump]) on Day 49, 9 days after her most recent injection. The AE was considered mild in intensity, related to study product and injection procedure, and resolved on Day 327 (was considered chronic and/or stable). No action was taken with regard to the AE.

One (1.0%) subject each in the treatment group experienced an AESI, an AE with late onset (>21 days after the most recent treatment) related to study product or injection procedure, and an AE leading to study discontinuation (which was also considered an SAE). No subject died during the study.

TABLE 10
RELATED ADVERSE EVENTS BY PREFERRED TERM (SAFETY POPULATION)

Preferred Term	Treatment Group (N=97) n (%)
Subjects with at least 1 related adverse event	20 (20.6)
Injection site bruising	11 (11.3)
Dizziness	2 (2.1)
Headache	2 (2.1)
Abnormal sensation in eye	1 (1.0)
Injection site erythema	1 (1.0)
Injection site irritation	1 (1.0)
Injection site nodule	1 (1.0)
Injection site pain	1 (1.0)
Injection site discolouration	1 (1.0)
Injection site swelling	1 (1.0)
Skin mass (small lump)[a]	1 (1.0)

a One subject experienced 2 events of skin mass on Day 49, 9 days after the most recent injection; reported terms were small lump on lower left cheek, near corner of mouth and small lump below left corner of mouth. The AE was considered mild in intensity, related to study product and injection procedure. These were considered chronic and stable (not resolved) at the end of study participation but did resolve without medical intervention after the subject exited the study per report from the Investigator.
Note: N = number of subjects in safety population, n = number of subjects in specific category. Percentages calculated as 100 × (n/N). Subjects reporting more than 1 event in a category were counted only once in that category (n). Events were coded by Medical Dictionary for Regulatory Activities version 23.1.

One subject experienced a unilateral 1-line change in the Snellen Visual Acuity test from Baseline at Month 1 post injection (0+, -1), but reported no ocular symptoms or vision loss. All other eye and safety assessments were normal throughout the completion of the Month 1 visit. Subject did not return for additional assessments.

Three subjects in the control group experienced a change in Snellen Visual Acuity test from baseline to a post-baseline visit. These occurrences are due to the subjects not wearing their corrective lenses for the post-baseline assessments.

The frequency, intensity and duration of pre-defined events reported by the subject in the daily diary are presented in Tables 11 and 12. Overall, for either side of the face, 92 (98.9%) subjects in the treatment group reported symptoms. The most common symptoms overall were tenderness (93.5%),

bruising (93.5%), swelling (87.1%), and pain (including burning) (83.9%). Overall, almost all symptoms were mild or moderate in intensity (97.8%).

TABLE 11
FREQUENCY AND INTENSITY OF PRE-DEFINED EVENTS REPORTED IN THE DAILY DIARY
Summary of Subject Diary Symptoms by Session and Maximum Severity Safety Population

	Treatment Group (N=97)			
Symptom	Any n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Number of Subjects with Diaries at Visit: 93				
Overall Any Symptom	92 (98.9)	61 (66.3)	29 (31.5)	2 (2.2)
Pain (including burning)	78 (83.9)	70 (89.7)	8 (10.3)	0
Tenderness	87 (93.5)	78 (89.7)	9 (10.3)	0
Redness	59 (63.4)	53 (89.8)	5 (8.5)	1 (1.7)
Bruising	87 (93.5)	64 (73.6)	21 (24.1)	2 (2.3)
Swelling	81 (87.1)	64 (79.0)	16 (19.8)	1 (1.2)
Itching	25 (26.9)	24 (96.0)	1 (4.0)	0
Lumps/Bumps	48 (51.6)	44 (91.7)	4 (8.3)	0

Note: N = Number of subjects in Safety Population, n = Number of subjects in specific category. For 'Any' column, percentages calculated as 100 x (n/number of subjects with response indicating symptom or none at applicable treatment session). For intensity columns, percentages calculated as 100 x (n/number of subjects at treatment session with that symptom). Subjects reporting multiple events of the same symptom are counted once for that event within the most severe category.

TABLE 12
FREQUENCY AND DURATION OF PRE-DEFINED EVENTS REPORTED IN THE DAILY DIARY
Summary of Subject Diary Symptoms by Session and Number of Days with Symptoms Safety Population

	Treatment Group (N=97)			
Symptom	1 Day n (%)	2-7 Days n (%)	8-14 Days n (%)	15-28 Days n (%)
Number of Subjects with Diaries at Visit: 93				
Overall Any Symptom	3 (3.3)	23 (25.0)	44 (47.8)	22 (23.9)
Pain (including burning)	19 (24.4)	54 (69.2)	4 (5.1)	1 (1.3)
Tenderness	7 (8.0)	64 (73.6)	14 (16.1)	2 (2.3)
Redness	15 (25.4)	39 (66.1)	4 (6.8)	1 (1.7)
Bruising	6 (6.9)	21 (24.1)	41 (47.1)	19 (21.8)
Swelling	7 (8.6)	62 (76.5)	11 (13.6)	1 (1.2)
Itching	12 (48.0)	12 (48.0)	1 (4.0)	0
Lumps/Bumps	8 (16.7)	30 (62.5)	7 (14.6)	3 (6.3)

Note: N = Number of subjects in Safety Population, n = Number of subjects in specific category. Percentages calculated as 100 x (n/number of subjects who reported 'Mild' or higher for the respective symptom in their subject diary).

Extension study (12-24 months)

During the extended follow-up period, control group subjects were offered Sculptra treatment (Designated as Group A), and treatment group subjects (designated as Group B) returned for

continued safety and effectiveness evaluations up to 24 months. A total of 111 subjects (39 Group A, 72 Group B) entered the extension study and were included in the extension population.
Group A subjects received the same safety assessments as in the Base study. All subjects had the same effectiveness assessments as during the base study.

During the extension study, a total of 9 (23.1%) subjects in Group A experienced an AE considered related to study product or injection procedure. No subject in Group A experienced an AE with late onset (>21 days after the most recent treatment), an AESI, or an AE leading to study discontinuation.

During the extension study, no new related AEs were reported in Group B. One subject (1.4%) experienced an AE with late onset (>21 days after the most recent treatment) related to study product or injection procedure in the base study which ongoing when enrolled in the extension study. The subject withdrew prior to the AE resolving. No subject in Group B experienced an AESI or an AE leading to study discontinuation.

No subjects in the extension study experienced an SAE considered related to study product or procedure.

A summary of related AEs is presented in Table 13.

TABLE 13
RELATED ADVERSE EVENTS BY PREFERRED TERM (EXTENSION POPULATION)

Preferred Term	**Group A (N=39) n (%)**	**Group B (N=72) n (%)**
Subjects with at least 1 related adverse event	9 (23.1)	1 (1.4)
Injection site bruising	5 (12.8)	0
Injection site pain	2 (5.1)	0
Injection site pruritus	1 (2.6)	0
Injection site swelling	1 (2.6)	0
Injection site nodule	0	1 (1.4)
Sinusitis	1 (2.6)	0

Source: CSR, Table 14.3.2.1
Note: N = number of subjects in extension population, n = number of subjects in specific category. Percentages calculated as 100 × (n/N). Subjects reporting more than 1 event in a category were counted only once in that category (n). Events were coded by Medical Dictionary for Regulatory Activities version 23.1. Group A subjects were untreated in the Base study but received *Sculptra Aesthetic* in the Extension study; Group B subjects received *Sculptra Aesthetic* in the Base study but were untreated in this extension study.

Subject diaries captured self-assessed, pre-defined, expected, post-treatment symptoms. The most common symptoms for Group A were tenderness, swelling, bruising, pain (including burning), and redness. Almost all symptoms were mild or moderate in intensity (94.9%).

TABLE 14
SUMMARY OF SUBJECT DIARY SYMPTOMS, OVERALL (GROUP A)
(EXTENSION POPULATION)

Characteristic	**Group A-Treated Control (N=39) n (%)**
Number of subjects with diaries at visit	
Overall, Any Symptom	39 (100)
Pain (including burning)	32 (82.1)
Tenderness	37 (94.9)
Redness	32 (82.1)
Bruising	36 (92.3)
Swelling	37 (94.9)
Itching	15 (38.5)
Lumps/bumps	26 (66.7)

Source: CSR, Table 14.3.8.1
Note: N = number of subjects in extension population; n = number of subjects in specific category. Percentages calculated as 100 × (n/number of subjects with response indicating symptom or none at applicable treatment session). Subjects reporting multiple events of the same symptom were counted only once for that event within the most severe category. Group A subjects were untreated in the Base study but received *Sculptra Aesthetic* in the Extension study.

Snellen visual acuity assessment had no subjects in Group A with a change from any treatment visit pre-injection to any treatment visit (post-injection). Only 1 subject (2.6%) in Group A had a visual acuity line change at any follow-up visit. The one subject had ≥2 visual acuity line change at Month 13 (pre-injection) but was normal at the post-injection visit at Month 13 and throughout the rest of the study.

POST MARKETING SURVEILLANCE

The adverse events received from post-marketing surveillance (voluntary reporting and published literature) for *Sculptra* in the US and other countries include:

- papules/nodules with or without inflammation or discoloration,
- swelling, mass formation/induration,
- lack of effect,
- pain/tenderness,
- erythema,
- granuloma/foreign body reaction,
- visual disturbance including transient blurred vision, reduced visual acuity, increased lacrimation, eyelid ptosis, dry eye and blindness,
- bruising/hematoma,
- inflammation, injection site reactions including burning sensation, discomfort, exfoliation, irritation and warmth,
- eye disorders including, dry eye, eye pain, eyelid ptosis, eye swelling, increased lacrimation and visual disturbance such as transient blurred vision, blindness and reduced visual acuity,
- nerve injury including paresthesia, hypoesthesia and facial nerve paralysis,
- bacterial infections and abscess formation,
- skin discoloration, hypersensitivity/allergic reaction and angioedema,
- pruritus, facial asymmetry/deformity,
- atrophy/scarring,
- rash,
- ischemia/necrosis including pallor, vascular occlusion and ulcer,
- acne,
- urticaria, dermatitis,
- device dislocation,
- blisters/ vesicles,
- muscle disorders including muscular weakness and muscular twitching,
- symptoms of reactivation of herpes infection,
- discharge,
- capillary disorder including telangiectasia,
- encapsulation,
- other dermatological events including localized alopecia, skin dryness, skin tightness, skin wrinkling, skin hypertrophy and photosensitive reaction,
  non-dermatological events including anxiety, arthralgia, depression, diplopia, dizziness, dyspnea, emotional distress, fatigue, headache, insomnia, lymphadenopathy, malaise, nausea, ocular hyperemia, jaw pain, pyrexia, skin sarcoidosis and weight decreased.

When required, depending on event, treatments may include massage/manipulation, warm compress, nitroglycerine paste, corticosteroids, antibiotics, antihistamines, NSAIDs, aspiration/drainage of the product, saline injections and surgery. Events which did not resolve or where resolution information is not available at last contact were reported.

Scarring, mostly a non-serious event, was reported in association with skin discoloration, nodules, lumps, indurations, granulomas, hyperpigmentation, hypertrophic scars, and suspicion of keloid formation. Time to onset when specified ranged from within 1 week to 24 months post-*Sculptra* injection and outcome ranged from 'recovered' to 'ongoing' at last contact.

Skin discoloration was 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 when specified usually ranged from within 1 week to 12 months post-injection. Outcome ranged from 'recovered' to 'ongoing' at last contact.

SAEs have rarely been reported. The most commonly reported serious adverse events for *Sculptra* with more than 5 reported events include papule/nodules, swelling/edema, granuloma, symptoms of visual disturbance, infection/abscess, mass/induration, hypersensitivity, paresthesia and facial nerve paralysis, ischemia/necrosis, inflammation. Other concurrent events included pain, bruising/hematoma, erythema, discoloration, deformity, scarring/atrophy, pruritus, rash, muscular weakness, urticaria and blisters.

Injection site nodules mostly occurred several months post-injection. Such nodules are occasionally associated with inflammation or discoloration, 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, *e.g.*, intralesional corticosteroids, others were 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 nodules was required.

Granulomas usually occur several months after injection; in few cases onset was more than 1-year post-injection. While events were reported as granuloma, only a few cases were confirmed by biopsy. 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.

Vascular compromise may occur due to an inadvertent intravascular injection or as a result of vascular compression associated with implantation of any injectable product. This may manifest as blanching, discoloration, necrosis or ulceration at the implant site or in the area supplied by the blood vessels affected; or rarely as ischemic events in other organs due to embolization. Isolated rare cases of ischemic events affecting the eye leading to visual loss, and the brain resulting in cerebral infarction, following facial aesthetic treatments have been reported. Visual disturbances including blindness have been reported following injection of *Sculptra* into the temple area, periorbital areas, and/or cheek. Events requiring medical intervention, and events which did not resolve or where resolution information is not available were reported.

Serious edema was 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, antihistamines and/or anti-inflammatories. Recovery occurred within 7-10 days without sequelae.

Serious erythema, serious pain, and serious pruritus reported with bruising and heat sensation, were mostly reported within 24 hours post-injection. Treatment included corticosteroids, antihistamines and/or anti-inflammatories. Events usually resolved within 7-10 days post-injection without sequelae and with no significant impact on daily life.

Serious hypersensitivity reactions were 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 antihistamines.

Serious infections such as subcutaneous abscesses, cellulitis, folliculitis, and methicillin-resistant *Staphylococcus aureus* at the injection site, were reported. Time to onset of events mostly ranged from 1 day to a few weeks. Of these cases a few required hospitalization with administration of intravenous antibiotics. Most of the patients were recovered or were recovering at the last contact.

Delayed-onset inflammation near the site of dermal filler injections is one of the known adverse events associated with dermal fillers. Cases of delayed-onset inflammation have been reported to occur at the dermal filler treatment site following viral or bacterial illnesses or infections, vaccinations, or dental procedures. Typically, the reported inflammation was responsive to treatment or resolved on its own.

Adverse reactions should be reported to Galderma Laboratories, L.P. at 1-855-425-8722.

CLINICAL STUDIES

SCULPTRA FOR CORRECTION OF SHALLOW TO DEEP NASOLABIAL FOLD CONTOUR DEFICIENCES AND OTHER FACIAL WRINKLES (RECONSTITUTED WITH 5 ML SWFI)

Clinical Studies 5 mL reconstitution

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, 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 *Cosmoplast* 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 wrinkles reached optimal correction of WAS equal to 1 or 0, or until the maximum of 4 treatment sessions were completed.

The study subjects recorded AEs 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 subjects 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 pretreatment 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 15.

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 15).

TABLE 15
STUDY POPULATION DEMOGRAPHICS

	Controlled Phase Study		**Extension Phase Study**
	Sculptra Aesthetic	***Cosmoplast***	***Sculptra Aesthetic***
Demographic	**N(%)**	**N(%)**	**N(%)**
Total study 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 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. At each treatment session with control, multiple mid to deep dermal injections of an average of 1.0 mL *Cosmoplast* per nasolabial fold per session were performed into the left and right nasolabial folds according to product Instructions for Use. Table 16 presents the amount of *Sculptra Aesthetic* injected as a function of baseline wrinkle severity.

TABLE 16
SUMMARY SCULPTRA AESTHETIC AND CONTROL INJECTIONS

Baseline (Pre-Injection, before first treatment) WAS	**1**		**2**		**3**		**4**		**ALL**	
	SA	**COS**	**SA**	**COS**	**SA**	**COS**	**SA**	**COS**	**SA**	**COS**
Number of pts 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	28, 20.0	1.9, 16.0	11.7, 19.0	27, 16.0	28, 20.0	1.6, 16.0
Number of Session Total Number of Sessions	18	9	157	95	140	149	55	50	370	303
Mean	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	1.0, 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.

E. Effectiveness results
Controlled Phase (0-13 month) and Extension Phase (13-25 Months)

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 Month 13 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 17 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
WRINKLE SCALE (WAS) THROUGHOUT THE STUDY SCULPTRA AESTHETIC TREATED SUBJECTS

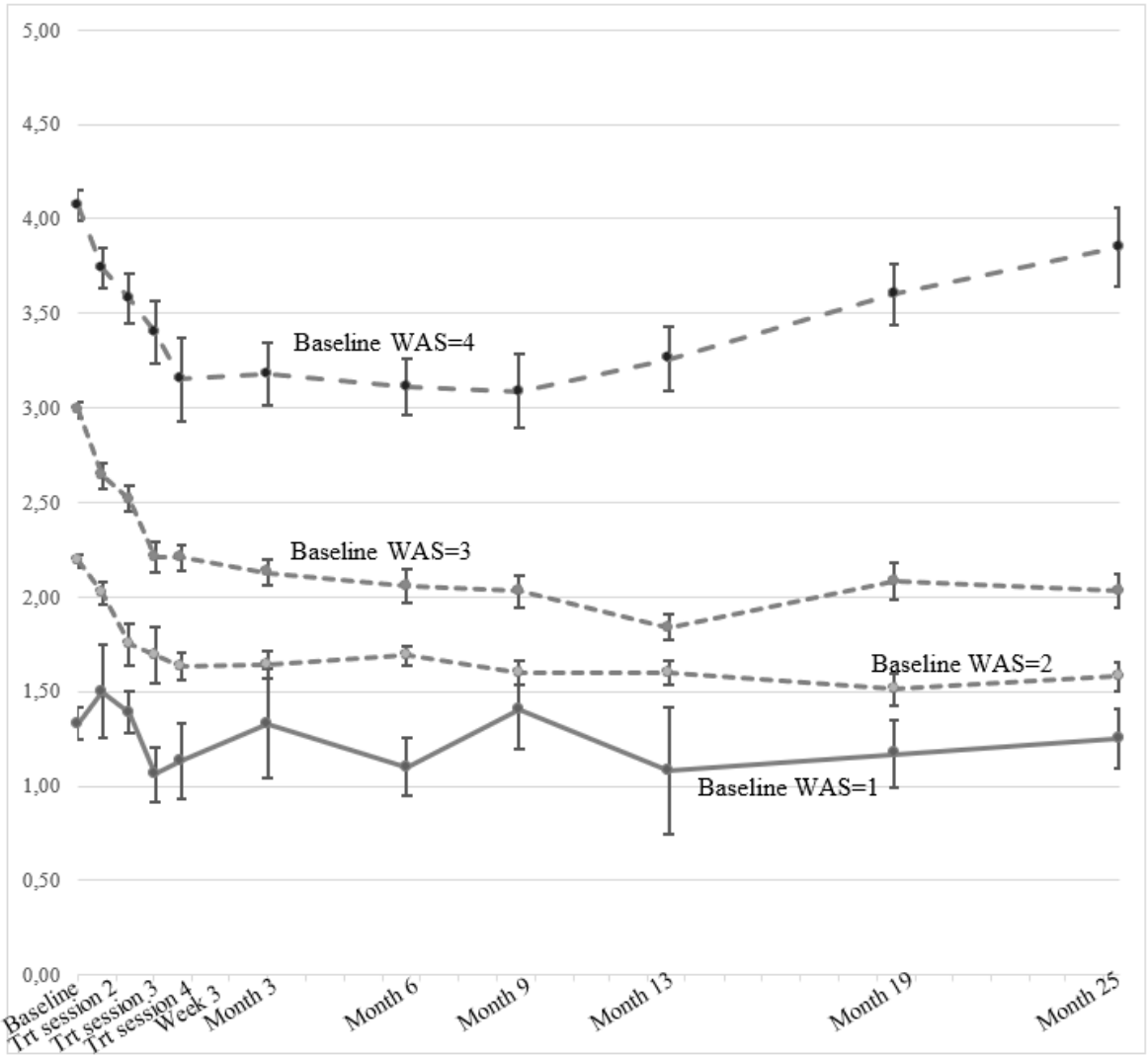


TABLE 17

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	0.078	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 (0.077)	-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
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	<0.00 1	<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

Post Approval Study

A. Study Design

The 5-year post approval study was a prospective, open-label, multicenter study conducted in the US at 20 investigational sites to evaluate the long-term safety of *Sculptra Aesthetic* in immuno-competent subjects, stratified by Fitzpatrick Skin Types (FST) I-III, IV, and V-VI. Subjects received up to four treatments spaced 3 weeks apart. Subjects continued with follow-up visits at Months 3, 6, 9, and 13, and Years 2, 3, 4, and 5 calculated from the day of first treatment.

A total of 867 subjects were enrolled and treated with *Sculptra Aesthetic* to correct shallow to deep NLF contour deficiencies and, if present, other facial wrinkles for which grid pattern (cross-hatch) injection technique was appropriate.

B. Study Endpoints

The following variables were evaluated in this study:

- The device-related long-term incidence of chronic inflammation (nodules, papules, granulomas, skin necrosis, hypersensitivity, and other injection site reactions) in subjects with FST I-VI.
- The incidence of hypertrophic scarring, keloid formation, and changes in skin pigmentation in subjects with FST IV-VI.

Secondary objectives included an evaluation of the time to onset, duration, severity, relationship to *Sculptra Aesthetic* and/or injection procedure, and outcome of all AEs, including AEs mentioned under the primary objectives, during the course of the study, by FST. Evaluations of changes in the WAS from baseline to post-treatment in NLFs and other facial wrinkles and Investigator/subject global assessments through Year 5 were also included.

C. Study Population

A total of 867 subjects were enrolled and treated (Table 18); 661 subjects (76.2%) completed the study, and 206 subjects (23.8%) were discontinued early.

TABLE 18
SUMMARY OF DEMOGRAPHICS AND BASELINE CHARACTERISTICS BY FITZPATRICK SKIN TYPE (INTENT-TO-TREAT POPULATION)

Demographic Measures	Fitzpatrick Skin Type I-III (N=557)	Fitzpatrick Skin Type IV-VI (N=310)	Overall (N=867)
Age (years)			
N	557	310	867
Mean (SD)	55.7 (9.25)	52.6 (9.56)	54.6 (9.48)
Median	56.0	53.0	55.0
Min, Max	22, 75	25, 74	22, 75
Sex, [n (%)]			
Male	33 (5.9)	38 (12.3)	71 (8.2)
Female	524 (94.1)	272 (87.7)	796 (91.8)
Ethnicity, [n (%)]			
Hispanic or Latino	54 (9.7)	123 (39.7)	177 (20.4)
Not Hispanic or Latino	503 (90.3)	187 (60.3)	690 (79.6)
Race, [n (%)]			
American Indian or Alaskan Native	0	5 (1.6)	5 (0.6)
Asian	5 (0.9)	9 (2.9)	14 (1.6)
Black or African American	0	88 (28.4)	88 (10.1)
Native Hawaiian or Other Pacific Islander	1 (0.2)	1 (0.3)	2 (0.2)
White / Caucasian	551 (98.9)	203 (65.5)	754 (87.0)
Other	0	4 (1.3)	4 (0.5)
Fitzpatrick Classification Skin Type[a], [n (%)]			
Type I	32 (5.7)	0	32 (3.7)
Type II	212 (38.1)	0	212 (24.5)
Type III	313 (56.2)	0	313 (36.1)
Type IV	0	168 (54.2)	168 (19.4)
Type V	0	96 (31.0)	96 (11.1)
Type VI	0	46 (14.8)	46 (5.3)

a: Fitzpatrick Skin Phototypes range from Type I = Fair-skinned to Type VI = Dark-skinned.
Source: CSR, Table 14.1.3.1

D. Treatments Delivered

A single regimen of *Sculptra Aesthetic* was administered to correct shallow to deep (WAS 2 to 4) NLF contour deficiencies and, if present, other facial wrinkles (i.e., marionette lines, cheek folds, and chin crease) Subjects received up to 4 treatment regimens. The mean total volume of *Sculptra Aesthetic* injected per subject was 13.9 mL overall (9.1 mL for NLFs, 5.4 mL for MLs, 6.4 mL for cheek folds, and 2.0 mL for chin crease).

E. Safety Findings

The overall incidence rate of injection site nodules and/or papules (NPs) was 28.5%, which exceeded the pre-specified 21% threshold for the 5-year endpoint. In general, NPs for FST IV-VI subjects were reported less frequently for each treated area when compared to the FST I-III subgroup. The incidence rates of NPs in each anatomic area were:

- Marionette lines: 27.2%
- Nasolabial folds: 19.0%
- Cheek folds: 5.4%

- Chin crease: 3.6%
- Non-treated areas: 0.8%

The overall incidence of AEIs other than NPs (including changes in skin pigmentation, granuloma, and unexpected change in wrinkle contour) was 1.0%, well within the pre-specified threshold of 3%.

F. Effectiveness Findings

Overall, efficacy data through the Year 5 visits indicate significant improvements in all treated facial areas with a long-lasting treatment effect of *Sculptra Aesthetic* treatment. In all four anatomic locations, statistically significant changes from baseline ($p<0.001$) in average WAS scores were observed at all timepoints through 5 years, however the score reductions (i.e., benefit) appeared to diminish over time, see Table 19.

TABLE 19
MEAN WAS CHANGE FROM BASELINE OVER TIME

Anatomical location (left and right combined where applicable)	**Mean WAS change from baseline**				
	13 months	**2 years**	**3 years**	**4 years**	**5 years**
Cheek folds	-1.6	-1.5	-1.4	-1.0	-0.7
Chin Crease	-1.5	-1.4	-1.1	-0.8	-0.4
Marionette lines	-1.7	-1.5	-1.2	-0.8	-0.4
Nasolabial folds	-1.7	-1.6	-1.2	-0.9	-0.5

Using the Global Aesthetic Improvement Scale (GAIS), Investigators reported overall improvements from baseline for 99.5%, 99.3%, 96.4%, 91.2%, 81.5%, and 68.8% of the subjects at Month 6, Month 13, Year 2, Year 3, Year 4, and Year 5 visits, respectively. Similar efficacy results were observed for the Subject Global Evaluations (SGEs) using the GAIS. Overall, subjects reported improvements (slightly improved, moderately improved, much improved) of 97.4%, 97.4%, 91.7%, 86.5%, 74.4%, and 66.3% at Month 6, Month 13, Year 2, Year 3, Year 4, and Year 5 visits, respectively.

G. Study Strengths/Limitations

The strength of this study is that long-term safety data were collected after up to 4 repeat treatments for 867 subjects representing the full spectrum of Fitzpatrick Skin Types, 76.2% (N = 661) of whom were followed through 5 years. Multiple areas of the lower face were treated, and the device-related long-term incidence of chronic inflammation was rigorously characterized per treated facial area. A limitation of the study was that the 28.5% overall incidence of any injection site nodule or papule exceeded the pre-specified co-primary endpoint of <21%. The incidence rate varied based on anatomic region and ranged from 3.6% (Chin Crease) to 27.2% (Marionette Lines). It is important to note that the pre-specified 21% protocol threshold was based on the pivotal study (DL6049-0301) with treatment confined to the NLFs only. For comparison, the rate of NPs in the NLFs was 19% (165/867, ITT Population) and 21% (139/661) for the population that completed the Year 5 visit.

Sub-analyses by individual study site are suggestive of other possible contributing factors associated with nodules/papules than the product alone. These observations raise limitations in making

definitive conclusions at this time, other than stating that current data reinforce the importance of proper training and product use.

SCULPTRA FOR CORRECTION OF SHALLOW TO DEEP NASOLABIAL FOLD CONTOUR DEFICIENCIES (RECONSTITUTED WITH 8 ML SWFI WITH THE ADDITION OF 1 ML 2% LIDOCAINE)

Clinical Studies 8 mL reconstitution

A. Study Design

Base study (0 to 48 weeks):

A randomized, treatment-controlled, evaluator-blinded, multicenter study was conducted to evaluate the safety and effectiveness of *Sculptra Aesthetic* for correction of nasolabial fold contour deficiencies. Sixty-four (64) subjects requiring correction of NLFs were enrolled and randomized in a 2:1 ratio to treatment with *Sculptra Aesthetic* reconstituted with 8 mL of SWFI with the addition of 1 mL 2% lidocaine (treatment group) or to *Sculptra Aesthetic* reconstituted with 5 mL of SWFI (reference group). Eight (8) subjects with FST IV and eight (8) subjects with FST V-VI were included but not randomized. These subjects were treated with *Sculptra Aesthetic* reconstituted with 8 mL of SWFI with the addition of 1 mL 2% lidocaine.

Subjects were treated to optimal correction at four-week intervals, with a maximum of four treatment sessions. Follow-up visits were conducted at Weeks 16, 24, 32, 40 and 48 after initial treatment.

Extension study (48 to 96 weeks):

Study subjects randomized and treated with *Sculptra Aesthetic* reconstituted with 8 mL of SWFI and completed the base study were followed for an additional 48 weeks in this extension study.

B. Study Endpoints

Base study (0 to 48 weeks):

The primary purpose was to evaluate the safety of *Sculptra Aesthetic* as a single regimen for correction of NLF contour deficiencies after changes in reconstitution to 8 mL SWFI with the addition of 1 mL 2% lidocaine and additional injection techniques compared to the originally approved label.

Primary effectiveness endpoint

Change from baseline on both sides of the face as assessed by the Blinded Evaluator using WAS at 48 Weeks after the first treatment session.

Secondary effectiveness endpoints

Secondary effectiveness endpoints included Global Aesthetic Improvement Scale (GAIS), subject satisfaction and change from baseline on both sides of the face as assessed by the Blinded Evaluator using WAS, at Weeks 16, 24, 32 and 40 as well as FACE-Q Appraisal of Lines: Nasolabial Folds Questionnaire at Baseline and at Weeks 24, 32, 40 and 48 and time in hours from treatment procedure until the earliest time the subject reported feeling comfortable returning to social engagement based on subject diary reporting.

Extension study (48 to 96 weeks):
All effectiveness endpoints described above were evaluated for the long- term extension study time points at Weeks 72 and 96 after the initial treatment.

C. Study Population

Base study (0 to 48 weeks):
A total of 80 subjects were enrolled, two prematurely discontinued from the study due to lost to follow-up. At baseline, all subjects had a WAS score of both NLFs of 2 (shallow wrinkles) to 4 (deep wrinkles) as assessed by the Treating Investigator. Subject demographics are presented in Table 20.

TABLE 20
DEMOGRAPHICS

Characteristic		***Sculptra Aesthetic* 5 mL (N=21)**	***Sculptra Aesthetic* 8 mL (N=59)**	**Total (N=80)**
Gender	Female / Male	20 (95.2%) / 1 (4.8%)	56 (94.9%) / 3 (5.1%)	76 (95.0%)/ 4 (5.0%)
Age (years)	Mean (SD)	51.4 (9.93)	51.6 (10.49)	51.5 (10.28)
	Min, Max	32, 69	23, 75	23, 75
Race	White	21 (100.0%)	51 (86.4%)	72 (90.0%)
	Black/African American	0	5 (8.5%)	5 (6.3%)
	Asian	0	1 (1.7%)	1 (1.3%)
	Native Hawaiian/Other Pacific Islander	0	0	0
	American Indian or Alaska Native	0	1 (1.7%)	1 (1.3%)
	Other	0	1 (1.7%)	1 (1.3%)
Ethnicity	Not Hispanic or Latino	15 (71.4%)	47 (79.7%)	62 (77.5%)
	Hispanic or Latino	6 (28.6%)	12 (20.3%)	18 (22.5%)
Fitzpatrick Skin Type (FST) n (%)	I	0	2 (3.4)	2 (2.5)
	II	6 (28.6)	11 (18.6)	17 (21.3)
	III	12 (57.1)	25 (42.4)	37 (46.3)
	IV	2 (9.5)	9 (15.3)	11 (13.8)
	V	1 (4.8)	9 (15.3)	10 (12.5)
	VI	0	3 (5.1)	3 (3.8)
Wrinkle Assessment Scale, Blinded Evaluator Left	Mean (SD)	3.0 (0.86)	3.0 (0.73)	3.0 (0.76)
	Median	3.0	3.0	3.0
	Min, Max	2, 4	2, 4	2, 4
Wrinkle Assessment Scale, Blinded Evaluator Right	Mean (SD)	2.9 (0.57)	2.8 (0.76)	2.8 (0.71)
	Median	3.0	3.0	3.0
	Min, Max	2, 4	2, 4	2, 4

Abbreviations: BMI = body mass index; cm = centimeters; kg = kilograms; SD = standard deviation;
*Other category includes 1 subject who was specified as Middle Eastern.

Extension study (48 to 96 weeks):
Of the 58 eligible subjects, 38 (65.5%) subjects were enrolled and 20 (34.5%) subjects were not enrolled. Of these 20 subjects not enrolled, the most common reason for non-enrollment was the subject intended to have facial cosmetic procedures/treatments that were prohibited in the extension study (9 [45.0%] subjects). A total of 35 (92.1%) subjects completed the study; 3 (7.9%) subjects prematurely discontinued the study due to being lost to follow-up.

D. Treatments Delivered
Base study (0 to 48 weeks):
The first treatment was administered at the baseline visit. At weeks 4, 8, and 12, additional treatments were performed if deemed necessary to obtain optimal aesthetic result. Subjects were treated to optimal correction, which was defined as a grade of 0 (no wrinkle) or grade 1 (just perceptible wrinkle) on the WAS and best correction that can be achieved as agreed upon by the Treating Investigator and the subject. *Sculptra Aesthetic* was injected using a linear threading, bolus or fanning technique in the subdermal plane; subcutaneously or supraperiosteally. Subjects were given a maximum of one vial per session, with a maximum of half the reconstituted product per side, (i.e. maximum 2.5 mL per side for subjects in the control group (5 mL reconstitution) and 4.5 mL per side for subjects in the treatment group (8 mL reconstitution with the addition of 1 mL 2% lidocaine). The median number of sessions per subject was 4.0 for both the 5-mL and 8-mL groups. The minimum number of sessions was 2 in the 5-mL group and 1 in the 8-mL group.

For the 8 mL treatment group, the median total volume injected (both sides) into the NLFs was 18.90 mL for all treatment sessions (range from 3.1 to 33.6 mL). In the 5 mL control group, the median total volume injected (both sides) into the NLFs was 10.3 mL for all treatment sessions (range from 4.2 to 17.0 mL).

Extension study (48 to 96 weeks):
No treatments were delivered in the extension study.

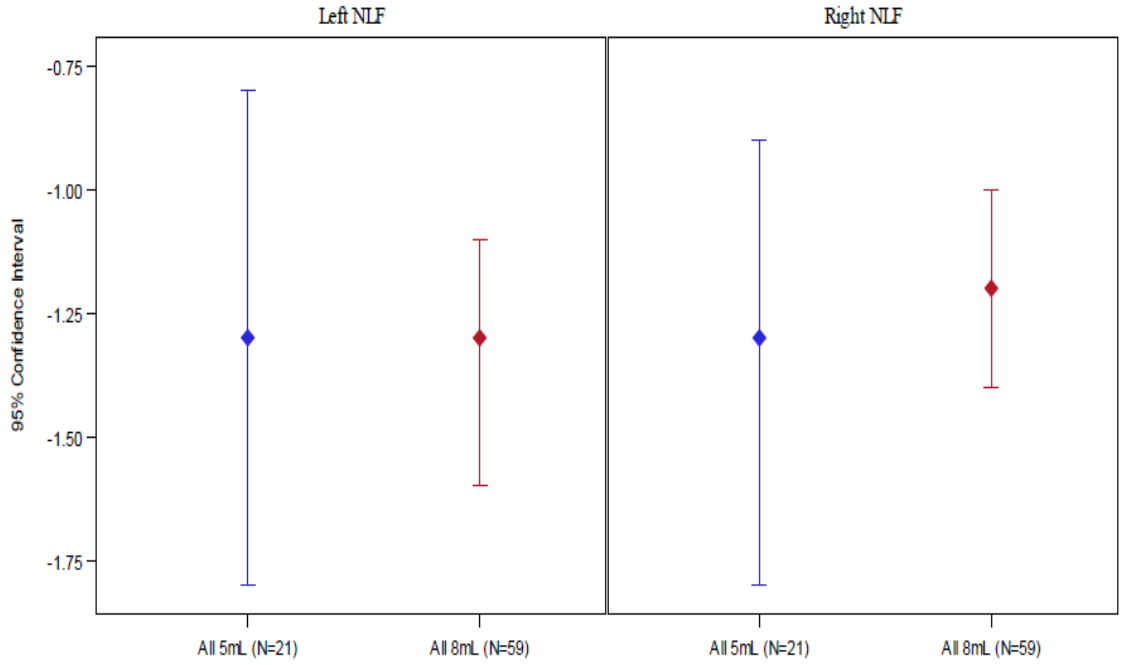
E. Effectiveness results
Base study (0 to 48 weeks):
The Week 48 change from baseline in WAS demonstrated comparable treatment effect in reducing wrinkle severity of NLFs with *Sculptra Aesthetic* reconstituted in 8 mL SWFI with the addition of 1 mL 2% lidocaine injected subdermally immediately after reconstitution with a linear threading, bolus and/or fanning technique to the control group. The mean change from baseline in the control group was -1.3 on both sides of the face, the mean change from baseline in the 8 mL treatment group was -1.3 on the left side and -1.2 on the right side, hence the pre-defined success criteria for the primary effectiveness analysis were met as shown in Table 21 and Figure 2.

TABLE 21
CHANGE FROM BASELINE, WAS SCORES (BLINDED EVALUATOR) AT WEEK 48: BOCF (ITT POPULATION)

Characteristic	All 5 mL (N=21)	All 8 mL (N=59)
Left nasolabial fold change from baseline		
Mean (standard deviation)	-1.3 (1.06)	-1.3 (0.97)
Median	-1.0	-1.0
Minimum, maximum	-4, 0	-3, 1
p-value		<0.001
95% confidence interval	-1.8, -0.8	-1.6, -1.1
Right nasolabial fold change from baseline		
Mean (standard deviation)	-1.3 (1.02)	-1.2 (0.81)
Median	-1.0	-1.0
Minimum, maximum	-3, 0	-3, 0
p-value		<0.001
95% confidence interval	-1.8, -0.9	-1.4, -1.0

WAS = Wrinkle Assessment Scale, BOCF = Baseline Observation Carried Forward.
One-sided test of the null hypothesis that the mean change from baseline was ≥0.
P-value and confidence interval calculated using t-test. Note: N = number of subjects; n = number of subjects in specific category

FIGURE 2
95% CONFIDENCE INTERVALS: WRINKLE ASSESSMENT SCALE MEAN CHANGE FROM BASELINE TO WEEK 48: BOCF (ITT POPULATION)



Additional analysis of the 95% confidence interval of the difference in change from baseline in the Blinded Evaluator WAS for the right side of the face was (-0.3, 0.7) and for the left side of the face (-0.6, 0.5). Thus, both intervals include 0 and comparable treatment effect between the two groups has been demonstrated, displayed in Table 22.

TABLE 22
ANALYSIS OF WAS (BLINDED EVALUATOR) AT WEEK 48
BASELINE OBSERVATION CARRIED FORWARD ANALYSIS
INTENT-TO-TREAT POPULATION

	All 5mL (N=21)	All 8mL (N=59)
Week 48/Early Term. - Wrinkle Assessment Scale		
Left NLF		
n	21	59
Mean (SD)	1.7 (0.97)	1.7 (1.09)
Median	2.0	2.0
Min, Max	0, 3	0, 4
Left NLF Change from Baseline		
n	21	59
Mean (SD)	-1.3 (1.06)	-1.3 (0.97)
Median	-1.0	-1.0
Min, Max	-4, 0	-3, 1
p-value [1]		<0.001
95% Confidence Interval	(-1.8, -0.8)	(-1.6, -1.1)
Difference 95% Confidence interval [2]		(-0.6, 0.5)
Right NLF		
n	21	59
Mean (SD)	1.5 (0.81)	1.6 (1.03)
Median	1.0	2.0
Min, Max	0, 3	0, 4
Right NLF Change from Baseline		
n	21	59
Mean (SD)	-1.3 (1.02)	-1.2 (0.81)
Median	-1.0	-1.0
Min, Max	-3, 0	-3, 0
p-value [1]		<0.001
95% Confidence Interval	(-1.8, -0.9)	(-1.4, -1.0)
Difference 95% Confidence interval [2]		(-0.3, 0.7)

[1] One-sided test of the null hypothesis that the mean change from baseline is greater than or equal to 0. P-value and confidence interval calculated using t-test.
[2] Difference confidence interval calculated using normal approximation.
Note: N = Number of subjects, n = Number of subjects in specific category. SD = Standard Deviation.

At Week 48, *Sculptra Aesthetic* reconstituted in 8 mL SWFI (+1 mL of lidocaine), effectively reduced the severity of NLFs in the majority of subjects resulting in a WAS responder rate (defined as at least 1 grade improvement on the WAS from baseline) of 74.1%. Responder rates over time based on Blinded Evaluator assessment are displayed in Table 23.

TABLE 23
RESPONDER RATE BASED ON WRINKLE ASSESSMENT SCALE (BLINDED EVALUATER) BY VISIT

	n/N (%)	
Responder Rate	**All 5 mL (N=21)**	**All 8 mL (N=59)**
Week 16	20/21 (95.2)	43/57 (75.4)
95% confidence interval	76.2%, 99.9%	62.2%, 85.9%
Week 24	17/21 (81.0)	44/58 (75.9)
95% confidence interval	58.1%, 94.6%	62.8%, 86.1%
Week 32	17/21 (81.0)	37/55 (67.3)
95% confidence interval	58.1%, 94.6%	53.3%, 79.3%
Week 40	17/21 (81.0)	46/59 (78.0)
95% confidence interval	58.1%, 94.6%	65.3%, 87.7%
Week 48	14/21 (66.7%)	43/58 (74.1%)
95% confidence interval	43.0%, 85.4%	61.0%, 84.7%

Confidence interval calculated using Clopper-Pearson method (based on binomial distribution).
N = number of subjects; n = number of subjects in specific category. Percentages calculated as 100 × (n/N) out of the number of subjects at each visit.

GAIS assessment. As shown in Table 24, all subjects in both the 5-mL and 8-mL groups showed aesthetic improvement compared to baseline at all visits for both sides of the face concurrently, as assessed by Treating Investigator Assessment (GAIS). Confidence intervals were >80% for both groups at all visits. No subject in either group experienced any worsening at any visit.

Aesthetic improvement compared to baseline, as evaluated by subject assessment (GAIS), is also summarized in Table 22. The majority of subjects in both the 5-mL and 8-mL groups showed aesthetic improvement (Subject Assessment) by GAIS at all visits. Confidence intervals were ⩾75% for both groups at all visits. No subject in either the 5-mL or 8-mL group experienced any worsening at any visit.

TABLE 24
GAIS (SUBJECT AND TREATING INVESTIGATOR) BY VISIT, ITT POPULATION, OBSERVED CASES

Characteristic	GAIS, Treating Investigator		GAIS, Subject Assessment	
	All 5 mL (N=21)	All 8 mL (N=59)	All 5 mL (N=21)	All 8 mL (N=59)
Week 16		n=56		n=57
Any improvement, n (%)[a]	21 (100)	56 (100)	20 (95.2)	54 (94.7)
95% confidence interval[b]	83.9%, 100%	93.6%, 100%	76.2%, 99.9%	85.4%, 98.9%
Any worsening[c]	0	0	0	0
Week 24		n=58		n=58
Any improvement, n (%)[a]	21 (100)	58 (100)	20 (95.2%)	53 (91.4%)
95% confidence interval[b]	83.9%, 100%	93.8%, 100%	76.2%, 99.9%	81.0%, 97.1%
Any worsening[c]	0	0	0	0
Week 32		n=57		n=57
Any improvement, n (%)[a]	21 (100)	57 (100)	20 (95.2%)	52 (91.2%)
95% confidence interval[b]	83.9%, 100%	93.7%, 100%	76.2%, 99.9%	80.7%, 97.1%
Any worsening[c]	0	0	0	0
Week 40				
Any improvement, n (%)[a]	21 (100)	59 (100)	20 (95.2)	51 (86.4%)
95% confidence interval[b]	83.9%, 100%	93.9%, 100%	76.2%, 99.9%	75.0%, 94.0%
Any worsening[c]	0	0	0	0
Week 48		n=57		n=58
Any improvement, n (%)[a]	21 (100)	57 (100)	21 (100)	51 (87.9%)
95% confidence interval[b]	83.9%, 100%	93.7%, 100%	83.9%, 100%	76.7%, 95.0%
Any worsening[c]	0	0		

a At least improved on both sides of the face concurrently and combined the categories of "very much improved", "much improved", and "improved."

b Confidence interval calculated using Clopper-Pearson method (based on binomial distribution).

c Any worsening on either side of the face and combined the categories of "worse", "much worse", and "very much worse."

Note: N = number of subjects; n = number of subjects in specific category. Percentages calculated as 100 × (n/N) out of the number of subjects at each visit.

Subject Satisfaction Questionnaire. Across Week 16 to Week 48, the majority of subjects in both the 5-mL and 8-mL groups responded as "satisfied" or "very satisfied" that the treatment, responding that the treatments made them look younger, improved their attractiveness and overall satisfaction with their appearance; made them feel better about themselves/improved self-confidence/confidence in life, made them look the way they felt, and improved facial symmetry/balance.
Likewise, across Week 16 to Week 48 the majority of subjects in both groups responded as "agree" or "strongly agree" that the treatments were natural looking, and the subtle treatment results over time were worth it. Additionally, the majority of subjects would recommend both the 5-mL and 8-mL treatment with Sculptra to a friend and have the treatment again, as assessed at all visits.

FACE-Q change from baseline scores indicated subjects were less bothered by the NLFs and more satisfied with their appearance. The sum of the subject's FACE-Q™ appraisal of lines NLF scores was converted to a Rasch transformed total score according to the FACE-Q™ manual; a higher total score indicated greater subject satisfaction. The mean total FACE-Q™ scores at baseline (prior to treatment) were 39.4 and 37.8 in the 5-mL and 8-mL groups, respectively. The change from baseline

in FACE-Q™ appraisal of lines NLF Rasch-transformed total scores, through Week 48, in both the 5-mL (mean increase from baseline range: 33.9 to 41.9) and 8-mL (mean increase from baseline range: 33.5 to 37.2) showed that subjects were more satisfied with how their NLFs looked following treatment at all post-baseline visits.

The median time in hours to feeling comfortable returning to social engagements was two hours or less in both group at all sessions.

Extension study (48 to 96 weeks):
The effectiveness of *Sculptra Aesthetic*, reconstituted with 8 mL SWFI + 1 mL of 2% lidocaine hydrochloride (HCl), in the treatment of both the left and right NLFs was maintained throughout this extension study, with mean reductions from baseline in left NLFs of -1.3 and -1.2 at Weeks 72 and 96, respectively, and mean reductions from baseline in right NLFs of -1.2 and -1.1 at Weeks 72 and 96, respectively, based on the WAS (Evaluator).

All subjects (100%) showed aesthetic improvement at all visits for both sides of the face concurrently, as assessed by the GAIS (Investigator assessment). The majority of subjects showed aesthetic improvement at all visits, as assessed by the GAIS (subject assessment). The percentage of subjects improved are displayed in Table 25.

TABLE 25
GLOBAL AESTHETIC IMPROVEMENT SCALE (SUBJECT ASSESSMENT) BY VISIT (EXTENSION POPULATION)

Characteristic	Extension 8 mL
Week 24	n=38
Any improvement, n (%)[a]	35 (92.1)
95% confidence interval[b]	78.6, 98.3
Any worsening[c]	0
Week 48	n=38
Any improvement, n (%)[a]	34 (89.5)
95% confidence interval[b]	75.2, 97.1
Any worsening[c]	0
Week 72 - extension	n=35
Any improvement, n (%)[a]	30 (85.7)
95% confidence interval[b]	69.7, 95.2
Any worsening[c]	1 (2.9)
Week 96 - extension	n = 35
Any improvement, n (%)[a]	30 (85.7)
95% confidence interval[b]	69.7, 95.2
Any worsening[c]	2 (5.7)

a At least improved on both sides of the face concurrently and combined the categories of "very much improved," "much improved," and "improved."
b Confidence interval calculated using Clopper-Pearson method (based on binomial distribution).
c Any worsening on either side of the face and combined the categories of "worse," "much worse," and "very much worse."

Note: n = number of subjects in specific category. Percentages calculated as 100 × (n/N) out of the number of subjects at each visit.

The FACE-Q™ appraisal of lines NLF scores were used to assess treatment outcome from the subject's perspective. The sum of the subject's FACE-Q™ appraisal of lines NLF scores was converted to a Rasch-transformed total score according to the FACE-Q™ manual; a higher total score indicated greater subject satisfaction.

The mean total score at baseline was 40.3. The higher total score at weeks 72 and 96 indicated subjects were satisfied with how their NLFs looked following treatment (mean increase from baseline of 29.1 and 29.2, respectively).

Subject satisfaction questionnaire results showed that the majority of subjects would choose to receive the treatment again at all visits in both Study 43USSA1705 and this extension study (Week 24 to Week 96 range: 89.5% to 92.1%).

SCULPTRA FOR CORRECTION OF FINE LINES AND WRINKLES IN THE CHEEK REGION FOR USE IN IMMUNE-COMPETENT SUBJECTS

A. Study Design

Base study (0-12 months)

A prospective, randomized, evaluator-blinded, no-treatment controlled multicenter study to assess the effectiveness and safety of treatment with *Sculptra Aesthetic* for correction of cheek wrinkles. One hundred forty-nine (149) subjects with intent to undergo correction of cheek wrinkles with a Galderma Cheek Wrinkles Scale (GCWS) At Rest score of 2 (moderate) or 3 (severe) on each side of the face were to be randomized (2:1) to either treatment with *Sculptra Aesthetic* (treatment group;N = 97) or no treatment (control group; N=52). The treatment group received *Sculptra Aesthetic* reconstituted with 8 mL of SWFI with the addition of 1 mL 2% lidocaine.

Subjects were treated to optimal correction at four-week intervals, with a maximum of four treatment sessions. Follow-up visits were conducted at Months 7, 9 and 12 after initial treatment.

Extension study (12 to 24 months):

During the extended follow-up period, control group subjects were offered Sculptra treatment (Group A), and treatment group subjects (Group B) returned for continued safety and effectiveness evaluations up to 24 months.

B. Study Endpoints

Base study (0-12 months)

The primary purpose was to evaluate the safety of *Sculptra Aesthetic* and effectiveness of *Sculptra Aesthetic* versus a no-treatment control in the correction of cheek wrinkles.

Primary effectiveness endpoint

Responder rate based on the GCWS At Rest, as assessed live by the Blinded Evaluator at Month 12. *A responder was defined as a subject with at least a 1-grade improvement from baseline in both cheeks concurrently.*

Secondary effectiveness endpoints

Secondary effectiveness endpoints included GAIS, subject satisfaction and responder rate on both sides of the face as assessed by the Blinded Evaluator using GCWS At Rest at Month 7 and 9 and GCWS Dynamic at Months 7, 9, and 12 as well as Satisfaction with Cheeks FACE Q™ questionnaire at all visits following the baseline visit for the treatment group and at Months 7, 9, and 12 for the control group, and time in hours from treatment procedure until the earliest time the subject reported feeling comfortable returning to social engagement based on subject diary reporting. The improvement rate based on the Independent Photographic Reviewer's assessment using random pairings of baseline and Month 12 photographs was also included as a secondary endpoint.

Extension study (12 to 24 months):

Effectiveness endpoints evaluated for the long-term extension included responder rate on both sides of the face as assessed by the Blinded Evaluator using GCWS At Rest and GCWS Dynamic at Months 19, 21, and 24 as well as Satisfaction with Cheeks FACE-Q™ questionnaire, subject satisfaction and GAIS at all visits, and time in hours from treatment procedure until the earliest time the subject reported feeling comfortable returning to social engagement based on subject diary reporting.

C. Study Population

Base study (0-12 months)

A total of 149 subjects were enrolled and randomized. A total of 134 (89.9%) subjects completed the study (90.7% treatment group, 88.5% control group); the most common reason for study discontinuation was subjects being lost to follow-up (4 [4.1%] subjects in the treatment group, 2 [3.8%] subjects in the control group). Subject demographics are presented in Table 26.

TABLE 26
DEMOGRAPHICS

	Control Group	Treatment Group	Total
	(N=52)	(N=97)	(N=149)
Age (years)			
n	52	97	149
Mean (SD)	60.4 (8.72)	60.9 (8.50)	60.7 (8.55)
Median	60.0	60.0	60.0
Min, Max	45, 88	41, 89	41, 89
Age Category, n (%)			
>=55 years	39 (75.0)	77 (79.4)	116 (77.9)
<55 years	13 (25.0)	20 (20.6)	33 (22.1)
Gender, n (%)			
Female	50 (96.2)	94 (96.9)	144 (96.6)
Male	2 (3.8)	3 (3.1)	5 (3.4)
Race, n (%)			
American Indian/Alaska Native	0	1 (1.0)	1 (0.7)
Asian	1 (1.9)	1 (1.0)	2 (1.3)
Black/African American	4 (7.7)	7 (7.2)	11 (7.4)

	Control Group	Treatment Group	Total
	(N=52)	(N=97)	(N=149)
Native Hawaiian/Other Pacific Islander	0	0	0
White	47 (90.4)	88 (90.7)	135 (90.6)
Other	0	0	0
Multiple [1]	0	0	0
Ethnicity, n (%)			
Not Hispanic or Latino	47 (90.4)	90 (92.8)	137 (91.9)
Hispanic or Latino	5 (9.6)	7 (7.2)	12 (8.1)
Fitzpatrick Skin Type Score, n (%)			
I	2 (3.8)	4 (4.1)	6 (4.0)
II	18 (34.6)	25 (25.8)	43 (28.9)
III	21 (40.4)	47 (48.5)	68 (45.6)
IV	6 (11.5)	12 (12.4)	18 (12.1)
V	4 (7.7)	5 (5.2)	9 (6.0)
VI	1 (1.9)	4 (4.1)	5 (3.4)
Fitzpatrick Skin Type Score, n (%)			
I	2 (3.8)	4 (4.1)	6 (4.0)
II	18 (34.6)	25 (25.8)	43 (28.9)
III	21 (40.4)	47 (48.5)	68 (45.6)
IV	6 (11.5)	12 (12.4)	18 (12.1)
V	4 (7.7)	5 (5.2)	9 (6.0)
VI	1 (1.9)	4 (4.1)	5 (3.4)
Galderma Cheek Wrinkles Scale (GCWS) – At Rest, Blinded Evaluator, n (%)			
Left			
None	0	0	0
Mild	0	0	0
Moderate	28 (53.8)	50 (51.5)	78 (52.3)
Severe	24 (46.2)	47 (48.5)	71 (47.7)
Very Severe	0	0	0
Galderma Cheek Wrinkles Scale (GCWS) – At Rest, Blinded Evaluator, n (%)			
Right			
None	0	0	0
Mild	0	0	0
Moderate	37 (71.2)	60 (61.9)	97 (65.1)
Severe	15 (28.8)	37 (38.1)	52 (34.9)
Very Severe	0	0	0

[1] 'Multiple' category includes subjects with more than one race selected on eCRF.

Note: N = Number of subjects, n = Number of subjects in specific category. Percentages calculated as 100 x (n/N). SD = Standard D eviation.

Extension study (12 to 24 months):
Of the 134 subjects eligible for the extension study, 111 subjects enrolled in the extension study. The most common reason for subjects not participating in the extension study was the requirement for follow-up visits. A total of 104 (93.7%) subjects completed the extension study. The most common reason for study discontinuation was the subject being lost to follow-up (5 [4.5%] subjects).

D. Treatments Delivered

Base study (0-12 months)
The first treatment was administered at the baseline visit. Additional treatments were performed if deemed necessary to obtain optimal aesthetic result one month after the last treatment in up to four treatment sessions in total. Subjects were treated to optimal correction, which was defined as at least a 1 grade improvement on the GCWS At Rest and best correction that could have been achieved as agreed upon by the Treating Investigator and the subject.
Sculptra was injected using the following injection techniques; linear threading, bolus, fanning and cross-hatching technique, in the subdermal plane; subcutaneously or supraperiosteally. Subjects were given a maximum of two vials per session, with a maximum of one vial per side, (i.e. maximum 9 mL per side). A summary of overall treatment administration characteristics for all treatment sessions is presented in Table 25. Overall, a total mean injection volume of 54.11 mL was received per subject in the treatment group. The median injection volume (left + right sides) at each treatment session was 16.00 mL. The minimum volume injected was 7.5 mL in session 1, 8.0 mL in session 2, 3.0 mL in session 3, and 6.1 mL in session 4; the maximum volume injected at each treatment session was 18.0 mL.

TABLE 27
OVERALL TREATMENT ADMINISTRATION CHARACTERISTICS (TREATMENT GROUP) (SAFETY POPULATION)

Characteristic	Treatment 1 (N=97) n (%)	Treatment 2 (N=95) n (%)	Treatment 3 (N=86) n (%)	Treatment 4 (N=67) n (%)	Total (N=345) n (%)
Number of vials used					
One	92 (94.8)	91 (95.8)	86 (100)	65 (97.0)	334 (96.8)
Two	5 (5.2)	4 (4.2)	0	2 (3.0)	11 (3.2)
Was 25-gauge needle used for injection					
Yes	97 (100)	95 (100)	86 (100)	67 (100)	345 (100)
Injection method[a]					
Linear antegrade	38 (39.2)	39 (41.1)	36 (41.9)	25 (37.3)	138 (40.0)
Linear retrograde	87 (89.7)	85 (89.5)	79 (91.9)	64 (95.5)	315 (91.3)
Bolus	20 (20.6)	22 (23.2)	18 (20.9)	14 (20.9)	74 (21.4)
Fanning	78 (80.4)	77 (81.1)	73 (84.9)	52 (77.6)	280 (81.2)
Cross hatching	33 (34.0)	34 (35.8)	38 (44.2)	26 (38.8)	131 (38.0)
Depth of injection, left side					
Subcutaneous	97 (100)	95 (100)	86 (100)	67 (100)	345 (100)
Supraperiosteal	67 (69.1)	63 (66.3)	56 (65.1)	45 (67.2)	231 (67.0)
Depth of injection, right side					
Subcutaneous	97 (100)	95 (100)	86 (100)	67 (100)	345 (100)
Supraperiosteal	67 (69.1)	63 (66.3)	56 (65.1)	45 (67.2)	231 (67.0)
Any anesthetics used before injection	62 (63.9)	61 (64.2)	53 (61.6)	35 (52.2)	211 (61.2)
Topical	56 (57.7)	55 (57.9)	49 (57.0)	31 (46.3)	191 (55.4)
Local injection	6 (6.2)	6 (6.3)	4 (4.7)	4 (6.0)	20 (5.8)
None	35 (36.1)	34 (35.8)	33 (38.4)	32 (47.8)	134 (38.8)
Any injection concomitant procedures	79 (81.4)	81 (85.3)	74 (86.0)	55 (82.1)	289 (83.8)
Massage	60 (61.9)	64 (67.4)	60 (69.8)	42 (62.7)	226 (65.5)
Ice pack	61 (62.9)	59 (62.1)	51 (59.3)	37 (55.2)	208 (60.3)
Other	6 (6.2)	6 (6.3)	6 (7.0)	5 (7.5)	23 (6.7)
None	18 (18.6)	14 (14.7)	12 (14.0)	12 (17.9)	56 (16.2)
Any technical problems	0	1 (1.1)	1 (1.2)	0	2 (0.6)

a Injector was to check all that applied.

Note: N = number of treatments given to subjects in safety population, n = number of treatments given for specific category. Percentages calculated as 100 × (n/N).

Extension study (12 to 24 months):

Only Group A subjects received treatment with *Sculptra* in the Extension study and followed the same treatment schedule as the Base study. Overall, similar injection volumes were seen in the Extension study.

Overall, a total mean injection volume of 62.84 mL was received per subject in Group A. The median injection volume (left + right sides) at each treatment ranged from 16.50 to 16.80 mL. The minimum volume injected was 8.5 mL at treatment 4 and 9.0 mL at treatments 1, 2, and 3; the maximum volume injected at each treatment was 18.0 mL.

E. Effectiveness results

Base study (0 to 12 months):

The primary effectiveness endpoint was the responder rate based on the GCWS At Rest, as assessed live by the Blinded Evaluator, at Month 12. A responder was defined as a subject with at least a 1-grade improvement from baseline in both cheeks concurrently. As shown in Table 28, there was a

statistically significantly higher responder rate based on the GCWS At Rest (Blinded Evaluator) at Month 12 for the treatment group compared with the control group (70.7% versus 25.9%, respectively; p<.0001).

TABLE 28
RESPONDER RATE BASED ON THE GCWS AT REST (BLINDED EVALUATOR) AT MONTH 12
(MULTIPLE IMPUTATION ANALYSIS - INTENT-TO-TREAT POPULATION)

Statistic	Control Group	Treatment Group
Observed cases responder rate, n/N (%)[a]	12/46 (26.1)	63/88 (71.6)
Estimated responder rate[b]	25.9	70.7
95% confidence interval[c]	13.4, 38.3	61.1, 80.4
P-value[d]		
Mean[e]		<.0001
Maximum[e]		<.0001
Difference 95% confidence interval[c,f]		29.4, 60.3

a Defined as at least a 1-grade improvement from baseline on both sides of the face concurrently.
b Estimated with 10 imputation datasets and full conditionals, which included the assigned treatment, side of face, and all GCWS up to Month 12 (inclusive).
c Confidence interval calculated using multiple imputation methods.
d Two-sided p-value as calculated via Fisher's exact test.
e Across 10 imputation data sets.
f Difference confidence interval calculated using normal approximation.

Note: N = number of subjects; n = number of subjects in specific category. Percentages calculated as 100 × (n/N) out of the number of subjects at each visit. Ten datasets were multiply imputed; only subjects with a baseline score were included. One subject (control group) who did not have a baseline value was excluded from analysis. Fourteen subjects (5 control group, 9 treatment group) had Month 12 scores imputed.

Females reported a responder rate of 72.9% (62/85) compared to males that reported 33.3% (1/3). Due to the small number of male subjects, conclusions cannot be drawn.

Responder rates over time based on Blinded Evaluator assessment, displayed in Table 27, demonstrate there was a statistically significantly higher responder rate for the treatment group compared with the control group based on the GCWS At Rest (Blinded Evaluator) also at Months 7 (66.2% versus 38.6%, respectively; p = 0.0043) and 9 (70.6% versus 31.1%, respectively; p<.0001).

TABLE 29
RESPONDER RATE BASED ON THE GCWS AT REST (BLINDED EVALUATOR) BY VISIT
(OBSERVED CASES ANALYSIS - INTENT-TO-TREAT POPULATION)

Statistic	Control Group	Treatment Group
Month 7 responder rate, n/N (%)[a]	17/44 (38.6)	51/77 (66.2)
95% confidence interval[b]	24.4, 54.5	54.6, 76.6
P-value[c]		0.0043
Difference 95% confidence interval[d]		9.7, 45.4
Month 9 responder rate, n/N (%)[a]	14/45 (31.1)	60/85 (70.6)
95% confidence interval[b]	18.2, 46.6	59.7, 80.0
P-value[c]		<.0001
Difference 95% confidence interval[d]		22.8, 56.1
Month 12 responder rate, n/N (%)[a]	12/46 (26.1)	63/88 (71.6)
95% confidence interval[b]	14.3, 41.1	61.0, 80.7
P-value[c]		<.0001
Difference 95% confidence interval[d]		29.7, 61.3

GCWS = Galderma Cheek Wrinkles Scale

a Defined as at least a 1-grade improvement from baseline on both sides of the face concurrently.

b Confidence interval calculated using Clopper-Pearson method (based on binomial distribution).

c Two-sided p-value as calculated via Fisher's exact test.

d Difference confidence interval calculated using normal approximation.

Note: N = number of subjects; n = number of subjects in specific category. Percentages calculated as 100 × (n/N) out of the number of subjects at each visit.

GCWS Dynamic. A displayed in Table 30, there was a statistically significantly higher responder rate for the treatment group compared with the control group based on the GCWS Dynamic (Blinded Evaluator) at Months 7 (67.5% versus 27.3%, respectively; p<.0001), 9 (64.7% versus 22.2%, respectively; p<.0001), and 12 (70.5% versus 28.3%, respectively; p<.0001).

TABLE 30

RESPONDER RATE BASED ON THE GCWS DYNAMIC (BLINDED EVALUATOR) BY VISIT

(OBSERVED CASES ANALYSIS - INTENT-TO-TREAT POPULATION)

Statistic	Control Group	Treatment Group
Month 7 responder rate, n/N (%)[a]	12/44 (27.3)	52/77 (67.5)
95% confidence interval[b]	15.0, 42.8	55.9, 77.8
P-value[c]		<.0001
Difference 95% confidence interval[d]		23.5, 57.1
Month 9 responder rate, n/N (%)[a]	10/45 (22.2)	55/85 (64.7)
95% confidence interval[b]	11.2, 37.1	53.6, 74.8
P-value[c]		<.0001
Difference 95% confidence interval[d]		26.6, 58.3
Month 12 responder rate, n/N (%)[a]	13/46 (28.3)	62/88 (70.5)
95% confidence interval[b]	16.0, 43.5	59.8, 79.7
P-value[c]		<.0001
Difference 95% confidence interval[d]		26.1, 58.3

a Defined as at least a 1-grade improvement from baseline on both sides of the face concurrently.
b Confidence interval calculated using Clopper-Pearson method (based on binomial distribution).
c Two-sided p-value as calculated via Fisher's exact test.
d Difference confidence interval calculated using normal approximation.

Note: N = number of subjects; n = number of subjects in specific category. Percentages calculated as 100 × (n/N) out of the number of subjects at each visit.

Improvement rate based on the Independent Photographic Reviewer's (IPR) assessment using random pairings of 2D-photographs from baseline and Month 12 were conducted at study completion. An improved subject was defined as a subject for whom the IPR correctly identified the Month 12 photograph in the pair of pre- and post-treatment photographs at rest[1]. The responder rate was 37% in the treatment group and 16% in the no treatment group. The IPR responder rates are expected to be lower due to the challenges and limitations of evaluating changes in wrinkle severity on 2D-photography.

As shown in Table 31, the percentage of responders (as assessed by the GAIS - Treating Investigator) ranged from 68.1% to 96.3% across Month 1 through Month 12 for the treatment group and from 4.3% to 6.8% across Month 7 through Month 12 for the control group. Excluding Month 1, CIs were >80% for the treatment group from Month 2 through Month 12.

[1] Note: The definition of responder for the control group was changed to match the same definition for the treatment group

TABLE 31
GLOBAL AESTHETIC IMPROVEMENT SCALE IMPROVEMENT RATES BY TREATING INVESTIGATOR BY VISIT
(INTENT-TO-TREAT POPULATION)

Time Point	Control Group	Treatment Group
Month 1 responder: any improvement, n/N (%)[a]		64/94 (68.1)
95% confidence interval[b]		57.7, 77.3
Month 2 responder: any improvement, n/N (%)[a]		78/87 (89.7)
95% confidence interval[b]		81.3, 95.2
Month 3 responder: any improvement, n/N (%)[a]		78/81 (96.3)
95% confidence interval[b]		89.6, 99.2
Month 7 responder: any improvement, n/N (%)[a]	3/44 (6.8)	74/77 (96.1)
95% confidence interval[b]	1.4, 18.7	89.0, 99.2
Month 9 responder: any improvement, n/N (%)[a]	2/45 (4.4)	79/85 (92.9)
95% confidence interval[b]	0.5, 15.2	85.3, 97.4
Month 12 responder: any improvement, n/N (%)[a]	2/46 (4.3)	83/88 (94.3)
95% confidence interval[b]	0.5, 14.8	87.2, 98.1

a A responder was defined as a subject that had "very much improved", "much improved", or "improved" on both sides of the face.

b Confidence interval calculated using Clopper-Pearson method (based on binomial distribution).

Note: N = number of subjects; n = number of subjects in specific category. Percentages calculated as 100 × (n/N) out of the number of subjects at each visit. Global Aesthetic Improvement Scale was first assessed in the control group at Month 7.

Aesthetic improvement compared to baseline, as evaluated by subject assessment (GAIS), is also summarized in Table 32. The percentage of responders ranged from 57.4% to 93.5% across Month 1 through Month 12 for the treatment group and from 6.5% to 7.0% across Month 7 to Month 12 for the control group. Excluding Months 1 and 2, CIs were >80% for the treatment group from Month 3 through Month 12.

TABLE 32
GLOBAL AESTHETIC IMPROVEMENT SCALE IMPROVEMENT RATES BY SUBJECT BY VISIT
(INTENT-TO-TREAT POPULATION)

Time Point	Control Group	Treatment Group
Month 1 responder: any improvement, n/N (%)[a]		54/94 (57.4)
95% confidence interval[b]		46.8, 67.6
Month 2 responder: any improvement, n/N (%)[a]		69/87 (79.3)
95% confidence interval[b]		69.3, 87.3
Month 3 responder: any improvement, n/N (%)[a]		72/81 (88.9)
95% confidence interval[b]		80.0, 94.8
Month 7 responder: any improvement, n/N (%)[a]	3/43 (7.0)	72/77 (93.5)
95% confidence interval[b]	1.5, 19.1	85.5, 97.9
Month 9 responder: any improvement, n/N (%)[a]	3/44 (6.8)	76/85 (89.4)
95% confidence interval[b]	1.4, 18.7	80.9, 95.0
Month 12 responder: any improvement, n/N (%)[a]	3/46 (6.5)	81/88 (92.0)
95% confidence interval[b]	1.4, 17.9	84.3, 96.7

a A responder was defined as a subject that had "very much improved", "much improved", or "improved" on both sides of the face.

b Confidence interval calculated using Clopper-Pearson method (based on binomial distribution).

Note: N = number of subjects; n = number of subjects in specific category. Percentages calculated as 100 × (n/N) out of the number of subjects at each visit. Global Aesthetic Improvement Scale was first assessed in the control group at Month 7.

A summary of subject satisfaction questionnaire results over time is provided below.

Across Month 7 to Month 12, the percentages of subjects in the treatment group who responded with "very good" or "excellent" for the following questions were as follows:

- Made them look younger (48.1% to 52.9%)
- Made them feel better about themselves (49.4% to 54.1%)
- Improved their self-confidence (46.6% to 50.6%)
- Improved overall satisfaction with their appearance (46.6% to 55.3%)
- Made them look/feel more confident in their life (45.5% to 50.6%)
- Made them look the way they felt (44.3% to 50.6%)
- Improved their skin firmness (52.3% to 60.0%)
- Improved their skin radiance (51.1% to 57.6%)
- Improved their skin sagging (40.9% to 49.4%)
- Made their skin look more refreshed (50.0% to 57.6%)

Across Month 7 to Month 12, the majority of subjects in the treatment group responded as "agree" or "strongly agree" that:

- The treatment results were natural looking (85.9% to 93.5%)
- The subtle treatment results over time were worth it (80.0% to 81.8%)

Across Month 7 to Month 12, the majority of subjects in the treatment group would recommend the treatment to a friend (range: 88.6% to 89.6%).

Across Month 7 to Month 12, the majority of subjects in the treatment group would choose to receive the treatment again (range: 84.4% to 89.4%).

FACE-Q change from baseline scores indicate subjects were more satisfied with the appearance of their cheeks following treatment. A summary of the change from baseline in Satisfaction with Cheeks FACE-Q™ Questionnaire Rasch-transformed scores over time is presented in Table 31. The mean score at baseline (prior to treatment) was 35.2 and 33.9 for the treatment and control groups, respectively. Based on the Rasch-transformed scores, subjects were more satisfied with how their cheeks looked following treatment at all post-baseline visits from Month 1 through Month 12 (mean increase from baseline range: 21.3 to 40.0), whereas subjects in the control group were not more satisfied with how their cheeks looked at all post-baseline visits from Month 7 through Month 12 (mean decrease from baseline range: -3.6 to -4.1).

TABLE 33
SATISFACTION WITH CHEEKS FACE-Q™ QUESTIONNAIRE: RASCH-TRANSFORMED SCORES IN SUBJECT SATISFACTION OVER TIME (INTENT-TO-TREAT POPULATION)

		Control Group (N=52)		Treatment Group (N=97)	
Visit	Statistic	Score	Change from Baseline	Score	Change from Baseline
Baseline	n	50		97	
	Mean (standard deviation)	33.9 (13.62)	--	35.2 (19.16)	--
	Median	35.0	--	35.0	--
	Minimum, maximum	0, 63	--	0, 100	--
Month 1	n			94	94
	Mean (standard deviation)	--	--	56.3 (23.73)	21.3 (24.25)
	Median	--	--	63.0	20.0
	Minimum, maximum	--	--	0, 100	-35, 80
	95% confidence interval	--	--	--	16.4, 26.3
Month 2	n			87	87
	Mean (standard deviation)	--	--	65.9 (25.50)	31.6 (28.45)
	Median	--	--	63.0	35.0
	Minimum, maximum	--	--	0, 100	-44, 87
	95% confidence interval	--	--	--	25.6, 37.7
Month 3	n			81	81
	Mean (standard deviation)	--	--	73.3 (22.41)	38.6 (26.51)
	Median	--	--	77.0	45.0
	Minimum, maximum	--	--	13, 100	-78, 78
	95% confidence interval	--	--	--	32.8, 44.5
Month 7	n	43	42	77	77
	Mean (standard deviation)	30.6 (20.17)	-4.1 (20.34)	74.0 (23.03)	38.6 (26.30)
	Median	35.0	-2.0	70.0	38.0
	Minimum, maximum	0, 63	-40, 50	0, 100	-40, 87
	95% confidence interval	--	-10.5, 2.2	--	32.7, 44.6
Month 9	n	45	44	85	85
	Mean (standard deviation)	30.2 (19.10)	-3.6 (21.36)	73.4 (23.48)	37.9 (26.63)
	Median	35.0	0.0	77.0	38.0
	Minimum, maximum	0, 63	-40, 40	0, 100	-28, 87
	95% confidence interval	--	-10.1, 2.9	--	32.2, 43.6
Month 12	n	46	45	88	88
	Mean (standard deviation)	30.6 (20.64)	-3.6 (21.76)	75.6 (24.36)	40.0 (29.07)
	Median	35.0	-5.0	77.0	46.0
	Minimum, maximum	0, 91	-40, 47	0, 100	-44, 87
	95% confidence interval	--	-10.1, 3.0	--	33.8, 46.1

Source: Table 14.2.6.2

Note: N = number of subjects; n = number of subjects in specific category. Confidence interval calculated via t-distribution.

Based on subject diaries, the median time to feeling comfortable returning to social engagement across the 4 treatment sessions ranged from 3.9 hours (treatment 1) to 7.1 hours (treatment 4).

Overall, across all treatment sessions, 90% of subjects felt comfortable returning to social engagement by 7.1 hours post-treatment. The remaining 10% did not complete the return to social engagement assessment. There were no subjects with missing or incomplete data from the subject diary that reported related adverse events associated with social circumstances or social avoidant behavior."

Extension study (12 to 24 months):
GCWS data showed that the effects of Sculptra treatments were maintained through 24 months as displayed in Table 34 below.

TABLE 34
RESPONDER RATE BASED ON THE GCWS AT REST (BLINDED EVALUATOR) BY VISIT (OBSERVED CASES ANALYSIS - EXTENSION POPULATION)

Statistic	**Group B**
Month 19 responder rate, n/N (%)[1]	56/66 (84.8)
95% confidence interval[2]	73.9, 92.5
Month 21 responder rate, n/N (%)[1]	50/65 (76.9)
95% confidence interval[2]	64.8, 86.5
Month 24 responder rate, n/N (%)[1]	50/65 (76.9)
95% confidence interval[2]	64.8, 86.5

Source: CSR, Table 14.2.1.1
GCWS = Galderma Cheek Wrinkles Scale
1. Defined as at least a 1-grade improvement from pre-treatment on both sides of the face concurrently.
2. Confidence interval calculated using Clopper-Pearson method (based on binomial distribution).
Note: N = Number of subjects, n = Number of subjects in specific category. Percentages calculated as 100 x (n/N) out of the number of subjects at each visit. Group B subjects received *Sculptra Aesthetic* in Study 43USSA1812 but were untreated in this extension study.

The percentage of responders (as assessed by the GAIS - Treating Investigator), ranged from 93.8% to 97.0% across Month 19 (first assessment time point) through Month 24 for Group B, with CIs >80% for Group B from Month 19 through Month 24. The percentage of responders (as assessed by the GAIS – subject assessment), ranged from 86.2% to 93.8% across Month 19 through Month 24 for Group B, with CIs >80% for Group B at Month 21. In general, subjects remained satisfied with the treatment throughout this extension study. The treated control subjects reported similar improvements in GAIS. The results are displayed in Table 35.

TABLE 35
GLOBAL AESTHETIC IMPROVEMENT SCALE IMPROVEMENT RATES BY TREATING INVESTIGATOR AND BY SUBJECT BY VISIT (EXTENSION POPULATION)

	By treating investigator	By subject
Time Point	**Group B**	**Group B**
Month 19 responder: any improvement, n/N (%)[1]	64/66 (97.0)	58/67 (86.6)
95% confidence interval[2]	89.5, 99.6	76.0, 93.7
Month 21 responder: any improvement, n/N (%)[1]	63/65 (96.9)	61/65 (93.8)
95% confidence interval[2]	89.3, 99.6	85.0, 98.3
Month 24 responder: any improvement, n/N (%)[1]	61/65 (93.8)	56/65 (86.2)
95% confidence interval[2]	85.0, 98.3	75.3, 93.5

Source: CSR; Table 14.2.4.1, Table 14.2.4.2

1. A responder was defined as a subject that had "very much improved," "much improved," or "improved" on both sides of the face.
2. Confidence interval calculated using Clopper-Pearson method (based on binomial distribution).

Note: N = number of subjects; n = number of subjects in specific category. Percentages calculated as 100 × (n/N) out of the number of subjects at each visit. Global Aesthetic Improvement Scale was first assessed in Group B at Month 19. Group A subjects were untreated in Study 43USSA1812 but received *Sculptra Aesthetic* in this extension study; Group B subjects received *Sculptra Aesthetic* in Study 43USSA1812 but were untreated in this extension study.

HOW SUPPLIED

Sculptra is supplied as a sterile freeze-dried preparation for injection in a clear glass vial, which is sealed by a penetrable stopper, covered by an aluminum seal with a flip-off cap. Each carton of *Sculptra* contains two vials of poly-L-lactic acid, sodium carboxymethylcellulose (USP), non-pyrogenic mannitol (USP).

STORAGE

Sculptra can be stored at room temperature, up to 30ºC (86ºF). DO NOT FREEZE. Refrigeration is not required.

STERILITY

Each vial of *Sculptra* is packaged for single-use only. Do not re-sterilize.

IF THE VIAL, SEAL, OR THE FLIP-OFF CAP ARE DAMAGED, DO NOT USE AND CONTACT GALDERMA LABORATORIES, L.P. DALLAS, TX 75201 USA 1-855-425-8722.

INSTRUCTIONS FOR USE

Sculptra has been evaluated in immune-competent people as a single regimen for correction of shallow to deep nasolabial fold contour deficiencies and other facial wrinkles.
Sculptra has been evaluated for correction of fine lines and wrinkles in the cheek region for use in immune-competent subjects

Sculptra use should be limited to use in a single regimen of up to four sequential sessions each spaced three to four-weeks apart.

Educational resources are available through myGAINtraining.com, which provides training on the anatomy of the treatment area, effective patient assessment, and appropriate injection techniques. Health care professionals may contact Galderma for educational and training resources specific to the correction of fine lines and wrinkles in the cheek region.

Completion of device-specific use training is required and will be verified prior to purchase of *Sculptra* for the correction of fine lines and wrinkles in the cheek region for use in immune-competent subjects.

The following supplies are used with *Sculptra* but are to be provided by the end-user:

- Sterile Water for Injection (SWFI), USP
- Single-use 5 mL sterile syringe
- Single-use 1 or 3 mL (depending on healthcare professional preference) sterile syringes (at least 2)
- 18 G sterile needles (at least 2)
- **26 G** (5 mL reconstitution volume) or **25 G** (8 mL reconstitution volume) sterile needles (several should be available). It is recommended to use a thin wall needle to reduce the risk of clogging.
- Antiseptic (such as alcohol)
- 2% sterile lidocaine solution (8 mL reconstitution volume)

Reconstitution

Sculptra may be reconstituted with either 5 mL of SWFI and stored for up to 72 hours or reconstituted with 8 mL of SWFI for immediate use according to the instructions below.

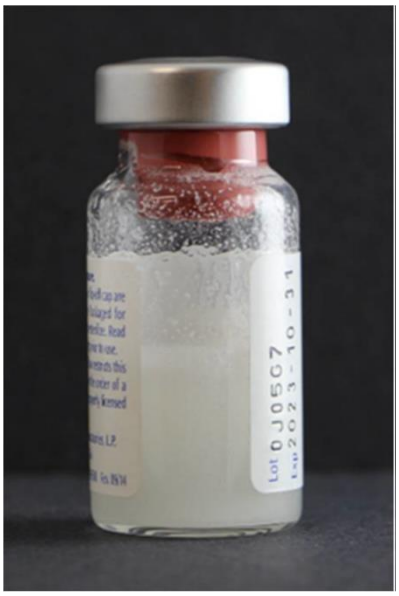
5 mL Reconstitution

(for correction of shallow to deep nasolabial fold contour deficiencies and other facial wrinkles)
Sculptra is reconstituted in the following way:

1. Remove the flip-off cap from the vial and clean the penetrable stopper of the vial with an antiseptic. If the vial, seal, or flip-off cap is damaged, do not use, and call Galderma Laboratories, L.P. at 1-855-425-8722.
2. Attach an 18 G sterile needle to a sterile single-use 5 mL syringe.
3. Draw 5 mL of SWFI into the 5 mL syringe.

4. Introduce the 18 G sterile needle into the stopper of the vial and slowly add all SWFI into the vial.
5. Let the vial stand for at least 2 hours to ensure complete hydration; do not shake during this period. Upon reconstitution, *Sculptra* can be stored for up to 72 hours at temperatures between 5-30ºC. Refrigeration is not required.
6. Product should be gently agitated immediately prior to use. Agitate the vial until a uniform translucent suspension is obtained that will have some foam on the top, see Figure 3. A single vial swirling agitator may be used. The reconstituted product is usable within 72 hours of reconstitution. As it is a single use vial, discard any material remaining after use or after 72 hours following reconstitution.

FIGURE 3
RECONSTITUTED PRODUCT 5 mL



7. Reconstituted *Sculptra* is a suspension with particles that will sediment at standing. To maintain a uniform suspension throughout the procedure, intermittently agitate the *Sculptra* vial between the withdrawals to syringes. Clean the penetrable stopper of the vial with an antiseptic and use a new 18 G sterile needle to withdraw an appropriate amount of the suspension (typically 1 mL) into a single–use 1 or 3 mL sterile syringe. Tilt the vial horizontally and withdraw suspension from the lower lateral of the vial to avoid withdrawing foam. Do not store the reconstituted product in the syringe.
8. Replace the 18 G needle with a **26 G** sterile needle before injecting the product into the deep dermis. Do not inject *Sculptra* using needles of an internal diameter smaller than 26 G. If clogging of the needle occurs, remove the needle, attach a new sterile needle, then expel a few drops of *Sculptra* to eliminate the air and re-check for needle blockage.
9. To withdraw remaining contents of the vial, repeat steps 7 through 8. Do not inject the foam.
10. Discard any remaining product immediately after single session/patient use.

8 mL Reconstitution with optional addition of 1 mL 2% lidocaine

(for correction of shallow to deep nasolabial fold contour deficiencies and for correction of fine lines and wrinkles in the cheek region)

Sculptra is reconstituted in the following way:

1. Remove the flip-off cap from the vial and clean the penetrable stopper of the vial with an antiseptic. If the vial, seal, or flip-off cap is damaged, do not use, and call Galderma Laboratories, L.P. at 1-855-425-8722.

2. Attach an 18 G sterile needle to a sterile single-use 5 mL syringe.

3. Draw 5 mL of SWFI into the 5 mL syringe.

4. Introduce the 18 G sterile needle into the stopper of the vial, find the open slit in the stopper and slowly add all SWFI into the vial letting the water flow on to the inner wall of the vial. Remove the syringe and needle.

5. Shake the vial vigorously for about 1 minute to dissolve the excipients. Inspect the vial for any lumps and if needed, shake more. A translucent suspension with some foam on the top will be obtained, see Figure 4. A single vial swirling agitator may be used.

6. Add another 3 mL of SWFI using an 18 G needle. Remove the syringe and needle. Shake again in order to get a homogenous suspension that will have some foam on the top.

7. If using lidocaine, add 1 mL of 2% lidocaine solution immediately prior to injection. Clean the penetrable stopper of the vial with an antiseptic, add the lidocaine solution using a new single use 1 mL sterile syringe and 18 G sterile needle. Remove the syringe and needle. Shake again in order to get a homogenous suspension that will have some foam on the top.

FIGURE 4
RECONSTITUTED PRODUCT 8 mL + 1 mL

8. Reconstituted *Sculptra* is a suspension with particles that will sediment at standing. To maintain a uniform suspension throughout the procedure, intermittently agitate the *Sculptra* vial between the withdrawals to syringes. Clean the penetrable stopper of the vial with an antiseptic and use a new

18 G sterile needle to withdraw an appropriate amount of the suspension (typically 1 mL) into a single- use 1 or 3 mL sterile syringe. Tilt the vial horizontally and withdraw suspension from the lower lateral of the vial to avoid withdrawing foam. Do not store the reconstituted product in the syringe.

9. Replace the 18 G needle with a **25 G** sterile needle before injecting the product into the subdermal region. Do not inject *Sculptra* using needles of an internal diameter smaller than 25 G. If clogging of the needle occurs, remove the needle, attach a new sterile needle, then expel a few drops of *Sculptra* to eliminate the air and re-check for needle blockage. It is recommended to use a thin wall needle to reduce the risk of clogging.
10. To withdraw remaining contents of the vial, repeat steps 8 through 9. Do not inject the foam.

11. Discard any remaining product immediately after single session/patient use.

Patient treatment

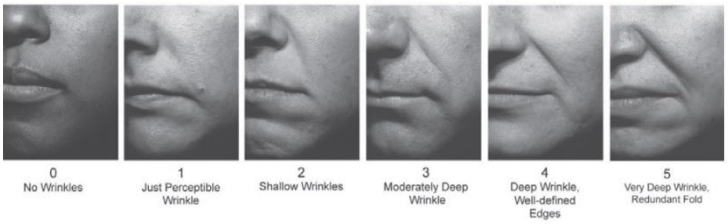
1. Patient Counseling

The patient should be fully apprised of the indications, contraindications, warnings, precautions, treatment responses, adverse reactions, and method of administration with *Sculptra*.

- Each patient should be informed that the amount of *Sculptra* and the number of injection sessions will depend on the patient's need.
    - For correction of nasolabial fold contour deficiencies, a treatment interval of at least three to four weeks between injection sessions is recommended.
    - For correction of other facial wrinkles, a minimum treatment interval of three weeks between sessions is recommended.
    - For correction of fine lines and wrinkles in the cheek region, a minimum treatment interval of four weeks between sessions is recommended.
- Each patient should be informed that up to four injection sessions may be needed to achieve the desired results.
- For patients who have experienced medically important adverse events, a decision for touchup or re-treatment should take the cause and severity of previous reactions into consideration.
- Patients should be informed that typically, at the end of the injection session, they will experience some degree of swelling due to the water (SWFI) used to reconstitute *Sculptra* and the injection procedure. This will give the appearance of a full correction by the end of the injection session, but the injection-related swelling typically resolves in several hours to a few days, resulting in the reappearance of the original contour deficiency. For correction of nasolabial fold contour deficiencies:

  Using the standard Wrinkle Assessment Scale (WAS) photographs (see Figure 5) provided for patient counseling, a patient should be informed of the optimal cosmetic correction that may be expected by that patient. A one-grade improvement has typically been demonstrated in clinical studies.

FIGURE 5
WRINKLE ASSESSMENT SCALE (WAS)



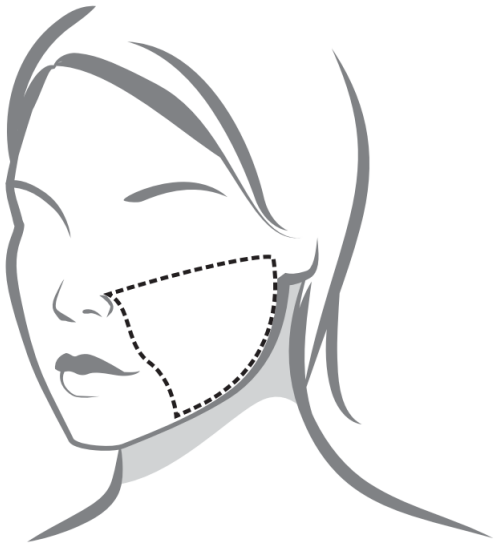
- For correction of fine lines and wrinkles in the cheek region:
  The treatment is depictured below in Figure 6. Before treatment, the patient should be informed of the optimal correction that may be expected by that patient. A one-step improvement on the scale below has been demonstrated in a clinical study.

  Galderma Cheek Wrinkle Scale

  - None: No Lines or wrinkles.
  - Mild: Only a few superficial lines
  - Moderate: Many superficial lines or a few shallow wrinkles.
  - Severe: Many shallow wrinkles or a few moderate depth wrinkles.
  - Very severe: Many moderate wrinkles or at least one deep wrinkle with or without redundant folds.

FIGURE 6

TREATMENT AREA CHEEK REIGON



- Patients should be informed that typically the wrinkle deficiency will gradually improve over time (several weeks) after injection as the treatment effect of *Sculptra* occurs.
- Patients should be informed that, if needed, their healthcare professional may utilize a topical or a local anesthetic prior to injecting *Sculptra.*

2. Patient Assessment

- A complete medical history should be taken to determine if *Sculptra* injection is appropriate.
- Before and after treatment, healthcare professional are encouraged to conduct vision assessments, including visual acuity, extraocular motility, and visual field testing.
- During the initial treatment session with *Sculptra*, only a limited correction should be made. In contrast to other wrinkle fillers, *Sculptra* provides a gradual improvement of the depressed area over several weeks as the treatment effects occur.
- Re-evaluate the patient no sooner than three to four weeks after the injection session to determine if additional correction is needed.

3. Patient Preparation

Each injection session is to be conducted with aseptic technique and universal precautions due to the potential for contact with patient body fluids: blood from the injection site.

- To prepare for an injection session, all make-up should be removed.
- The treatment area should be cleaned with a suitable antiseptic solution.
- Before injecting *Sculptra* a treatment plan should be determined and the face mapped. The mapping is done using a water-soluble pencil.
- An ice pack can be applied on the site for a short period or additional topical, local injection or nerve block anesthesia may be used to further reduce pain on injection. If additional (topical or local) anesthetic or ice is used, the area should be cleaned after the anesthetic is removed.

4. Injection Needle

- *Sculptra* should be injected using a sterile **26 G** (with 5 mL reconstitution) or **25 G** (with 8 mL reconstitution) needle. It is recommended to use a thin wall needle to reduce the risk of clogging.
  Sculptra should not be injected with needles with a diameter smaller than specified above or with needles that have been bent.
- If the needle becomes occluded or dull during an injection session, needle replacement is necessary.
- If clogging occurs, remove the needle, attach a new sterile needle, then expel a few drops of *Sculptra* to eliminate the air and re-check for needle blockage.
- To maintain a uniform suspension throughout the procedure, intermittently agitate *Sculptra* in the syringe.
- Before initial injection, expel a few drops of *Sculptra* through the attached needle to eliminate air and to check for needle blockage.

5. Depth of Injection

- *Sculptra* should be injected into the deep dermis or in the subdermal regions (i.e. subcutaneously or supraperiosteally).
- Introduce a straight, sterile, bevel-up needle into the skin. It is recommended to introduce the needle at an approximately 30-40 degree angle to the skin and then advance the needle until the desired depth is reached.

6. Injection procedure

Before injecting *Sculptra*, always perform a reflux maneuver to avoid intravascular injection. If blood returns to the syringe, the needle is in a blood vessel and should be withdrawn, pressure should be applied to the injected area until bleeding stops and a new syringe should be prepared. If no blood is pulled back into the syringe, the injection may be started.

To guide the needle to the desired plane, create a firm needle insertion plane by stretching the skin. A change in tissue resistance is felt when the needle crosses from the dermis into subcutaneous layer. If the needle is inserted at too shallow (small) an angle or if the needle tip is not sufficiently advanced, then the needle tip may be in the mid or superficial (papillary) dermis, the needle bevel may be visible through the skin. If *Sculptra* is injected too superficially, the injected area will blanch immediately or shortly after injection. If immediate blanching occurs, the injection should be stopped and the area massaged until it returns to a normal color. Blanching may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with American Society for Dermatologic Surgery guidelines.[2]

Health care practitioners are encouraged to be prepared with the following in the event of an intravascular injection:

- ensuring supplies are immediately available, as recommended by the American Society for Dermatologic Surgery guidelines
- identifying a local ophthalmologist or ophthalmology subspecialist to be available in the event of an ophthalmic adverse event related to a dermal filler injection
- conducting a basic neurologic examination in the event of an ophthalmic adverse event due to the association of such events with central nervous system deficits

a. Threading or Tunneling Technique in a Grid Pattern (cross-hatch) (applicable for correction of shallow to deep nasolabial fold contour deficiencies and other facial wrinkles and for correction of fine lines and wrinkles in the cheek region)

- When the needle tip is in the correct plane, the needle angle should be lowered to 10-20 degrees and the needle should be advanced parallel to the surface of the skin.
- Start the first injection at the base of the nasolabial fold. After completing the length with injections parallel to the nasolabial fold, the cross-hatch pattern is achieved with additional injections perpendicular to the first injection. *Sculptra* should be injected into tissue that is medial to the nasolabial fold wrinkle defect.

b. Bolus technique (applicable for correction of shallow to deep nasolabial fold contour deficiencies and for correction of fine lines and wrinkles in the cheek region)

Allow the needle to pass through the skin to the subdermal regions, and inject a small bolus of product, holding the needle as still as possible.

[2] Jones, Derek; Fitzgerald, Rebecca; Cox, Sue Ellen; et al. Preventing and Treating Adverse Events of Injectable Fillers: Evidence-Based Recommendations from the American Society for Dermatologic Surgery Multidisciplinary Task Force, Dermatologic Surgery: February 2021 - Volume 47 - Issue 2 - p 214-226

c. Linear threading (applicable for correction of shallow to deep nasolabial fold contour deficiencies and for correction of fine lines and wrinkles in the cheek region)
Advance the needle in the desired plane and inject while slowly moving the needle in a retrograde fashion.

d. Fanning technique (applicable for correction of shallow to deep nasolabial fold contour deficiencies and for correction of fine lines and wrinkles in the cheek region)
Using a single injection point, inject the product in multiple threads without removing the needle from the skin in the desired plane. The direction of the needle should continually be changed in a radial fashion to create new injection lines.

7. Volume per Injection

The maximum volume of *Sculptra* per individual injection should be limited to 0.1 mL – 0.2 mL, spaced at a distance of 0.5 -1 cm. Avoid overcorrection.

8. Volume per Treatment Site

During the initial treatment sessions, only a limited correction should be made. In contrast to other wrinkle fillers, *Sculptra* provides a gradual correction of a contour deficiency over several weeks.

A treatment session to correct WAS 2 - 4 nasolabial fold contour deficiencies consists of multiple injections of 0.1-0.2 mL of *Sculptra* to a maximum of 2.5 mL in 5 mL reconstitution or 4.5 mL in 8 mL reconstitution with the addition of 1 mL 2% lidocaine per nasolabial fold per session. The volume of *Sculptra* per surface area has not been determined.

A treatment session to correct fine lines and wrinkles in the cheek region consists of multiple injections of 0.1-0.2 mL of *Sculptra* to a maximum of 9 mL in in 8 mL reconstitution with the optional addition of 1 mL 2% lidocaine per cheek per session. The volume of *Sculptra* per surface area has not been determined.

9. Massage during the Injection Session

The treatment area should be massaged in a circular fashion after every 3-4 injections to evenly distribute the product.

10. Degree of Correction - Treat, Wait, Assess

The contour deficiency should be under-corrected, never fully corrected or overcorrected (overfilled) during any injection session. Under-correction of the treatment area allows for gradual improvement of the contour deficiency as the *Sculptra* effect occurs over the minimum of 3-4 weeks between assessment and possible next injection session.

11. Post-treatment Care

- Immediately after a *Sculptra* injection session, redness, swelling, and/or bruising may appear in the treatment area. To reduce the risk of edema and/or bruising after injection, an ice pack wrapped in cloth (avoid any direct contact of the ice with the skin) is applied to the treated areas. See ADVERSE EVENTS for details of the incidence and severity of adverse event observed immediately post-injection during the clinical trial.

- To help *Sculptra* distribute evenly in the contour deficiency, it is important at the end of the treatment session to manually massage in a circular fashion the treatment area for a minimum of 2 minutes. A facial moisturizer should be used to perform the massage. It is recommended that the patient should massage the treated areas for five minutes, five times per day for five days after the injection session to promote a natural-looking correction.

- Early occurrence of subcutaneous nodules at the injection site (within 3 to 6 weeks after the treatment) may be minimized by adhering to proper dilution and injection techniques (e.g., avoiding superficial injections or over-correction). In addition, massaging the treatment area to ensure proper distribution of the product may also minimize the appearance of nodules. Nodules usually resolve spontaneously. However, as reported in published literature, some nodules may require medical treatment such as subcision (break-up of nodules with sterile saline solution), and delayed occurrence of subcutaneous nodules at the injection site (usually will manifest within 3 to 4 months after the treatment) may require treatment such as intralesional injections of corticosteroids, subcision and/or excision.

PATIENT INSTRUCTIONS
It is recommended that the following information is shared with patients by the healthcare provider:

- Within the first 24 hours, an ice pack wrapped in cloth (avoiding any direct contact of the ice with the skin) should be applied to the treatment area to reduce swelling and bruising. *Sculptra* may cause redness, swelling, or bruising when first injected into the skin, typically resolving in hours to one week. Hematoma may also occur, typically resolving in hours to about two weeks. Worsening or prolonged symptoms or signs should be reported to the health care provider. The original skin depression may initially reappear, but the depression should gradually improve within several weeks as the treatment effect of *Sculptra* occurs. The healthcare professional will assess the need for additional *Sculptra* injection sessions after at least four weeks.
- It is recommended to massage in a circular fashion the treated areas for 5 minutes, 5 times per day for 5 days following any injection session, according to the healthcare professional's advice.
- Treatment with *Sculptra* can result in small papules in the treated area. These subcutaneous papules are typically not visible and asymptomatic and may be noticed only upon pressing on the treatment area. However, visible nodules, sometimes with redness or color change to the skin, have been reported. Patients should report these events and any other side effects to their health care provider.
- Aesthetic make-up may be applied a few hours post-treatment if no complications are present.
- Exposure of the treated area to sun and UV lamp exposure and extreme temperatures are to be avoided until any initial swelling and redness has resolved. Patients should be informed about appropriate sunscreen protection according to the healthcare professional's advice.

ANY SIDE EFFECTS, ADVERSE EVENTS, PRODUCT QUESTIONS OR PRODUCT COMPLAINTS SHOULD BE REPORTED TO:
Galderma Laboratories, L.P.
Dallas, TX 75201 USA
1-855-425-8722

Distributed by:
Galderma Laboratories, L.P.
2001 Ross Avenue
Suite 1600
Dallas, TX 75201 USA

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SCULPTRA FOR RESTORATION AND/OR CORRECTION OF THE SIGNS OF FACIAL FAT LOSS (LIPOATROPHY) IN PEOPLE WITH HUMAN IMMUNODEFICIENCY VIRUS

CONTRAINDICATIONS

Sculptra should not be used in any person who has hypersensitivity to any of the components of *Sculptra* (see DEVICE DESCRIPTION).

Sculptra should not be used in patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.

Sculptra should not be used in patients with known history of or susceptibility to keloid formation or hypertrophic scarring.

WARNINGS

- Do not overcorrect (overfill) the volume deficiencies or contour defects, because the depression is expected to gradually improve during several weeks after injection as the treatment effect of *Sculptra* occurs (see INSTRUCTION FOR USE – Patient Treatment).

- *Sculptra* must not be injected intramuscularly or intravascularly. Localised superficial necrosis and scarring may occur after injection in or near vessels. It is thought to result from the injury, obstruction, or compromise of blood vessels. Areas with limited collateral blood flow has an increased risk of ischaemia. Special caution should be taken if the patient has undergone a prior surgical procedure in the planned treatment area. Aspiration prior to injection is recommended.

- Introduction of product into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Take extra care when injecting soft tissue fillers, for example inject the product slowly and apply the least amount of pressure necessary. Rare but serious adverse events (SAEs) associated with the intravascular injection of soft tissue fillers in the face have been reported and include temporary or permanent vision impairment, blindness, cerebral ischemia or cerebral hemorrhage, leading to stroke, skin necrosis, and damage to underlying facial structures. Immediately stop the injection if a patient exhibits any of the following symptoms, including changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist should an intravascular injection occur.

- *Sculptra* use at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes or hives) or infection is present should be deferred until the inflammatory process has resolved and is controlled.

- *Sculptra* post-treatment reactions have included delayed occurrence of subcutaneous papules and nodules. The subcutaneous papules and nodules were often confined to the injection site, typically palpable, asymptomatic and non-visible, occurring days to months after injection and had a prolonged time course to resolution. See ADVERSE EVENTS section for details.

- The kinetics of *Sculptra* resorption in humans has not been determined. In an intradermal implantation study in rabbits all animals had "several relatively large remnants" of injectable PLLA visible at 64 weeks after implantation. The tissue response to injectable PLLA was generally greater than the vehicle or negative plastic controls and was 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 injectable PLLA.

PRECAUTIONS

- *Sculptra* vials are for single patient and single session use only in order to avoid contamination. Do not reuse the vial and do not re-sterilize the vial. Discard immediately after use. Do not use if the package or vial is opened or damaged.

- In order to minimize the risks of potential complications (such as formation of papules/nodules, perforation of vessels, or trauma to nerves and other vulnerable structures), *Sculptra* should only be used by health care practitioners who have appropriate training, experience, and who are knowledgeable about the anatomy at and around the site of injection and who are fully familiar with the product, product educational materials, and the entire package insert and patient labeling.

- Health care practitioners are encouraged to discuss all potential risks of soft tissue injection with their patients prior to treatment and ensure that patients are aware of signs and symptoms of potential complications.

- The safety and effectiveness of injecting *Sculptra*: 1) in larger amounts, 2) at different frequencies, 3) at anatomic sites different than specified for the intended use of the product, or 4) at anatomic sites that have had other dermal filler injections, have not been evaluated.

- A 5-year post approval study was conducted to evaluate the longer-term safety and effectiveness of *Sculptra* for correction of facial fat loss (lipoatrophy) in people with human immunodeficiency virus.

- The safety and effectiveness of *Sculptra* for use in the lips has not been evaluated. *Sculptra* should not be injected into the red area (vermillion) of the lips.

- Avoid superficial injections as this may be associated with increased local adverse events (AEs) such as nodules and papules. Take special care when using *Sculptra* in patients with thin

skin. Please refer to PATIENT TREATMENT for injection technique instruction.

- *Sculptra* injection in the periorbital area has not been studied. An increased risk of papules and nodules has been reported in published literature after injections in the periorbital area.

- Safety and effectiveness of *Sculptra* has not been evaluated in patients who are pregnant, lactating, breast feeding, or under 18 years of age.

- Safety and effectiveness of *Sculptra* has not been evaluated in patients with the following: connective tissue disease, bleeding disorders, active hepatitis, serious abnormalities in laboratory findings other than CD4 cell count, HIV viral load and lactic acid, disease such as cancer, stroke and/or myocardial infarction and on any immunosuppressive therapy.

- Safety and effectiveness of *Sculptra* has not been systematically evaluated with other drugs (other than lidocaine) or substances, filler products, implants or devices used prior or during the same treatment session.

- Other filler products should not be directly mixed with *Sculptra*. No studies of interactions of *Sculptra* mixed with drugs (other than lidocaine) or other substances or implants have been made.

- It is not known whether *Sculptra* is radiopaque in humans. The microparticles of *Sculptra* may be visible on computer tomography (CT) scans, magnetic resonance imaging (MRI), ultrasound or standard, plain radiography. Patients should be informed that the device may be radiopaque, so that they can inform their health care professionals, including radiologists. In an animal study, *Sculptra* implants were observed in 10/10 rats via MRI and ultrasound imaging 24 hours after subcutaneous injection. Ninety (90) days after injection, *Sculptra* was observed in 3/10 rats via ultrasound and no animals via MRI. *Sculptra* was not observed at either time point via CT scan or standard, plain radiography.

- Injections into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.

- Patients with bleeding disorders or patients using substances that affect platelet function, thrombolytics or anticoagulants may, as with any injection, experience increased bruising, hematoma or localized bleeding at injection site.

- Injection procedures are associated with a risk of infection. Aseptic technique and standard practice to prevent cross-infections are to be followed.

- After use, treatment syringes and needles are considered contaminated biohazards. Handle and dispose contaminated syringes and needles in accordance with accepted medical practice and applicable local, state and federal requirements.

- The patient should be informed that he or she should minimize exposure of the treatment area to sun and avoid UV lamp exposure and extreme temperatures until any initial swelling and redness has resolved.

- If laser treatment, chemical peeling or any other procedure based on active dermal response is considered after treatment with *Sculptra*, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if *Sculptra* is administered before the skin has healed completely after such a procedure.

ADVERSE EVENTS

Clinical Studies

Adverse event data from five clinical studies that included 567 patients are summarized in Tables 36, 37, 38 and 39 below.

TABLE 36
NUMBER OF PATIENTS WITH TREATMENT-RELATED ADVERSE EVENTS OBSERVED IN CLINICAL STUDIES WITH TWO-YEAR FOLLOW-UP

	VEGA STUDY **50 Patients**	**C&W STUDY***** **29 Patients**	**AVERAGE DURATION (DAYS)**
INJECTION PROCEDURE RELATED ADVERSE EVENTS			
Bruising	3 (6%)	11 (38%)	6
Edema	2 (4%)	2 (7%)	3
Discomfort	0	3 (10%)	3
Hematoma	14 (28%)	0	17
Inflammation	0	3 (10%)	3
Erythema	0	3 (10%)	3
DEVICE-RELATED ADVERSE EVENTS			**AVERAGE ONSET** (Months)**
Injection site subcutaneous papule*	26 (52%)	9 (31%)	7

*Subcutaneous papules refer to lesions of 5 mm or less, typically palpable, asymptomatic and non-visible.

**Onset data available from VEGA study only. Duration not noted for subcutaneous papules because most were ongoing at study completion.

*** Safety data were collected *post hoc* for 27 of the patients at approximately two years from study start.

TABLE 37
NUMBER OF PATIENTS WITH TREATMENT-RELATED ADVERSE EVENTS OBSERVED IN CLINICAL STUDIES WITH ONE-YEAR FOLLOW-UP

	APEX 002 STUDY **99 Patients**	**BLUE PACIFIC STUDY** **99 patients**
INJECTION PROCEDURE RELATED ADVERSE EVENTS		
Bruising	1 (1%)	30 (30%)
Edema	3 (3%)	17 (17%)
Discomfort	19 (19%)	15 (15%)
Erythema	0	3 (3%)
DEVICE-RELATED ADVERSE EVENTS		
Injection site subcutaneous papule	6 (6%)	13 (13%)

The duration of (AEs) in Table 37 was not collected. The most common device related effect was the delayed occurrence of subcutaneous papules which were confined to the injection site and were typically palpable, asymptomatic, and non-visible. The study protocols did not include evaluation of treatment for subcutaneous papules, therefore, no information is available on how the papules were treated. In the VEGA study, the average onset of subcutaneous papules was 7 months after initial injection (range 0.3 – 25 months). Subcutaneous papules resolved spontaneously in 6/26 patients (24%) during the study. No information of onset and duration of papules is available from the Chelsea & Westminster study.

Treatment related (AEs), not included in Tables 36 and 37, observed in clinical studies with a frequency of less than 5% were: injection site tenderness, injection site lesion, injection site bleeding, injection site induration, injection site infection and fever.

TABLE 38
OVERALL INCIDENCE (≥ 5%) OF ADVERSE EVENTS BY PREFERRED TERM 'FACES' (5 YEAR, OPEN-LABEL) STUDY

Preferred Term	Female with Fitzpatrick Skin Type I-III (N=70)	Female with Fitzpatrick Skin Type IV-VI (N=70)	Male with Fitzpatrick Skin Type I-III (N=74)	Male with Fitzpatrick Skin Type IV-VI (N=76)	Overall (N=290)
	Subjects[a] n (%)	Subjects[a] n (%)	Subjects[a] n (%)	Subjects[a] n (%)	Subjects[a] n (%)
Upper respiratory tract infection	12 (17.1)	11 (15.7)	11 (14.9)	9 (11.8)	43 (14.8)
Sinusitis	15 (21.4)	7 (10.0)	12 (16.2)	7 (9.2)	41 (14.1)
Diarrhea	8 (11.4)	7 (10.0)	13 (17.6)	9 (11.8)	37 (12.8)
Injections site nodule	7 (10.0)	5 (7.1)	14 (18.9)	6 (7.9)	32 (11.0)
Depression	6 (8.6)	6 (8.6)	5 (6.8)	15 (19.7)	32 (11.0)
Insomnia	5 (7.1)	6 (8.6)	8 (10.8)	13 (17.1)	32 (11.0)
Hypertension	8 (11.4)	7 (10.0)	10 (13.5)	6 (7.9)	31 (10.7)
Injection site papule	8 (11.4)	6 (8.6)	10 (13.5)	6 (7.9)	30 (10.3)
Bronchitis	9 (12.9)	3 (4.3)	7 (9.5)	9 (11.8)	28 (9.7)
Urinary tract infection	12 (17.1)	7 (10.0)	2 (2.7)	4 (5.3)	25 (8.6)
Herpes simplex	4 (5.7)	3 (4.3)	6 (8.1)	9 (11.8)	22 (7.6)
Pneumonia	5 (7.1)	5 (7.1)	7 (9.5)	5 (6.6)	22 (7.6)
Anxiety	7 (10.0)	3 (4.3)	5 (6.8)	7 (9.2)	22 (7.6)
Injection site bruising	9 (12.9)	5 (7.1)	3 (4.1)	3 (3.9)	20 (6.9)
Headache	5 (7.1)	3 (4.3)	9 (12.2)	3 (3.9)	20 (6.9)
Gastro-esophageal reflux disease	9 (12.9)	2 (2.9)	6 (8.1)	3 (3.9)	20 (6.9)
Fatigue	6 (8.6)	3 (4.3)	6 (8.1)	4 (5.3)	19 (6.6)
Back pain	5 (7.1)	4 (5.7)	2 (2.7)	7 (9.2)	18 (6.2)
Arthralgia	6 (8.6)	4 (5.7)	4 (5.4)	2 (2.6)	16 (5.5)

a. Subjects experiencing multiple episodes of a given adverse event are counted once within each Preferred Term.

TABLE 39
SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS 'FACES' (5 YEAR, OPEN-LABEL) STUDY

All-Treated Population

Parameter / Time Period	Female with Fitzpatrick Skin Type I-III (N=70)	Female with Fitzpatrick Skin Type IV-VI (N=70)	Male with Fitzpatrick Skin Type I-III (N=74)	Male with Fitzpatrick Skin Type IV-VI (N=76)	Overall (N=290)
	Subjects n (%)	Subjects n (%)	Subjects n (%)	Subjects n (%)	Subjects n (%)
Any TEAE					
From the First Injection to End of Study	65 (92.9)	54 (77.1)	69 (93.2)	65 (85.5)	253 (87.2)
TEAE Severity[a]					
From the First Injection to End of Study					
Mild	11 (15.7)	15 (21.4)	16 (21.6)	13 (17.1)	55 (19.0)
Moderate	36 (51.4)	28 (40.0)	26 (35.1)	32 (42.1)	122 (42.1)
Severe	18 (25.7)	11 (15.7)	27 (36.5)	20 (26.3)	76 (26.2)
TEAE Relationship to Study Treatment					
From the First Injection to End of Study					
Related to Injection Procedure	25 (35.7)	16 (22.9)	28 (37.8)	17 (22.4)	86 (29.7)
Related to Study Product	22 (31.4)	16 (22.9)	19 (25.7)	10 (13.2)	67 (23.1)

a. A subject was counted only once as the most severe category.

The most frequently reported treatment-related or injection-related AEs were injection site nodules and injection site papules. Overall, a total of 54 subjects (18.6%) reported 170 injection site nodule or papule AEs. Most nodule and papule events were mild or moderate in intensity and resolved spontaneously, without treatment. The majority were reported in the cheek area and were described as mild in intensity, non-serious, palpable and non-visible. Most were reported during the first year (153 of 170 events [90%]); the median number of days from first treatment to the onset of injection site nodules and papules was 56.0 and 96.0 days, respectively. No subject discontinued treatment (temporarily or permanently) or study due to an injection site nodule/papule AE. No granulomas were reported in the study.

Nine of 54 subjects reported injection site nodule/ papule TEAEs as ongoing at the end of the study. Of the remaining events reported as resolved, the median duration for injection site nodules and papules was 119.0 and 189.5 days, respectively. From first injection to end of study, male subjects with Fitzpatrick skin type I-III had a higher incidence rate of injection site nodule (18.9% compared to 7.1%-10.0% for the other sub groups) and injection site papule (13.5% compared to 7.9%-11.4% for the other sub groups).

A pre-specified secondary objective of this study was to evaluate the incidence of hypertrophic scars or keloids in subjects by Fitzpatrick skin types IV-VI, assessed approximately 6 months after completion of treatment. No hypertrophic scars or keloids were reported in subjects with Fitzpatrick skin types IV-VI. Only one subject (Fitzpatrick skin type II) reported a mild hypertrophic scar that was unrelated to *Sculptra* treatment by the investigator. Moreover, six subjects reported a previous history of hypertrophic scars or keloids; No TEAEs of hypertrophic scars or keloids were reported in these subjects.

POST MARKETING SURVEILLANCE

The adverse events received from post-marketing surveillance (voluntary reporting and published literature) for *Sculptra* in the US and other countries include:

- papules/nodules with or without inflammation or discoloration,
- swelling,
- mass formation/induration,
- device ineffective
- pain/tenderness,
- erythema
- granuloma /foreign body reaction,
- bruising/bleeding including hematoma,
- inflammation,
- injection site reactions including burning sensation, discomfort, exfoliation, irritation and warmth
- eye disorders including, dry eye, eye pain, eyelid ptosis, eye swelling, increased lacrimation and visual disturbance such as transient blurred vision, blindness and reduced visual acuity,
- bacterial infections and abscess formation including cellulitis and pustules,
- nerve injury including paresthesia, hypoesthesia, and facial nerve paralysis,
- skin discoloration,
- hypersensitivity/allergic reaction and angioedema,
- pruritus,
- facial asymmetry/deformity,
- atrophy/scarring,
- rash,
- ischemia/necrosis including pallor, vascular occlusion and ulcer,
- acne,
- urticaria,
- dermatitis,
- device dislocation,
- blisters/vesicles,
- muscle disorders including muscular weakness and muscular twitching,
- symptoms of reactivation of herpes infection,
- discharge,
- capillary disorder including telangiectasia,
- encapsulation,

- other dermatological events including alopecia, skin dryness, skin tightness, skin wrinkling, , skin hypertrophy and photosensitive reaction,
- non dermatological events including anxiety, arthralgia, depression, diplopia, dizziness, dyspnea, emotional distress, fatigue, headache, insomnia, lymphadenopathy, malaise, nausea, ocular hyperemia, jaw pain, pyrexia, skin sarcoidosis and weight decreased.

When required, depending on event, treatments may include massage/manipulation, warm compress, nitroglycerine paste, corticosteroids, antibiotics, antihistamines, NSAIDs, aspiration/drainage of the product, saline injections and surgery. Events which did not resolve or where resolution information is not available at last contact were reported.

Scarring, mostly a non-serious event, was reported in association with skin discoloration, nodules, lumps, indurations, granulomas, hyperpigmentation, hypertrophic scars, and suspicion of keloid formation. Time to onset when specified ranged from within 1 week to 24 months post-*Sculptra* injection and outcome ranged from 'recovered' to 'ongoing' at last contact.

Skin discoloration was 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 when specified usually ranged from within 1 week to 12 months post-injection. Outcome ranged from 'recovered' to 'ongoing' at last contact.

SAEs have rarely been reported. The most commonly reported SAEs for *Sculptra* with more than 5 reported events include papule/nodule, swelling/edema, granuloma, symptoms of visual disturbance, infection/abscess, mass/induration, hypersensitivity, paresthesia and facial nerve paralysis, ischemia/necrosis, inflammation. Other concurrent events included pain, bruising/hematoma, erythema, discoloration, deformity, scarring/atrophy, pruritus, rash, muscular weakness, urticaria and blisters.

Injection site nodules mostly occurred several months post-injection. Such nodules are occasionally associated with inflammation or discoloration, 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, *e.g.* intralesional corticosteroids, others were 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 nodules was required.

Granulomas usually occur several months after injection; in few cases onset was more than 1-year post-injection. While events were reported as granuloma, only a few cases were confirmed by biopsy. 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.

Vascular compromise may occur due to an inadvertent intravascular injection or as a result of vascular compression associated with implantation of any injectable product. This may manifest as

blanching, discoloration, necrosis or ulceration at the implant site or in the area supplied by the blood vessels affected; or rarely as ischemic events in other organs due to embolization. Isolated rare cases of ischemic events affecting the eye leading to visual loss, and the brain resulting in cerebral infarction, following facial aesthetic treatments have been reported. Visual disturbances including blindness have been reported following injection of *Sculptra* into the temple area, periorbital areas, and/or cheek. Events requiring medical intervention, and events which did not resolve or where resolution information is not available were reported.

Serious edema was 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, antihistamines and/or anti-inflammatories. Recovery occurred within 7-10 days without sequelae.

Serious erythema, serious pain, and serious pruritus reported with bruising and heat sensation, were mostly reported within 24 hours post-injection. Treatment included corticosteroids, antihistamines and/or anti-inflammatories. Events resolved within 7-10 days post-injection without sequelae and with no significant impact on daily life.

Serious hypersensitivity reactions were 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 antihistamines.

Serious infections such as subcutaneous abscesses, cellulitis, folliculitis, and methicillin-resistant *Staphylococcus aureus* at the injection site, were reported. Time to onset of event mostly ranged from 1 day to 1 week. Of these cases a few required hospitalization with administration of intravenous antibiotics. All patients recovered or were recovering at the last contact.

Delayed-onset inflammation near the site of dermal filler injections is one of the known adverse events associated with dermal fillers. Cases of delayed-onset inflammation have been reported to occur at the dermal filler treatment site following viral or bacterial illnesses or infections, vaccinations, or dental procedures. Typically, the reported inflammation was responsive to treatment or resolved on its own.

Adverse reactions should be reported to Galderma Laboratories, L.P. at 1-855-425-8722.

EFFECTIVENESS

Clinical studies

Clinical data including skin thickness measurements and serial photographs were collected in five clinical studies.

Vega Study

A. Study design

This was a 96-week, open-label, uncontrolled, single-center study to determine the treatment effects of *Sculptra* on the signs of lipoatrophy of the face in 50 patients infected with human immunodeficiency virus. Patients had a mean age of 45 years (range 33-58), 84% were Caucasian

and 98% were male. All patients had little or no adipose tissue in cheek area at baseline, indicating severe facial lipoatrophy (mean adipose thickness of 0.5±0.7 mm, ranging from 0.0 to 2.1 mm).

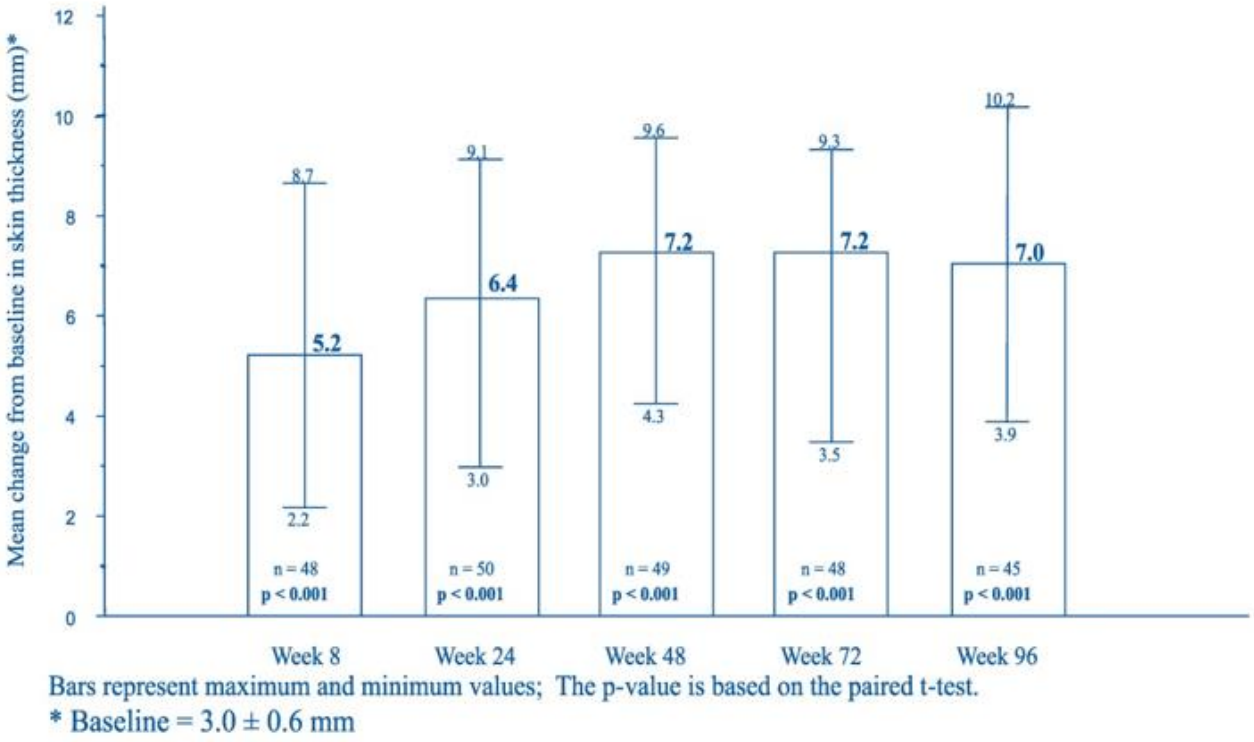
B. Treatment

Injection sessions were conducted at approximately two-week intervals, and the majority (86%) of the patients received four to five injection sessions. Generally, one vial of product was injected intradermally into multiple points of each cheek at each injection session. The quantity of injected product and number of injection sessions depended upon the severity of the facial depression.

C. Results

The mean increases from baseline in skin thickness are presented in Figure 7 below.

FIGURE 7
MEAN INCREASES ABOVE BASELINE IN SKIN THICKNESS (MM) OBSERVED IN THE VEGA STUDY



All patients experienced increases in skin thickness in the treatment area (minimum increase of 2.2 mm noted at Week 8 visit). Statistically significant increases above baseline values of mean skin thickness were noted at all time points (Weeks 8, 24, 48, 72 and 96) during the study. Increases in mean skin thickness changes above baseline persisted for up to 2 years.

Chelsea & Westminster (C&W) Study

A. Study design

This was a 24-week, open-label, single-center, uncontrolled study in 30 human immunodeficiency virus positive patients with facial lipoatrophy. Patients were placed into groups of 12 or 24 weeks of follow-up. Patients had a mean age of 41 (range 32-60), 72% were Caucasian and 93% were male.

B. Treatment

All patients received a fixed treatment regimen of three injection sessions conducted at two-week intervals. Each vial of *Sculptra* was reconstituted with 2 mL of SWFI and 1 mL of 2% lidocaine to give a total volume of 3 mL. Up to 3 mL of the reconstituted product was injected bilaterally into multiple points into the cheek and nasolabial areas.

C. Results

Baseline skin thickness in the treatment areas ranged from 2.1 to 2.7 mm and results after treatment are presented in the Table 40 below.

TABLE 40
RANGE OF MEAN INCREASES IN SKIN THICKNESS FROM BASELINE

	12 WEEKS AFTER 1ST TREATMENT N=27*	**24 WEEKS AFTER 1ST TREATMENT N=14***
Cheek Areas	3.9 – 5.7 mm	4.9 mm
Nasolabial Areas	3.9 – 6.0 mm	4.9 – 5.3 mm

Baselines ranged from 2.1 to 2.7 mm; all changes were significant ($p<0.001$).

* Number of patients varies dependent upon which group they were placed.

Significant changes from Baseline ($p<0.001$) in mean skin thickness were observed in the areas treated (left and right nasolabial and cheeks) with *Sculptra* in all patients. A mean increase in skin thickness of approximately 4-6 mm was observed twelve weeks after the initiation of treatment for all treated patients.

APEX 002 and Blue Pacific Studies

A. Study design

Data were obtained from two, single-center, open-label, 12-month investigator-initiated studies in human immunodeficiency virus positive patients with facial lipoatrophy. Ninety-nine patients between 31 and 65 years of age were enrolled in each study. The majority of patients were Caucasian males.

B. Treatment

Patients were treated with *Sculptra* injections at an interval of approximately 3 to 6 weeks and received up to 6 injection sessions.

C. Results

The results from these studies are shown in Table 37 and were provided for safety information only.

DL6049-0417 (FACES Study)

A. Study design

This was a 5 year, open-label, uncontrolled study to evaluate the safety of *Sculptra* for treatment of the signs of facial lipoatrophy in subjects with HIV. Required protocol visits were minimized and data collection was streamlined to include only those endpoints of interest. Subject retention in this study was notable; a total of 290 subjects were treated, of whom 224 completed the 5 year study, representing a 77.2% retention rate through 5 years of follow-up. A total of 76 subjects (26.2%) reported serious TEAEs. 17 subjects (5.9%) died during the study. No SAEs or deaths were related to injection procedure or related to the study product.

Patient demographics were as follows: mean age (range), 47.4 years (26-74); 51% male, 49% female; 53.4% Caucasian, 23.8% African American, 20.7% Other; Fitzpatrick skin type I (4.1%), II (18.0%), III (27.6%), IV (17.0%), V (15.0%), VI (18.4%). Overall, most patients presented with Grade 2 (35.4%) or Grade 3 (34.4%) lipoatrophy at baseline using the James Scale (Grade 1=Mild/localized facial lipoatrophy, the appearance is almost normal to Grade 4=Widespread atrophy. The facial skin now lies directly on the muscles over a wide area, extending up toward the orbital region). Cheeks (95.6%), nasolabial folds (78.9%), and temples (70.4%) were the most frequently reported areas affected by lipoatrophy. On entry, 118 subjects had CD4 counts of 500 or greater (normal range, 'immunocompetent'), and 158 subjects had CD4 counts < 500 (CDC categories 2 or 3).

B. Treatment

Patients were treated with *Sculptra* injections at an interval of approximately 4 to 6 weeks until optimal correction was achieved. Patients received supplemental injections at yearly follow-up visits if needed to maintain an optimal treatment effect.

C. Results

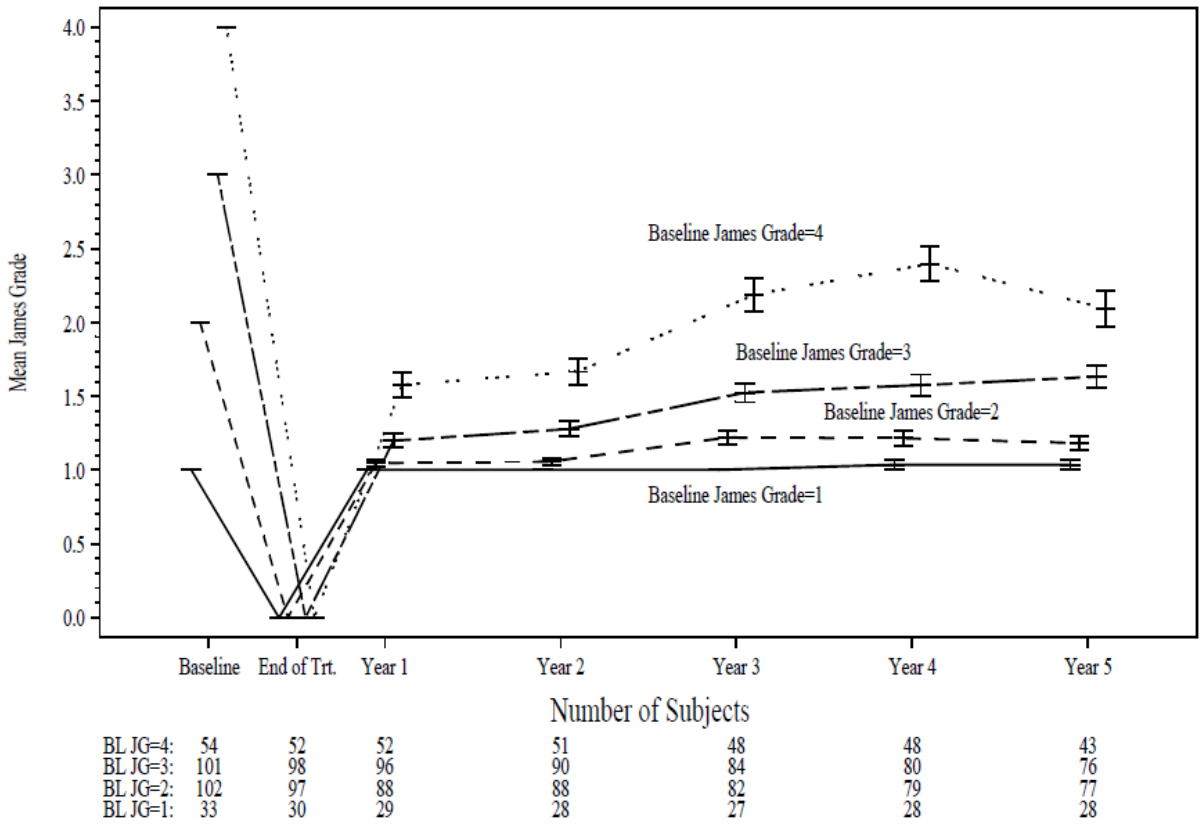
A total of 290 subjects received *Sculptra* during the study. During the treatment phase of the study, subjects had a mean of 6.0 treatment sessions (range:1-18 sessions). Most subjects (89.0%) received additional touch-up sessions (mean: 3.9, range: 1-6 sessions) after the initial treatment phase of the study. Overall, subjects had a mean of 9.5 treatment sessions (treatment phase + touch-up treatments) over the course of the entire study period (range: 1-20). Approximately 10 mL of *Sculptra* was administered at each treatment session.

Overall, the efficacy of *Sculptra* for the treatment of HIV-associated lipoatrophy is supported by the following:

- The proportions of subjects with a "very good" or "excellent" satisfaction score were 85.0% and 81.2% for the physician's and subject's satisfaction with treatment questionnaires respectively for the Year 5 visit.
- Improvement from baseline to the Year 5 visit in subject-reported QoL, as assessed by a validated disease-specific health outcomes measure (MOS-HIV Health Survey questionnaire), was statistically significant ($p<0.05$) for the following measures: Health Distress, Quality of Life, Social Activity, and Mental Health Summary.

Figure 8 demonstrates the observed change in the James Score by timepoint and baseline grade.

FIGURE 8
MEAN JAMES GRADE (±SE) BY TIME POINT
STRATIFIED BY BASELINE GRADE



INDIVIDUALIZATION OF TREATMENT (see also Patient Treatment)

The quantity of *Sculptra* and the number of injection sessions will vary by patient. Treatment for severe facial fat loss typically requires the injection of one vial of *Sculptra* per cheek area per injection session. A typical treatment course for severe facial fat loss involves 3-6 injection sessions, with the sessions separated by four weeks. Full effects of the treatment course are evident within weeks to months. The patient should be reevaluated no sooner than four weeks after each injection session to determine if additional correction is needed. Patients should be advised that supplemental injection sessions may be required to maintain an optimal treatment effect.

HOW SUPPLIED

Sculptra is supplied as a sterile freeze-dried preparation for injection in a clear glass vial, which is sealed by a penetrable stopper, covered by an aluminum seal with a flip-off cap. Each carton of *Sculptra* contains two vials of poly-L-lactic acid, sodium carboxymethylcellulose (USP), non-pyrogenic mannitol (USP).

STORAGE

Sculptra can be stored at room temperature, up to 30ºC (86ºF). DO NOT FREEZE. Refrigeration is not required.

STERILITY

Each vial of *Sculptra* is packaged for single-use only. Do not re-sterilize.

IF THE VIAL, SEAL, OR THE FLIP-OFF CAP ARE DAMAGED, DO NOT USE AND CONTACT GALDERMA LABORATORIES, L.P. DALLAS, TX 75201 USA 1-855-425-8722.
INSTRUCTIONS FOR USE
The following supplies are used with *Sculptra* but are to be provided by the end-user:
• Sterile Water for Injection (SWFI), USP
• Single-use 5 mL sterile syringe
• Single-use 1 or 3 mL (depending on healthcare professional preference) sterile syringes (at least 2)
• 18 G sterile needles (at least 2)
• 26 G sterile needles (several should be available)
• Antiseptic (such as alcohol)

Reconstitution

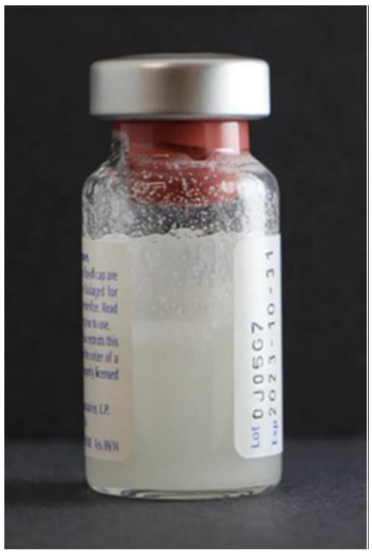
(for restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus.)

Sculptra is reconstituted in the following way:

1. Remove the flip-off cap from the vial and clean the penetrable stopper of the vial with an antiseptic. If the vial, seal, or flip-off cap is damaged, do not use, and call Galderma Laboratories, L.P. at 1-855-425-8722.
2. Attach an 18 G sterile needle to a sterile single-use 5 mL syringe.
3. Draw 5 mL of SWFI into the 5 mL syringe.
4. Introduce the 18 G sterile needle into the stopper of the vial and slowly add all SWFI into the vial.
5. Let the vial stand for at least 2 hours to ensure complete hydration; do not shake during this period. Upon reconstitution, *Sculptra* can be stored for up to 72 hours at temperatures between 5-30ºC. Refrigeration is not required.
6. Product should be gently agitated immediately prior to use. Agitate the vial until a uniform translucent suspension is obtained that will have some foam on the top, see Figure 9. A single vial swirling agitator may be used. The reconstituted product is usable within 72 hours of

reconstitution. As it is a single use vial, discard any material remaining after use or after 72 hours following reconstitution.

FIGURE 9
RECONSTITUTED PRODUCT 5 mL



7. Reconstituted *Sculptra* is a suspension with particles that will sediment at standing. To maintain a uniform suspension throughout the procedure, intermittently agitate the *Sculptra* vial between the withdrawals to syringes. Clean the penetrable stopper of the vial with an antiseptic and use a new 18 G sterile needle to withdraw an appropriate amount of the suspension (typically 1 mL) into a single–use 1 or 3 mL sterile syringe. Tilt the vial horizontally and withdraw suspension from the lower lateral of the vial to avoid withdrawing foam. Do not store the reconstituted product in the syringe.
8. Replace the 18 G needle with a **26 G** sterile needle before injecting the product into the deep dermis. Do not inject *Sculptra* using needles of an internal diameter smaller than 26 G. If clogging of the needle occurs, remove the needle, attach a new sterile needle, then expel a few drops of *Sculptra* to eliminate the air and re-check for needle blockage.
9. To withdraw remaining contents of the vial, repeat steps 7 through 8.
10. Discard any remaining product immediately after single session/patient use.

Patient treatment

1. Patient Counseling

The patient should be fully apprised of the indications, contraindications, warnings, precautions, treatment responses, adverse reactions, and method of administration with *Sculptra*.

- Each patient should be informed that the amount of *Sculptra* and the number of injection sessions, with four-week intervals between injection sessions, will depend on the patient's need.
- Each patient should be informed that up to six injection sessions for restoration or correction of HIV-associated lipoatrophy.
- For patients who have experienced medically important adverse events, a decision for touchup or re-treatment should take the cause and severity of previous reactions into consideration.
- Patients should be informed that typically, at the end of the injection session, they will experience some degree of swelling due to the water (SWFI) used to reconstitute *Sculptra* and the injection procedure. This will give the appearance of a full correction by the end of the injection session, but the injection-related swelling typically resolves in several hours to a few days, resulting in the reappearance of the original contour deficiency.
- Patients should be informed that the optimal correction after initial injection depends on patient's severity of the facial depression.
- Patients should be informed that typically the wrinkle deficiency will gradually improve over time (several weeks) after injection as the treatment effect of *Sculptra* occurs.
- Patients should be informed that, if needed, their healthcare professional may utilize a topical or a local anesthetic prior to injecting *Sculptra.*

2. Patient Assessment

- A complete medical history should be taken to determine if *Sculptra* injection is appropriate.
- Before and after treatment, health care practitioners are encouraged to conduct vision assessments, including visual acuity, extraocular motility, and visual field testing.

- During the initial treatment session with *Sculptra*, only a limited correction should be made. In contrast to other wrinkle fillers, *Sculptra* provides a gradual improvement of the depressed area over several weeks as the treatment effects occur.
- Re-evaluate the patient no sooner than four weeks after the injection session to determine if additional correction is needed.

3. Patient Preparation

Each injection session is to be conducted with aseptic technique and universal precautions due to the potential for contact with patient body fluids: blood from the injection site.

- To prepare for an injection session, all make-up should be removed.
- The treatment area should be cleaned with a suitable antiseptic solution.
- Before injecting *Sculptra* a treatment plan should be determined and the face mapped. The mapping is done using a water-soluble pencil.

- An ice pack can be applied on the site for a short period or additional topical, local injection or nerve block anesthesia may be used to further reduce pain on injection. If additional (topical or local) anesthetic or ice is used, the area should be cleaned after the anesthetic is removed.

4. Injection Needle

- *Sculptra* should be injected using a 26 G sterile needle. *Sculptra* should not be injected with needles that have been bent.
- If the needle becomes occluded or dull during an injection session, needle replacement is necessary.
- If clogging occurs, remove the needle, attach a new sterile needle, then expel a few drops of *Sculptra* to eliminate the air and re-check for needle blockage.
- To maintain a uniform suspension throughout the procedure, intermittently agitate *Sculptra* in the syringe.
- Before initial injection, expel a few drops of *Sculptra* through the attached needle to eliminate air and to check for needle blockage.

5. Depth of Injection

- *Sculptra* should be injected into the deep dermis or subcutaneous layer
- Introduce a straight, sterile, bevel-up needle into the skin. It is recommended to introduce the needle at an approximately 30-40 degree angle to the skin and then advance the needle until the desired depth is reached.

6. Injection procedure

Before injecting *Sculptra*, always perform a reflux maneuver to avoid intravascular injection. If blood returns to the syringe, the needle is in a blood vessel and should be withdrawn, pressure should be applied to the injected area until bleeding stops and a new syringe should be prepared. If no blood is pulled back into the syringe, the injection may be started.

To guide the needle to the desired plane, create a firm needle insertion plane by stretching the skin. A change in tissue resistance is felt when the needle crosses from the dermis into subcutaneous layer. If the needle is inserted at too shallow (small) an angle or if the needle tip is not sufficiently advanced, then the needle tip may be in the mid or superficial (papillary) dermis, the needle bevel may be visible through the skin. If Sculptra is injected too superficially, the injected area will blanch immediately or shortly after injection. If immediate blanching occurs, the injection should be stopped and the area massaged until it returns to a normal color. Blanching may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with American Society for Dermatologic Surgery guidelines.[3]

Health care practitioners are encouraged to be prepared with the following in the event of an intravascular injection:

[3] Jones, Derek; Fitzgerald, Rebecca; Cox, Sue Ellen; et al. Preventing and Treating Adverse Events of Injectable Fillers: Evidence-Based Recommendations from the American Society for Dermatologic Surgery Multidisciplinary Task Force, Dermatologic Surgery: February 2021 - Volume 47 - Issue 2 - p 214-226

- ensuring supplies are immediately available, as recommended by the American Society for Dermatologic Surgery guidelines
- identifying a local ophthalmologist or ophthalmology subspecialist to be available in the event of an ophthalmic adverse event related to a dermal filler injection
- conducting a basic neurologic examination in the event of an ophthalmic adverse event due to the association of such events with central nervous system deficits

a. Threading or Tunneling Technique in a Grid Pattern (cross-hatch)
When the needle tip is in the correct plane, the needle angle should be lowered to 10-20 degrees and the needle should be advanced parallel to the surface of the skin. Deposit a thin trail of *Sculptra* by doing a retrograde injection when slowly withdrawing the needle. To avoid deposition in the superficial skin, deposition should be stopped before the needle bevel is visible in the skin.

b. Bolus technique
The depot technique is most appropriate for injections into areas of thin skin at the level of the temples. When using this technique, *Sculptra* is injected as a small bolus. It is injected in the temporal fascia.

7. Volume per Injection

The maximum volume of *Sculptra* per individual injection should be limited to 0.1 mL – 0.2 mL, spaced at a distance of 0.5 -1 cm. Avoid overcorrection.

8. Volume per Treatment Site

- During the initial treatment sessions, only a limited correction should be made. In contrast to other wrinkle fillers, *Sculptra* provides a gradual correction of a contour deficiency over several weeks. The volume of product injected per treatment area will vary depending on the surface area to be treated. Treatment of an entire cheek typically requires injection of one vial of *Sculptra* per cheek per injection session. Multiple injections (typically administered in a grid or cross-hatched pattern) may be required to cover the targeted area. The total number of injections and thus total volume of *Sculptra* injected will vary based on the surface area to be corrected, not on the depth or severity of the deficiency to be corrected.

9. Massage During the Injection Session

The treatment area should be massaged in a circular fashion after every 3-4 injections to evenly distribute the product.

10. Degree of Correction - Treat, Wait, Assess

The contour deficiency should be under-corrected, never fully corrected or overcorrected (overfilled) during any injection session. Under-correction of the treatment area allows for gradual improvement of the contour deficiency as the *Sculptra* effect occurs over the minimum of four weeks between assessment and possible next injection session.

11. Post-treatment Care

- Immediately after a *Sculptra* injection session, redness, swelling, and/or bruising may appear in the treatment area. To reduce the risk of edema and/or bruising after injection, an ice pack wrapped in cloth (avoid any direct contact of the ice with the skin) is applied to the treated areas. See ADVERSE EVENTS for details of the incidence and severity of AE observed immediately post-injection during the clinical trial.

- To help *Sculptra* distribute evenly in the contour deficiency, it is important at the end of the treatment session to manually massage in a circular fashion the treatment area for a minimum of 2 minutes. A facial moisturizer should be used to perform the massage. It is recommended that the patient should massage the treated areas for five minutes, five times per day for five days after the injection session to promote a natural-looking correction.

- Early occurrence of subcutaneous nodules at the injection site (within 3 to 6 weeks after the treatment) may be minimized by adhering to proper dilution and injection techniques (e.g., avoiding superficial injections or over-correction). In addition, massaging the treatment area to ensure proper distribution of the product may also minimize the appearance of nodules. Nodules usually resolve spontaneously. However, as reported in published literature, some nodules may require medical treatment such as subcision (break-up of nodules with sterile saline solution), and delayed occurrence of subcutaneous nodules at the injection site (usually will manifest within 3 to 4 months after the treatment) may require treatment such as intralesional injections of corticosteroids, subcision and/or excision.

PATIENT INSTRUCTIONS

It is recommended that the following information is shared with patients by the healthcare provider:

- Within the first 24 hours, an ice pack wrapped in cloth (avoiding any direct contact of the ice with the skin) should be applied to the treatment area to reduce swelling and bruising. *Sculptra* may cause redness, swelling, or bruising when first injected into the skin, typically resolving in hours to one week. Hematoma may also occur, typically resolving in hours to about two weeks. Worsening or prolonged symptoms or signs should be reported to the health care provider. The original skin depression may initially reappear, but the depression should gradually improve within several weeks as the treatment effect of *Sculptra* occurs. The health care provider will assess the need for additional *Sculptra* injection sessions after at least four weeks.
- It is recommended to massage in a circular fashion the treated areas for 5 minutes, 5 times per day for 5 days following any injection session, according to the healthcare professional's advice.
- Treatment with *Sculptra* can result in small papules in the treated area. These subcutaneous papules are typically not visible and asymptomatic and may be noticed only upon pressing on the treatment area. However, visible nodules, sometimes with redness or color change to the skin, have been reported. Patients should report these events and any other side effects to their health care provider.
- Aesthetic make-up may be applied a few hours post-treatment if no complications are present.

- Exposure of the treated area to sun and UV lamp exposure and extreme temperatures are to be avoided until any initial swelling and redness has resolved. Patients should be informed about appropriate sunscreen protection according to the healthcare professional's advice.

ANY SIDE EFFECTS, ADVERSE EVENTS, PRODUCT QUESTIONS OR PRODUCT COMPLAINTS SHOULD BE REPORTED TO:
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