Title:	A Prospective, Open-Label, Multicenter Study to Evaluate the Long-Term Safety of Sculptra® Aesthetic in Immuno-Competent Subjects Stratified by Fitzpatrick Skin Type I-VI
Protocol number:	GLI.04.SPR.US10321
Study phase:	4
Sponsor name and address:	Galderma Laboratories, L.P. (GLLP) 14501 North Freeway Fort Worth, TX 76177
Study products:	Sculptra® Aesthetic (injectable poly-L-lactic acid)
Indication:	Use in immune-competent subjects for the correction of shallow to deep nasolabial fold contour deficiencies and other facial wrinkles in which deep dermal grid pattern (cross-hatch) injection technique is appropriate
Investigator agreement:	I have examined the above-referenced Galderma Laboratories, L.P. clinical trial protocol and have fully discussed the objectives of this clinical trial and the content of this clinical trial protocol with the Sponsor's team, recognize its confidentiality, and agree to conduct the described trial in compliance with Good Clinical Practices (GCP), the ethical principles contained within the Declaration of Helsinki, this protocol, and all applicable regulatory requirements.
Principal Investigator:	

_____

Signature Date

Name:

Address:

Title Page

Title:	A Prospective, Open-Label, Multicenter Study to Evaluate the Long-Term Safety of Sculptra®Aesthetic in Immuno-Competent Subjects Stratified by Fitzpatrick Skin Type I-VI)
Short Title:	Sculptra® Aesthetic Post-Approval Study
Protocol number:	GLI.04.SPR.US10321
Study phase:	4
IND/IDE Number	N/A
Sponsor:	Galderma Laboratories, L.P. (GLLP) 14501 North Freeway Fort Worth, TX 76177

For any medical questions related to the protocol please contact the Study Medical Monitor:

This study will be performed in compliance with applicable federal regulations and Good Clinical Practice (GCP). This Clinical Study Protocol follows guidelines outlined by the International Conference on Harmonization (ICH), the ethical principles contained within the Declaration of Helsinki, and all applicable regulatory requirements.

All the data provided to the investigator and his/her staff and all data obtained through this GLLP protocol will be regarded as confidential and proprietary in nature and should not be disclosed to any third party without GLLP's written consent.

Effective Date: 24 April 2015

Protocol Amendment 1

Purpose: A change is being made to protocol GLI.04.SPR.US10321 dated 7 January 2015 to address Institutional Review Board comments as follows:

- Clarification to the requirement to conduct a urine pregnancy test prior to treatment with study product.
- Clarification to the oral/systemic contraceptive requirement

Rational: Requested by IRB

Current study status: No sites have been initiated at time of this amendment.

Electronic Case Report Form revision required: No

Informed Consent modification required: Yes

Applicable Investigators: All

Itemized Changes: See table below

Protocol Section Protocol Page #	Reason for Change	Original Protocol Language	Updated Protocol Language (changes in bold font)
Protocol Synopsis, Exclusion criteria #16 Page 12 and 31	Typographical error (changed to be consistent with Section 13.3.2.2)	Pregnancy status should be checked by urine testing at Visit 1.	Pregnancy status **must** be checked by urine testing at Visit 1.
Protocol Synopsis, Exclusion criteria #16 Page 12 and 31	Clarification of oral/systemic contraceptive requirement	Effective birth control is defined as follows: (1) have had a hysterectomy or tubal ligation; or (2) use oral/systemic contraceptives; (3) use an intrauterine device; or (4) use double-barrier (eg, condom and spermicidal foam, gel or insert or condom and diaphragm); or (5) use implants or injectables, for at least 28 days prior to the start of the study; or (6) be post- menopausal for at least 1 year prior to entry into the study. Birth control regimen must be maintained throughout the study.	Effective birth control is defined as follows: (1) have had a hysterectomy or tubal ligation; or (2) use oral/systemic contraceptives **for at least 3 months prior to the start of the study**; or (3) use an intrauterine device; or (4) use double-barrier (eg, condom and spermicidal foam, gel or insert or condom and diaphragm); or (5) use implants or injectables, for at least 28 days prior to the start of the study; or (6) be post-menopausal for at least 1 year prior to entry into the study. Birth control regimen must be maintained throughout the study.
Protocol Synopsis, Study Design Page 10	Typographical error (changed to be consistent with p. 12)	This is a prospective, open-label; multicenter (at up to 20 sites) US study….	This is a prospective, open-label; multicenter (at **a minimum of** 20 sites) US study….

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1 SYNOPSIS

Compound: Sculptra® Aesthetic Poly-L-lactic acid	**STUDY CODE:** GLI.04.SPR.US10321
Title	A Prospective, Open-Label, Multicenter Study to Evaluate the Long-Term Safety of Sculptra® Aesthetic in Immuno-Competent Subjects Stratified by Fitzpatrick Skin Type I-VI
Trial Location	United States
Sponsor Medical Director	PPD Galderma Laboratories, LP
Study Objectives	The primary objective of the study is to assess the long-term safety of Sculptra® Aesthetic (injectable poly-L-lactic acid [PLLA]) in immune-competent subjects as a single regimen for correction of wrinkle assessment score (WAS) 2 to 4 nasolabial fold (NLF) contour deficiencies and other facial wrinkles in which deep dermal grid pattern (cross-hatch) injection technique is appropriate, for the following variables: • The device-related long-term incidence of chronic inflammation (nodules, papules, granulomas, skin necrosis, hypersensitivity, and other injection site reactions) in subjects with Fitzpatrick skin type I-VI. • The incidence of hypertrophic scarring, keloid formation, and changes in skin pigmentation in subjects with Fitzpatrick skin type IV-VI. Secondary objectives include the following: • To evaluate the time to onset, duration, severity, relationship to Sculptra® Aesthetic (injectable PLLA) and/or injection procedure, and outcome of all adverse events, including adverse events mentioned under the primary objectives, during the course of the study, by Fitzpatrick skin type. • To evaluate the change in the WAS from baseline to post treatment follow-up time points at Months 6, 13, and Years 2, 3, 4, and 5 in NLFs and other facial wrinkles. • To evaluate Investigator/subject global assessments at Months 6, 13, and Years 2, 3, 4, and 5.

Study Design	This is a prospective, open-label; multicenter (at a minimum of 20 sites) US study to evaluate the long-term safety of Sculptra® Aesthetic (injectable PLLA) in immuno-competent subjects, stratified by Fitzpatrick skin type[18] I-III, IV, and V-VI (see Appendix I).
Study Population	Immuno-competent male or female subjects 18 to 75 years of age with NLF contour deficiencies and other facial wrinkles as defined by WAS criteria.
Main selection criteria	**Inclusion criteria** In order to be eligible to enter into the study, subjects must fulfill all of the following inclusion criteria: 1. Subjects seeking correction of shallow to deep NLF contour deficiencies. Subjects must have a score of ≥2 and ≤4 on the photo-numeric wrinkle assessment scale of both the right and left NLFs at entry (see Appendix II). Subjects may also have other facial wrinkles (ie, cheek lines, marionette lines, and chin crease/chin fold) using the Assessment Scale for Other Facial Wrinkles (see Appendix III) for which deep dermal grid pattern (cross-hatch) injection technique is appropriate. 2. Subjects must sign a statement of informed consent including full copyright release of photographs to the Sponsor; initial and date "A Patient's Guide to Treatment with Sculptra® Aesthetic"; and Health Insurance Portability and Accountability Act (HIPAA) authorization. **Exclusion criteria** Subject will not be enrolled in the study if any of the following exclusion criteria are present/met: 1. Subjects seeking, at entry into the study, correction of other facial wrinkles with Sculptra® Aesthetic in the following anatomical sites/lines: horizontal forehead lines, glabellar frown lines, periorbital lines, periauricular lines, upper lip lines, lower lip lines, corner of the mouth lines and/or horizontal neck folds. 2. Subjects that are less than 18 or greater than 75 years of age. 3. Subjects with a score of 0, 1, or 5 on the photo-numeric wrinkle assessment scale of either the right or left NLFs (see Appendix II). 4. Personal history of allergic/anaphylactic reactions including hypersensitivity to local anesthetics (eg, lidocaine, etc), latex, or any of the Sculptra® Aesthetic constituents. 5. History of facial skin cancer or recurrence of facial skin cancer other than basal cell carcinoma within 5 years. 6. Known history of keloids or bleeding/coagulation disorder.

	7. History of human immunodeficiency virus, diabetes, connective tissue disorders (eg, lupus, scleroderma), or other serious systemic disease (eg, sarcoidosis). 8. Presence of surgical or non-surgical scars in the area to be treated. 9. Active inflammatory process or infection in the area to be treated (skin eruptions such as cysts, pimples, rashes, herpes simplex, herpes zoster, cancerous/precancerous lesions), or any other active or serious skin disease (eg, eczema, psoriasis of the face, severe rosacea, severe acne, etc.). 10. Subjects with an American Society of Anesthesiologists' Physical Status Classification System Score of ≥P3 (P3 = a subject with severe systemic disease) (see Appendix IV). 11. Subjects with medical conditions that might require the use of immunosuppressive (except for oral steroids that can be used for less than 1 month over the duration of the study) or anti-inflammatory medications during the trial (eg, severe asthma, rheumatoid arthritis, etc). 12. Viral, chemical, or any active hepatitis within the past year. 13. Planned surgical procedures with incisions and suturing in the area to be treated during the course of the study. 14. Planned major facial aesthetic procedure/plastic surgery (eg, rhinoplasty [with or without implant], facelift, congenital defect repair, etc) during the course of the study. 15. Subjects who have or plan to use exclusionary treatments/medications/ devices, as described below (or who are unable to comply with concomitant therapy restrictions as described in Section 8.8): a. Cosmetic permanent filler-type injectable products (eg, poly methylmethacrylate [PMMA], etc.) in the facial treatment area at any time prior to or during the study. b. Immunosuppressive medications including systemic steroids (eg, oral prednisone) within 6 months of treatment or for more than 1 month of treatment over the duration of the study. Intranasal/inhaled or topical steroids are acceptable. c. Previous injectable PLLA treatment in the face. d. Temporary dermal fillers within 18 months of treatment in the same area to be treated with Sculptra® Aesthetic. e. Botulinum toxin (any Type) within 6 months of treatment in the same area to be treated with Sculptra® Aesthetic. f. Subjects receiving antiplatelet (eg, full strength aspirin [> 81 mg/per day], high dose aspirin-containing products, clopidogrel, etc.); anticoagulant (eg, coumarin derivatives, unfractionated heparin, low molecular weight heparin, selective factor Xa inhibitor, thrombin inhibitor, etc.) or non- steroidal anti-inflammatory agents; in whom, in the Investigator's opinion, administration of Sculptra® Aesthetic may cause procedure-related complications at the injection site.

	g. Prescription facial wrinkle therapies that include retinoic acid derivatives, prescription strength alpha-hydroxyacids and beta-hydroxyacids and idebenone 1% in the area to be treated less than 3 months prior to enrollment. h. Hand-held light therapy devices for personal use such as LED or laser resurfacing, intense light pulse therapy or radiofrequency in the area to be treated less than 6 months prior to enrollment. 16. Women who are pregnant, nursing or intend to become pregnant over the duration of the study or women who are of childbearing potential not protected by effective contraceptive method of birth control and/or who are unwilling or unable to be tested for pregnancy. Pregnancy status must be checked by urine testing at Visit 1. Effective birth control is defined as follows: (1) have had a hysterectomy or tubal ligation; or (2) use oral/systemic contraceptives for at least 3 months prior to the start of the study; or (3) use an intrauterine device; or (4) use double-barrier (eg, condom and spermicidal foam, gel or insert or condom and diaphragm); or (5) use implants or injectables, for at least 28 days prior to the start of the study; or (6) be post- menopausal for at least 1 year prior to entry into the study. Birth control regimen must be maintained throughout the study. 17. Subjects who are unwilling or unable to give written consent to participate in the investigation or unable to comply with the requirements of the clinical trial protocol. 18. Subjects who have received any experimental drug or device within the previous 3 months prior to first treatment. 19. Subjects who are known alcohol or drug abusers. 20. Subjects who are suffering from any psychological condition, or are under treatment for any condition which, in the opinion of the Investigator and/or consulting physicians(s) may constitute an unwarranted risk or which may affect the subjects' compliance or adherence to study procedures **<u>Note</u>: No waiver, prospective or retrospective, to deviate in any way from the inclusion/exclusion criteria for clinical trial subjects, defined in the clinical trial protocol, can be granted to clinical Investigators.**
Total expected number of subjects	Approximately 863 subjects to be enrolled and treated (with a planned minimum of 15 subjects per site) in order to have 604 evaluable subjects at the end of the study.
Expected number of sites	Minimum of 20

Investigational Products	Sculptra® Aesthetic (injectable poly-L-lactic acid)
Formulation(s)	Sterile freeze dried injectable implant. Reconstituted with 5 mL sterile water for injection (SWFI) at least 2 hours prior to use at each investigational site.
Route(s) of administration	Deep dermal injection into the nasolabial and other appropriate facial wrinkles where grid pattern technique is appropriate.
Dose regimen	Each subject will receive a single regimen of Sculptra® Aesthetic. A single regimen consists of up to 4 injection sessions with 3-week intervals, of multiple 0.1 to 0.2 mL deep dermal injections in a grid pattern, spaced at a distance of approximately 1 cm. A maximum of 5 mL per side of the face that includes up to 2.5 mL per NLF will be administered per injection session.
Primary Endpoints Safety	The co-primary safety endpoints are: • The percentage (incidence rate) of subjects with any injection site nodule and/or papule over 5 years. • The percentage (incidence rate) of subjects with any of the following injection site events over 5 years: - Hypertrophic scarring - Keloid formation - Changes in the skin pigmentation at the site of injection compared to adjacent skin - Granuloma (confirmed by a biopsy) - Skin necrosis - Hypersensitivity reactions - Unexpected change in wrinkle contour The injection site adverse events listed above are defined as adverse events of interest in this study.
Secondary Endpoints Safety Efficacy	The secondary safety endpoints are: • The percentages (incidence rate) of subjects with any injection site nodule and/or papule; the percentage of subjects who experienced any adverse events of interest other than nodule or papule over 2 years; location and intervention for any adverse events of interest; adverse event severity, duration, time to onset, relationship to Sculptra® Aesthetic and relationship to injection procedure during the course of the study. The efficacy endpoints are:

	• Change from baseline to post-treatment follow-up time points in the WAS at Month 6, Month 13, and Years 2, 3, 4, and 5. • Investigator/Subject Global Assessments Scores at Month 6, Month 13, and Years 2, 3, 4, and 5.
Assessment Schedule	*Screening visit/initial treatment – Visit 1 (Day 1)* During this visit appropriate subjects will be screened and enrolled into the study based on the inclusion/exclusion criteria. The first treatment will be administered at this visit. Eligible subjects will receive bilateral injections of Sculptra® Aesthetic in the left and right NLF wrinkles (WAS 2 to 4) and, if present, other facial wrinkles for which deep dermal grid pattern (cross-hatch) injection technique is appropriate. *Additional treatment phase (if needed) – Visits 2 to 4 (Week 3 to Week 9)* The additional treatment phase will consist of one to three additional visits (as determined by each Investigator) at three-week intervals during which subjects may receive bilateral injections of Sculptra® Aesthetic. Only NLFs and other facial wrinkles treated at Visit 1 may be treated at these visits. *Follow-up phase – Visits 5 to 12 (Month 3 to Year 5)* Following the initial treatment visit, subjects' safety will be evaluated at each visit. Investigator and subject assessment of effectiveness will be evaluated only at Months 6 and 13, and then at Years 2, 3, 4, and 5.
Statistical Considerations	**Study population** The intent-to-treat (ITT) population, per protocol (PP) population, and Completer2 and Completer5 populations are defined as follows: The analysis populations for efficacy will be the ITT population that consists of all subjects who receive at least one Sculptra® Aesthetic injection; the PP population will consist of all subjects who receive at least one Sculptra® Aesthetic injection and are without any major protocol deviation. The analysis populations for safety will also include the ITT population and the PP population. The ITT population is the primary population for hypothesis testing. The Completer2 population consists of all subjects who receive at least one Sculptra® Aesthetic injection and finish the second year visit. The Completer5 population consists of all subjects who receive at least one Sculptra® Aesthetic injection and finish the fifth year visit.

	CCI [redacted]

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[redacted]

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[redacted]

Interim analysis
Interim analyses are planned following completion of all subjects' Month 13, Year 2, 3, and 4 follow-up visits. All safety and efficacy data up to the interim cut- off date will be cleaned, interim locked, analyzed and reported. Formal hypothesis testing will be performed at Year 2 and 5. The adjustment for type I error for the primary hypothesis is not necessary, since no change to the study such as early termination is planned after the interim analysis.

Missing data
The following rules will be applied to handle missing data in the safety analyses:

- If a subject discontinues the study before 5 years, all his/her safety information before discontinuation will be used in the safety analysis and no imputation of missing data between the date of discontinuation and the 5-year time point will be made. Sensitivity analyses for primary and secondary hypotheses will be conducted.
- If the timing of an adverse event cannot be identified because of missing data and the subject is treated, the adverse event will be considered as a treatment- emergent adverse event (TEAE).
- If the assessment of the intensity is missing, the most severe case will be assumed in the frequency tables of adverse event intensity.

	• If the assessment of the relationship to the Sculptra® Aesthetic or injection procedure is missing, a possible relationship to the Sculptra® Aesthetic will be assumed in the frequency tables of possibly related adverse events. Detailed plans for handling missing data will be contained in the statistical analysis plan.
Duration of Study Period	The study participation for each subject will be approximately 5 years in duration. Subjects will receive open-label treatment at their screening/ initial treatment visit (Visit 1, Day 1 – first injection session). Subjects will continue to receive open- label treatment for up to 9 weeks (Visit 2, Week 3 [second injection session]; Visit 3, Week 6 [third injection session]; and Visit 4, Week 9 [fourth injection session]) if needed and determined by the clinical trial Investigator. Subjects will continue with follow-up visits at Months 3, 6, 9, and 13, and Years 2, 3, 4, and 5.

2 FLOW CHART OF STUDY PROCEDURES

Table 1 - Flow Chart 1 – Overview of Study Procedures

Study Phase:	**Screening/ Initial Tx**	**Additional Treatment (if needed) (3 Week Intervals)**			**Follow-Up (All times Relative to the INITIAL Treatment Visit, Day 1)**							
Time Point: / **Procedures**	**Visit 1 Screening/ Initial Tx Visit**	**Visit 2**	**Visit 3 if needed**	**Visit 4 if needed**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12 End of Study or Early Termination**
	Day 1	**Week 3** ±3days	**Week 6** ±3days	**Week 9** ±3days	**Month 3** ±2 weeks	**Month 6** ±2 weeks	**Month 9** ±2 weeks	**Month 13** ±2 weeks	**Year 2** ±4 weeks	**Year 3** ±4 weeks	**Year 4** ±4 weeks	**Year 5** ±4 weeks
Obtain Written Informed Consent (Provide "A patient's Guide to Treatment with Sculptra® Aesthetic"), HIPAA Authorization, and Photographic Consent	●											
Review inclusion/exclusion criteria	●											
Perform physical examination	●[1]											
Review medical history and prior and concomitant medications/treatments	●											
Perform urine pregnancy test	●[2]											
Assess NLF (WAS) and other facial wrinkles (WAS) requiring treatment (refer to flow chart 2 for Visits 1 to 4)	●	●	●	●		●		●	●	●	●	●
Measure the length of nasolabial folds and other facial wrinkles requiring treatment	●	●	●	●		●		●	●	●	●	●
Assess Fitzpatrick Skin Type	●											
Standardized photography (refer to flow chart 2 for Visits 1 to 4)	●	●	●	●		●		●	●	●	●	●
Measure area of treatment grid	●	●[3]	●[3]	●[3]								
Administer local anesthetic (if applicable)	●[3]	●[3]	●[3]	●[3]								
Administer Sculptra® Aesthetic	●	●[3]	●[3]	●[3]								
Distribute Diary Card	●	●	●	●	●	●	●	●	●	●	●	
Adverse event assessment	●	●	●	●	●	●	●	●	●	●	●	●
Collect Diary Card		●	●	●	●	●	●	●	●	●	●	●

[1] Sitting heart rate and blood pressure, height, weight.

[2] Females of childbearing potential only.

[3] If needed and as determined by the Investigator.

[4] This should be conducted at each visit and at each monthly safety contact. Any changes should be updated.

Tx = treatment; WAS = wrinkle assessment score

Table 1 - Flow Chart 1 – Overview of Study Procedures (cont'd)

Study Phase:	**Screening/ Initial Tx**	**Additional Treatment (if needed) (3 Week Intervals)**			**Follow-Up (All times Relative to the INITIAL Treatment Visit, Day 1)**							
Time Point: / **Procedures**	**Visit 1 Screening/ Initial Tx Visit**	**Visit 2**	**Visit 3 if needed**	**Visit 4 if needed**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12 End of Study or Early Termination**
	Day 1	**Week 3** ±3days	**Week 6** ±3days	**Week 9** ±3days	**Month 3** ±2 weeks	**Month 6** ±2 weeks	**Month 9** ±2 weeks	**Month 13** ±2 weeks	**Year 2** ±4 weeks	**Year 3** ±4 weeks	**Year 4** ±4 weeks	**Year 5** ±4 weeks
Review of concomitant medications/treatment		●	●	●	●	●	●	●	●	●	●	●
Investigator Global Evaluation						●		●	●	●	●	●
Subject Global Evaluation						●		●	●	●	●	●
Schedule next clinic visit	●	●	●	●	●	●	●	●	●	●	●	
Schedule monthly safety contacts					Schedule monthly safety contacts between each follow-up visit							
Review subject contact information [4]	●	●	●	●	●	●	●	●	●	●	●	

1 Sitting heart rate and blood pressure, height, weight.

2 Females of childbearing potential only.

3 If needed and as determined by the Investigator.

4 This should be conducted at each visit and at each monthly safety contact. Any changes should be updated.

Tx = treatment; WAS = wrinkle assessment score

Table 2 - Flow chart 2 - procedures for WAS assessment and administration of local anesthetic and Sculptra® Aesthetic

Study Phase:	**Screening/ Initial Tx**	**Additional Treatment (If needed) (3 Week Intervals)**		
Time point: / **Procedures**	**Visit 1 Screening/ Initial**	**Visit 2**	**Visit 3 If needed**	**Visit 4 If needed**
	Day 1	**Week 3** ± 3 days	**Week 6** ± 3 days	**Week 9** ± 3 days
Assess WAS prior to any injection	●	●	●	●
Measure the length of NLF and other facial wrinkles requiring treatment	●	●	●	●
Standardized photography prior to any injection	●	●	●	●
Administer local anesthetic (if applicable)	●	●	●	●
Measure area of treatment grid	●	●	●	●
Assess WAS prior to injection of Sculptra® Aesthetic	●	●	●	●
Administer Sculptra® Aesthetic	●	●	●	●
Assess WAS after injection of Sculptra® Aesthetic	●	●	●	●
Standardized photography before/after injection of Sculptra® Aesthetic (ie "post-treatment photographs")	●	●	●	●

Tx=treatment; WAS = wrinkle assessment score

Procedures should be followed in the order given above. Administration of Sculptra® Aesthetic at Visits 2, 3, and 4 is based on need as determined by the Investigator. If it is determined that treatment with Sculptra® Aesthetic is not needed, then only the first 3 procedures must be performed.

3 LIST OF ABBREVIATIONS

ALT	alanine aminotransferase
AST	aspartate aminotransferase
CaHA	calcium hydroxylapatite
Completer2	subjects who receive at least one Sculptra® Aesthetic injection and finish the second year visit
Completer5	subjects who receive at least one Sculptra® Aesthetic injection and finish the fifth year visit
CRF	case report form
CSO	clinical supply operation
DRF	discrepancy resolution form
EU	European Union
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
ICH	International Committee on Harmonization
IP	investigational product
IRB	Institutional/Ethics Review Board
ITT	intent-to-treat
IVRS	interactive voice response system
IWRS	interactive web response system
LED	light emitting diode
NLF	nasolabial fold
PAS	postapproval study
PLA	polylactic acid
PLLA	poly-L-lactic acid
PMA	premarket approval application
PMMA	polymethyl methacrylate
P_{np2}	the percentage of subjects who experienced any injection site nodule and/or papule adverse event at 2 years
P_{np5}	the percentage of subjects who experienced any injection site nodule and/or papule adverse event at 5 years
P_{oci2}	the percentage of subjects who experienced any adverse event of interest other than nodule or papule at 2 years
P_{oci5}	the percentage of subjects who experienced any adverse event of interest other than nodule or papule at 5 years
PP	per protocol
PTC	product technical complaint
SWFI	sterile water for injection
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
USP	United States Pharmacopeia
WAS	wrinkle assessment score

4 INTRODUCTION AND RATIONALE

Aging facial skin is a challenge for dermatologists and plastic surgeons. The loss of elastic elements resulting from decreased collagen synthesis creates age lines, which can be quite worrisome for those affected.[1,2] Aging also induces volumetric changes in the face that result from alterations of the soft tissues inducing their redistribution. The repositioning of the soft tissues with age is best characterized as a forward drift from the malar region into the nasolabial zone and jowl.[3,4]

Topical treatment is usually ineffective for deep wrinkles.[1,2] In these cases, surgical correction by means of implantation is possible.

Injectable devices have become an increasingly popular alternative to surgical interventions for facial cosmetic enhancement.[5] Simultaneously, the number of these products available to practitioners has increased in recent years, offering various durations of correction and subject outcomes.

Short-term passive fillers, such as collagen and hyaluronic acid, correct lines and wrinkles via the addition of exogenous material to the dermis.[6] In general, the duration of passive fillers primarily depends upon their viscosity and chemical composition, and efficacy ranges from 3–12 months.[7]

Agents such as polyacrylamide gel and polymethyl methacrylate (PMMA), add permanent volume to the face for the correction of specific defects.[8]

Injected calcium hydroxylapatite (CaHA) has been noted to have a duration of approximately 9 to 12 months, and has been used for the correction of human immunodeficiency virus (HIV)-related facial lipoatrophy, as well as the correction of moderate-to-severe wrinkles.[8,9,10]

Injectable poly-L-lactic acid (PLLA), the investigational product (IP) in this study, has the legacy Dermik Laboratories compound code DL6049. Injectable PLLA is marketed as New Fill® in Europe and as Sculptra® Aesthetic in the United States. It is considered to be a device. It has been used successfully in the European Union (EU), Brazil, Australia and in North America to correct the signs of facial lipoatrophy associated with HIV.[11-14] Injectable PLLA is also approved in the EU, Brazil, Australia and Canada for cosmetic use. In the United States, injectable PLLA is indicated for use in immune-competent people as a single regimen for correction of shallow to deep nasolabial fold contour deficiencies and other facial wrinkles in which deep dermal grid pattern (cross-hatch) injection technique is appropriate. (This corresponds to wrinkle assessment scores (WAS) of 2 to 4 [see Appendix II] and the cross-hatch injection technique presented in Figures 3 to 7 in the Instructions for Use section of the Sculptra® Aesthetic package insert). Henceforth, in this document, DL6049 or injectable PLLA will be referred to as Sculptra® Aesthetic, unless there is a specific need to use the compound code or injectable PLLA. The protocol number for this post approval study is GLI.04.SPR.US10321.

The safety and effectiveness of Sculptra® Aesthetic for the treatment of nasolabial fold (NLF) wrinkles was evaluated in a randomized, evaluator blinded, parallel group, multicenter clinical trial in the US (Study DL6049-0301). Immuno-competent subjects with previously untreated NLF wrinkles with WAS of 2 (shallow) to 4 (deep) participated in the study.

The study consisted of 2 phases, namely the controlled phase (0 to 13 months Sculptra® Aesthetic versus Cosmoplast) and the long-term surveillance phase (13 to 25 months; Sculptra® Aesthetic only).

During the controlled phase of the study, subjects received bilateral injections of either Sculptra® Aesthetic or Cosmoplast in both NLF wrinkles for a maximum of 4 injection sessions over 9 weeks. Study treatment was planned to be stopped when both NLF wrinkles reached optimal correction of WAS equal to 1 or 0, or until the maximum of 4 injection sessions were completed.

Subjects treated with Sculptra® Aesthetic and Cosmoplast during the controlled phase showed a consistent, progressive, and significant improvement over baseline for the primary variable WAS beginning 3 weeks after the last treatment. Though the treatment effect of Sculptra® Aesthetic was maintained for up to 13 months, the Cosmoplast treatment effect returned to baseline within 3 months of the final treatment.

Commonly occurring short-term injection-related site reactions were reported in both treatment groups. In this clinical study the percentage of subjects with nodules and/or papules was greater after Sculptra® Aesthetic (17.2% [20 of 116]) than after the control treatment (12.8% [15 of 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, time to onset was 55 days (median) and 159 days (mean). After Sculptra® Aesthetic injection, the duration of nodules was 100 days (median) and 180 (mean) days, and 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 by the investigator. Table 3 shows adverse event data that were collected from patient diaries over the controlled phase (0 to 13 months Sculptra® Aesthetic versus Cosmoplast).

Table 3 - Intensity of adverse events after the initial treatment session, recorded in the 14 day subject diary (Controlled Phase) – All-Treated Population

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

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

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

After the first Sculptra® Aesthetic injection session, time to onset for nodules was 160 days (median) and 209 days (mean), and for papules, time to onset was 55 days (median) and 159 days (mean). After Sculptra® Aesthetic injection, the duration of nodules was 100 days (median) and 180 days (mean), and for papules, was 110 days (median) and 176 days (mean) (Table 4). One subject with a papule required a single 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 by the investigator. Table 4 shows injection-related side effects that were collected from the patient diaries and from the physicians over the entire course of the study.

Table 4 - Number of subjects with injection-related side effects observed in Sculptra Aesthetic US clinical study

SIDE EFFECTS TYPE *Immediate,* as recorded in subject diaries		**116 Subjects** **N (%)**
Localized Swelling		94 (81.0%)
Localized Tenderness		94 (81.0%)
Localized Redness		90 (77.6%)
Post-Injection Site Pain		82 (70.7%)
Localized Bruising		75 (64.7%)
Bleeding from Site(s)		39 (33.6%)
Localized Itching		23 (19.8%)
Other		19 (16.4%)
DELAYED, as reported by physicians		
Nodules and papules		20 (17.2%)
Delayed injection site pain*		1 (0.9%)
Average time to appearance after first injection:		
	Nodules	209 days
	Papules	159 days
Average time of duration:	Nodules	180 days
	Papules	176 days

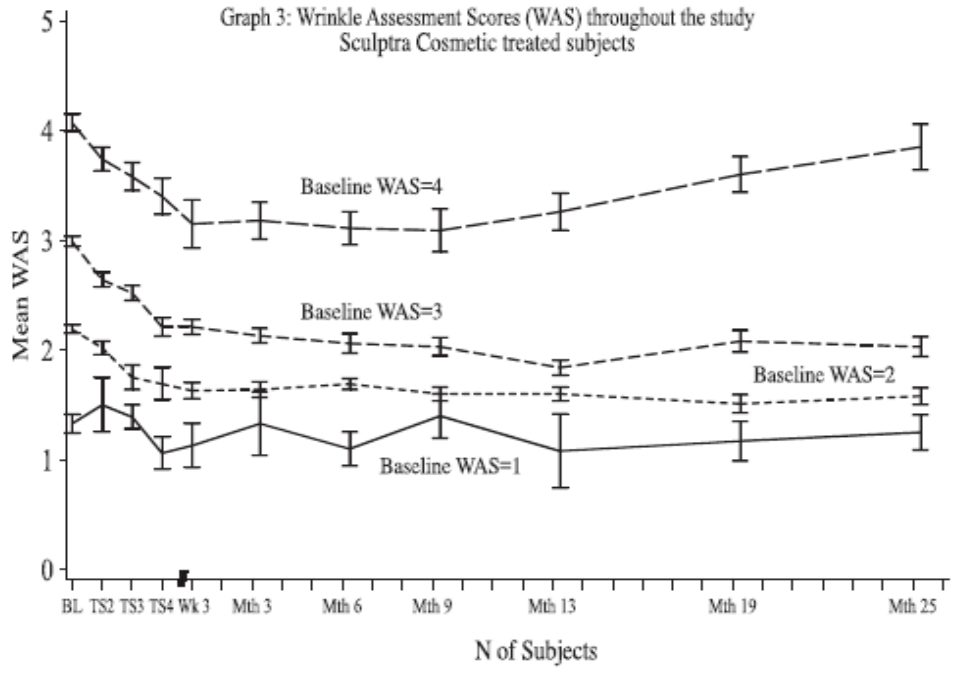
*one subject reported mild injection site pain approximately 20 months after first injection, no information on outcome was available at the end of the 25 month extension phase study

Most side effects were mild and resolved on their own. Five new Sculptra® Aesthetic - related events were reported more than 13 months after first injection with Sculptra® Aesthetic in 3 subjects: 2 papules (1.9%), 1 nodule (0.9%) and 2 injection site pain (0.9%).

Study subjects who had received Sculptra® Aesthetic in the controlled phase of the study were additionally followed for safety and efficacy at Months 19 and 25 after the last injection session.

During the long-term surveillance phase, the Sculptra® Aesthetic group continued to demonstrate statistically significant improvements over baseline in WAS. The effect depended on baseline WAS (see Figure 1).

Figure 1 – Wrinkle assessment scores throughout Study DL6049-0301



BL = Baseline (Pre-injection)
TS2 = Pre-treatment session 2 (3 weeks after initial treatment)
TS3 = Pre-treatment session 3 (6 weeks after initial treatment)
TS4 = Pre-treatment session 4 (9 weeks after initial treatment)
Wk3 = 3 weeks after last treatment session
Mth 3, 6, 9, 13, 19, 25 = 3, 6, 9, 13, 19, 25 months after last treatment session

Source: Sculptra® Aesthetic package insert

The experience with Sculptra® Aesthetic in immune-competent subjects with darker skin types (ie, Fitzpatrick types[18] IV-VI [see Appendix I]), was limited in the above study (ie, 22 out of 116 subjects treated with Sculptra® Aesthetic had skin type IV-VI). Thus, the Sponsor has committed to perform this postapproval study (PAS) to assess the safety of Sculptra® Aesthetic on at least 100 evaluable subjects with Fitzpatrick skin type IV-VI (including at least 15 with Fitzpatrick skin type IV and 85 with Fitzpatrick skin type types V or VI) up to 5 years (ie, completion of the follow-up phase). This PAS, in conjunction with the above pivotal study, would provide significant information to confirm the safety of Sculptra® Aesthetic in darker skin types over a longer period of observation and to assess device-related long-term incidence of chronic inflammation.

For detailed information regarding the efficacy and safety of Sculptra® Aesthetic, please refer to the Sculptra® Aesthetic package insert.

5 STUDY OBJECTIVES

5.1 PRIMARY

The primary objective of the study is to assess the long-term safety of Sculptra® Aesthetic in immune-competent subjects as a single regimen for correction of WAS 2 to 4 NLF contour deficiencies and other facial wrinkles in which deep dermal grid pattern (cross-hatch) injection technique is appropriate, for the following variables:

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

5.2 SECONDARY

Secondary objectives include the following:

- To evaluate the time to onset, duration, severity, relationship to Sculptra® Aesthetic and/or injection procedure, and outcome of all adverse events, including adverse events mentioned under the primary objectives, during the course of the study, by Fitzpatrick skin type.
- To evaluate the change in the WAS from baseline to post-treatment follow-up time points at Months 6, 13, and Years 2, 3, 4, and 5 in NLFs and other facial wrinkles.
- To evaluate Investigator/subject global assessments at Months 6, 13, and Years 2, 3, 4, and 5.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

This is prospective, open-label; multicenter US study to evaluate the long-term safety of Sculptra® Aesthetic in immuno-competent subjects, stratified by Fitzpatrick skin types[18] I-III, IV, and V-VI (see Appendix I).

For a detailed description, the study procedures are summarized in the study flowchart in Section 2.

This clinical study will be conducted in the US with approximately 863 subjects at a minimum of 20 sites, with a planned minimum of 15 subjects per site.

6.2 DURATION OF STUDY

The study participation for each subject will be approximately 5 years in duration. Subjects will receive open-label treatment at the screening/initial treatment visit (Visit 1, Day 1 – 1st injection session). Subjects will continue to receive open-label treatment for up to 9 weeks (Visit 2, Week 3 [2nd injection session]; Visit 3, Week 6 [3rd injection session]; and Visit 4, Week 9 [4th injection session]) if needed and determined by the clinical study Investigator. Subjects will continue with follow-up visits at Months 3, 6, 9, and 13, and Years 2, 3, 4, and 5.

6.3 INTERIM ANALYSIS

Interim analyses are planned following completion of all subjects' Month 13, Year 2, 3, and 4 follow-up visits. All safety and efficacy data up to the interim cut-off date will be cleaned, interim locked, analyzed and reported. CCI [redacted]

7 SELECTION OF SUBJECTS

7.1 NUMBER OF SUBJECTS PLANNED

It is planned to enroll a total of 863 subjects (including at least 22 with Fitzpatrick skin type IV and 122 with Fitzpatrick skin type V-VI) in order to have at least 604 evaluable subjects (at least 15 with Fitzpatrick skin type IV and 85 with Fitzpatrick skin type V-VI) at the end of the study (please refer to Section 13.2 for determination of sample size).

7.2 INCLUSION CRITERIA

In order to be eligible to enter into the study, subjects must fulfill all of the following inclusion criteria:

1. Subjects seeking correction of shallow to deep NLF contour deficiencies. Subjects must have a score of ≥ 2 and ≤ 4 on the photo-numeric wrinkle assessment scale of both the right and left NLFs at entry as assessed by the clinical investigator (see Appendix II).

   Subjects may also have other facial wrinkles (ie, cheek lines, marionette lines, and chin crease/chin fold) using the Assessment Scale for Other Facial Wrinkles (see Appendix III) for which deep dermal grid pattern (cross-hatch) injection technique is appropriate.

2. Subjects must sign a statement of informed consent including full copyright release of photographs to the Sponsor; initial and date "A Patient's Guide to Treatment with Sculptra® Aesthetic"; and Health Insurance Portability and Accountability Act (HIPAA) authorization.

Note: No waiver, prospective or retrospective, to deviate in any way from the inclusion/exclusion criteria for clinical study subjects, defined in the study protocol, can be granted to clinical investigators.

7.3 EXCLUSION CRITERIA

Subject will not be enrolled in the study if any of the following exclusion criteria are present/met:

1. Subjects seeking, at entry into the study, correction of other facial wrinkles with Sculptra® Aesthetic in the following anatomical sites/lines: horizontal forehead lines, glabellar frown lines, periorbital lines, periauricular lines, upper lip lines, lower lip lines, corner of the mouth lines and/or horizontal neck folds.

2. Subjects who are less than 18 or greater than 75 years of age.

3. Subjects with a score of 0, 1, or 5 on the photo-numeric wrinkle assessment scale of either the right or left NLFs (see Appendix II).

4. Personal history of allergic/anaphylactic reactions including hypersensitivity to local anesthetics (eg, lidocaine, etc.), latex, or any of the Sculptra® Aesthetic constituents.

5. History of facial skin cancer or recurrence of facial skin cancer other than basal cell carcinoma within 5 years.

6. Known history of keloids or bleeding/coagulation disorder.

7. History of human immunodeficiency virus, diabetes, connective tissue disorders (eg, lupus, scleroderma), or other serious systemic disease (eg, sarcoidosis).

8. Presence of surgical or non-surgical scars in the area to be treated.

9. Active inflammatory process or infection in the area to be treated (skin eruptions such as cysts, pimples, rashes, herpes simplex, herpes zoster, cancerous/pre-cancerous lesions), or any other active or serious skin disease (eg, eczema, psoriasis of the face, severe rosacea, severe acne, etc.).

10. Subjects with an American Society of Anesthesiologists' Physical Status Classification System Score[15] of ≥ P3 (P3 = a subject with severe systemic disease) (see Appendix IV).

11. Subjects with medical conditions that might require the use of immunosuppressive (except for oral steroids that can be used for less than 1 month over the duration of the study) or anti-inflammatory medications during the trial (eg, severe asthma, rheumatoid arthritis, etc.).

12. Viral, chemical, or any active hepatitis within the past year.

13. Planned surgical procedures with incisions and suturing in the area to be treated during the course of the study.

14. Planned major facial aesthetic procedure/plastic surgery (eg, rhinoplasty [with or without implant], facelift, congenital defect repair, etc.) during the course of the study.

15. Subjects who have or plan to use exclusionary treatments/medications/devices, as described below (or who are unable to comply with concomitant therapy restrictions as described in Section 8.8):

    a. Cosmetic permanent filler-type injectable products (eg, PMMA, etc) in the facial treatment area at any time prior to or during the study.

    b. Immunosuppressive medications including systemic steroids (eg, oral prednisone) within 6 months of treatment or for more than 1 month of treatment over the duration of the study. Intranasal/inhaled or topical steroids are acceptable.

    c. Previous injectable PLLA treatment in the face.

    d. Temporary dermal fillers within 18 months of treatment in the same area to be treated with Sculptra® Aesthetic.

    e. Botulinum toxin (any type) within 6 months of treatment in the same area to be treated with Sculptra® Aesthetic.

    f. Subjects receiving antiplatelet (eg, full strength aspirin [> 81 mg/per day], high dose aspirin-containing products, clopidogrel, etc.); anticoagulant (eg, coumarin derivatives, unfractionated heparin, low molecular weight heparin, selective factor Xa inhibitor, thrombin inhibitor, etc.) or nonsteroidal anti-inflammatory agents; in whom, in the Investigator's opinion, administration of Sculptra® Aesthetic may cause procedure- related complications at the injection site.

    g. Prescription facial wrinkle therapies that include retinoic acid derivatives, prescription strength alpha-hydroxyacids and beta-hydroxyacids and idebenone 1% in the area to be treated less than 3 months prior to enrollment.

    h. Hand-held light therapy devices for personal use such as LED or laser resurfacing, intense light pulse therapy or radiofrequency in the area to be treated less than 6 months prior to enrollment.

16. Women who are pregnant, nursing or intend to become pregnant over the duration of the study or women who are of childbearing potential not protected by effective contraceptive method of birth control and/or who are unwilling or unable to be tested for pregnancy. Pregnancy status must be checked by urine testing at Visit 1.

    Effective birth control is defined as follows: (1) have had a hysterectomy or tubal ligation; or (2) use oral/systemic contraceptives for at least 3 months prior to the start of the study; or (3) use an intrauterine device; or (4) use double- barrier (eg, condom and spermicidal foam, gel or insert or condom and diaphragm); or (5) use implants or

injectables, for at least 28 days prior to the start of the study; or (6) be postmenopausal for at least 1 year prior to entry into the study. The birth control regimen must be maintained throughout the study.

17. Subjects who are unwilling or unable to give written consent to participate in the investigation or unable to comply with the requirements of the clinical trial protocol.

18. Subjects who have received any experimental drug or device within the previous 3 months prior to first treatment.

19. Subjects who are known alcohol or drug abusers.

20. Subjects who are suffering from any psychological condition, or are under treatment for any condition which, in the opinion of the Investigator and/or consulting physicians(s) may constitute an unwarranted risk or which may affect the subjects' compliance or adherence to study procedures.

Note: No waiver, prospective or retrospective, to deviate in any way from the inclusion/exclusion criteria for clinical study subjects, defined in the study protocol, can be granted to clinical investigators.

8 TREATMENTS

8.1 INVESTIGATIONAL PRODUCT

The Sponsor will supply the Sculptra® Aesthetic and the sterile water for injection (SWFI). Only Sculptra® Aesthetic and SWFI provided by the Sponsor can be used for this study. CCI [redacted] The investigational site will supply the syringes and other materials needed for the injections, such as alcohol wipes and other types of topical/local anesthetics (if used). See package insert for a complete list of required supplies. The investigational site will also be responsible for proper disposal of syringes and any other biohazard material(s).

Background therapy (eg, treatments for underlying disease) or other drug therapy not identified in this study protocol will not be supplied by the Sponsor.

Sculptra® Aesthetic is an injectable implant that contains PLLA, a biocompatible, biodegradable, synthetic polymer from the alpha-hydroxy-acid family. CCI [redacted]

Sculptra® Aesthetic is reconstituted with 5 mL sterile water for injection (SWFI) as outlined in the package insert.

Each subject will receive a single regimen of Sculptra® Aesthetic to correct shallow to deep (WAS 2 to 4) NLF contour deficiencies and, if present, other facial wrinkles for which grid pattern (cross-hatch) injection technique is appropriate (ie, marionette lines, cheek folds, and chin crease/chin fold with WAS between 2 and 4 on the applicable scale [see Appendix III]). A single regimen consists of up to 4 injection sessions with 3-week intervals, of multiple 0.1 to 0.2 mL deep dermal injections in a grid pattern, spaced at a distance of approximately 1 cm. A maximum of 10 mL (5 mL per side of the face), 2 vials of Sculptra® Aesthetic, is allowed at each injection session and is up to the discretion of the Investigator. A maximum of 2.5 mL may be placed in each NLF at each injection session. (For injection technique and procedures, see the Sculptra® Aesthetic Package insert). Only NLFs and other facial wrinkles treated during Visit 1 may be treated at subsequent visits.

Study treatment injections should be stopped when both NLFs and other facial wrinkles have reached a grade of 0 to 1 on the appropriate wrinkle assessment scale (see Appendix II and Appendix III). Correction should be limited to no more than 100% of the defect. (If only 1 wrinkle has reached the target grade of 0 to 1 the other side should continue to be treated until the target grade is achieved [or a maximum of 4 injection sessions and a maximum of 2.5 mL per NLF per session]).

The selection of topical and/or injectable anesthetic agents for local anesthesia will be at the discretion of the Investigator; however, injectable anesthetics should not be mixed into the Sculptra® Aesthetic vials.

8.2 COMPENSATION FOR LACK OF BLINDING

This is a single group (open label) study; however every effort will be implemented to prevent bias.

8.3 METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUP

After a subject has signed the informed consent form, a unique subject number will be assigned. This subject number that will be entered in a case report form (CRF) used to identify that subject over the course of the clinical trial.

Subjects will be stratified according to their Fitzpatrick skin types[18] (see Appendix I) .When a subject is withdrawn from the study, the subject will not be permitted to re-enter or rescreen into this clinical trial.

8.4 PACKAGING AND LABELING

The Sculptra® Aesthetic will be packaged and labeled by the Sponsor or designee, for clinical study use only. The Sculptra® Aesthetic will have a tear-off portion on the label. Each tear-off label will be removed and will be affixed to the source documents. Labeling will include a unique identifier number to permit accountability of Sculptra® Aesthetic, to individual vials.

The SWFI and CCI will be supplied in bulk, with commercial labeling.

8.5 STORAGE CONDITIONS

Sculptra® Aesthetic is to be stored at room temperature, defined as 15°C to 30°C (86°F). DO NOT FREEZE. Refrigeration is not required. The Sculptra® Aesthetic must be in a secured, limited access area. After reconstitution, Sculptra® Aesthetic can be used and stored at room temperature for up to 72 hours.

SWFI and CCI will be stored according to the manufacturer's recommendations.

A daily temperature log must be maintained to ensure proper storage for study-supplied Sculptra® Aesthetic, SWFI and CCI.

8.6 RESPONSIBILITIES

The Investigator, the pharmacist, or other personnel allowed to store and dispense the Sculptra® Aesthetic will be responsible for ensuring that the Sculptra® Aesthetic used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with the applicable regulatory requirements.

All Sculptra® Aesthetic shall be dispensed in accordance with the clinical trial protocol. It is the Investigator's responsibility to ensure that an accurate record of all Sculptra® Aesthetic (dispensed and returned) is maintained.

Any quality issue noticed with the receipt or use of the Sculptra® Aesthetic (deficient product in condition, appearance, pertaining documentation, labeling, expiration date, etc.) should be promptly reported to the Sponsor or designee as a product technical complaint (PTC).

Under no circumstances will the Investigator supply Sculptra® Aesthetic to a third party, allow the Sculptra® Aesthetic, SWFI or CCI to be used other than as directed by this clinical trial protocol, or dispose of Sculptra® Aesthetic in any other manner.

The following information for Sculptra® Aesthetic and local anesthetics (if used) will be recorded in the subject's medication record at each visit:

- Generic and trade name of local anesthetics

- Concentration, frequency and volume of anesthetics injected/applied
- Date and time of anesthetic administration
- Location of Sculptra® Aesthetic administration
- Date and time of Sculptra® Aesthetic administration
- Amount of Sculptra® Aesthetic used per injection area/WAS/session (derived from volume injected, length and width of injection area)
- Number of Sculptra® Aesthetic injection sessions and time interval between injection sessions derived from date and time of Sculptra® Aesthetic administration

8.7 RETRIEVAL AND/OR DESTRUCTION OF INVESTIGATIONAL PRODUCT

8.7.1 Partially used or unused treatment

It is the Sponsor's responsibility to ensure the destruction of all partially used or unused Sculptra® Aesthetic. A detailed treatment log of the unused, returned Sculptra® Aesthetic will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team. The site will be responsible for the destruction of the used Sculptra® Aesthetic vials, CCI and the SWFI. All unused Sculptra® Aesthetic vials, CCI and SWFI will be returned to the Sponsor.

All used/unused Sculptra® Aesthetic, CCI and SWFI will be stored at the study site until it is reconciled by the Sponsor/designee. The Sponsor/designee will verify that a final report of accountability (including product disposition) is prepared to the vial unit level and maintained in the Investigator study file.

8.7.2 Potential recall

A potential defect in the quality of Sculptra® Aesthetic may be subject to initiation by the Sponsor of a recall procedure. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall Sculptra® Aesthetic and eliminate potential hazards.

8.8 CONCOMITANT TREATMENT

No concomitant facial injectable dermal fillers (including Sculptra® Aesthetic) will be allowed during the first 2 years after the initial single treatment regimen.

The following medications/fillers and procedures are prohibited in the facial area for the first 2 years of the study, after which they may be used only above the zygoma at the discretion of the Investigator:

- Procedures/treatments

- Botulinum toxin products (eg, Botox cosmetic® injections, etc.)
- Nonpermanent cosmetic filler-type products (eg, bovine collagen, hyaluronic acids, etc.).
- Cosmetic permanent filler-type injectable products (eg, PMMA, silicone, preformed implant, etc.).
- Superficial dermal resurfacing procedures including chemical peel, dermabrasion, or microderm treatments.
- Deep dermal resurfacing procedures including laser therapy.
- Prescription facial wrinkle therapies, prescription strength alpha-hydroxyacids and beta-hydroxyacids applied in the treatment area.

The following treatments/medications are prohibited for the entire 5-year duration of the study:

- Any investigational product or device
- Procedures/treatments
  - Sculptra® Aesthetic treatment in any anatomical site
  - Cosmetic permanent and nonpermanent filler-type injectable products in the Sculptra® Aesthetic treated facial area
  - Deep dermal resurfacing procedures including laser therapy in the Sculptra® Aesthetic treated facial area
  - Superficial dermal resurfacing procedures including chemical peel, dermabrasion, or microderm treatments in the Sculptra® Aesthetic treated facial area.
- Medications
  - Immunosuppressive medications including systemic steroids (eg, oral prednisone) for more than 1 month over the duration of the study. Intranasal/inhaled and topical steroids are allowed.
- Devices:
  - Hand-held light therapy devices for personal use such as light emitting diode (LED) or other in the treatment area.
- Medications at the discretion of the Investigator:
  - Subjects requiring antiplatelet (eg, full strength aspirin [> 81 mg/per day], high-dose aspirin-containing products, clopidogrel, etc.); anticoagulant (eg, coumarin derivatives, unfractionated heparin, low molecular weight heparin, selective factor Xa inhibitor, thrombin inhibitor, etc.) or nonsteroidal anti- inflammatory agents; in whom, in the Investigator's opinion, administration of Sculptra® Aesthetic may cause procedure-related complications at the injection site.

Note: Other products for treatment of concurrent conditions are allowed providing, as judged by the Investigator, they will not interfere with the evaluation of Sculptra® Aesthetic.

8.9 POST-STUDY TREATMENT

Sculptra® Aesthetic is provided to the subject at no cost during participation in this clinical trial. Sculptra® Aesthetic is commercially accessible to the subject poststudy.

8.10 TREATMENT ACCOUNTABILITY AND COMPLIANCE

The Investigator or his/her designee will ensure accountability by completion of logs at the time of Sculptra® Aesthetic /SWFI usage. The Monitor assigned to the study will check Sculptra® Aesthetic and SWFI supplies received at the site and compare them with the unused Sculptra® Aesthetic and SWFI supplies and with the treatment log forms. The Sculptra® Aesthetic will have tear-off labels to facilitate accounting.

The Sponsor/designee will verify that a final report of accountability (including product disposition) is prepared to the Sculptra® Aesthetic and SWFI vial unit level and maintained in the Investigator study file.

8.11 PRODUCT TECHNICAL COMPLAINTS

Product technical complaints should be reported to the Sponsor/designee. A PTC is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, reliability, safety, durability, effectiveness, or performance of a drug, device or combination product. Examples may include but are not limited to: appearance issues, odor, broken vials, damaged stoppers, low fills, and foreign matter in the product, lack of effectiveness. These complaints may or may not represent a potential risk to the subject. For these types of events, a PTC Form must be completed by the site personnel and forwarded to the study monitor on the next working day.

As Sculptra® Aesthetic is considered a medical device, any adverse events related to the device and all serious adverse events are also considered PTCs. These PTCs will be reported to the Sponsor through the CRF at the same time as they are entered by the site.

9 ASSESSMENT OF THE INVESTIGATIONAL PRODUCT

9.1 SAFETY

9.1.1 Primary safety criteria

All adverse events will be collected throughout the study including, but not limited to, injection- site adverse events such as:

- Hypertrophic scarring,
- Keloid formation,
- Changes in skin pigmentation at the site of injection compared to adjacent skin,

- Papule (<0.5 cm),
- Nodule (≥0.5 cm),
- Granuloma (confirmed by a biopsy),
- Skin necrosis,
- Hypersensitivity reactions, and
- Unexpected changes in wrinkle contour (eg, overcorrected contours, uneven contours; changes in skin texture, elasticity, sensation; and changes to local facial muscle function adjacent to the NLF injection site such as smile, frown, lip pursing and mouth opening).

The injection site adverse events listed above are defined as adverse events of interest in this study.

Information collected in the CRFs will include adverse event, location (for all adverse events), severity, date of onset, date of resolution, relationship to the Sculptra® Aesthetic and relationship to the injection procedure, as well as medical interventions required to resolve/treat the event.

9.1.2 Secondary safety criteria

The adverse event data (see Section 9.1.1) will also be used to evaluate the secondary safety endpoints.

9.2 EFFICACY

9.2.1 Wrinkle assessments

9.2.1.1 Nasolabial fold assessments and measurements

The NLF WAS, which is obtained from the wrinkle assessment scale, will be used by the Investigator:

1. As an initial screening tool at Visit 1 to determine inclusion criteria
2. During the treatment phase to determine if further treatment is needed.
3. During follow-up visits to evaluate any changes in the treatment area.

The Investigator will classify the severity of both the left and right NLF (separately) by comparing the subject to the pictures on a validated[16], 6-point, photo-numeric scale as follows (see Appendix II):

0 – no wrinkles
1 – just perceptible wrinkle
2 – shallow wrinkle

3 – moderately deep wrinkle
4 – deep-wrinkle, well-defined edges
5 – very-deep wrinkle, redundant folds

Each grade in the wrinkle assessment scale is exemplified by a photograph (see Appendix II). The grade represents the "best fit" based on the overall depth and length of the NLF (full point increments must be used). Assessments will be made based on a "snap-shot" at a certain time point and are not based on a comparison to the pretreatment photographs. Nasolabial fold WAS will be collected at the screening/initial treatment visit (Visit 1) and Visit 2, and if applicable, at Visits 3 and 4. Nasolabial fold WAS will also be obtained at Month 6, Month 13, and Years 2, 3, 4, and 5 visits (see Section 2, Flow chart of study procedures and Section 12 for details).

In addition, NLF measurements will be collected, at Visit 1 and Visit 2, and if applicable, at Visits 3 and 4. NLF measurements will also be collected at Month 6 Month 13, and at Years 2, 3, 4, and 5 visits (see Section 2, Flow chart of study procedures and Section 12 for details).

9.2.1.2 Other facial wrinkle assessments and measurements

The other facial wrinkles WAS will be used by the Investigator:

1. At entry to determine eligibility for treatment
2. During the treatment phase to determine if further treatment is needed
3. During follow-up visits to evaluate any changes in the treatment area

The Investigator will classify the severity of both the left and right facial wrinkles separately (ie, cheek wrinkles, marionette lines, and the severity of the chin crease/chin fold) by comparing the subject to the pictures on the Assessment Scale for Other Facial Wrinkles (see Appendix III)[17] as follows:

0 – no wrinkles
1 – just perceptible wrinkle
2 – shallow wrinkle
3 – moderately deep wrinkle
4 – deep-wrinkle, well-defined edges
5 – very-deep wrinkle, redundant fold

Each grade in the wrinkle assessment scale is exemplified by a photograph (see Appendix III). The grade represents the "best fit" based on the overall depth and length of the facial fold (full point increments must be used). Assessments will be made based on a "snap-shot" at a certain time point and are not based on a comparison to the pre-treatment photographs. Other facial wrinkles WAS will be collected at the screening/initial treatment visit (Visit 1) and Visit 2, and if applicable, at Visits 3 and 4. Other facial wrinkles WAS will also be obtained at Month 6, Month 13, and Years 2, 3, 4, and 5 visits (see Section 2, Flow chart of study procedures and Section 12 for details).

9.2.2 Investigator global evaluation

Investigator global evaluations will be collected at the Month 6, Month 13, and Year 2, 3, 4, 5 visits after the initial injection of study treatment (see Section 2, Flowchart of study procedures). Assessments will be made in comparison to baseline (pretreatment) using the Visit 1 center profile photograph as reference.

The treating Investigator will rate the subject's NLFs and other facial wrinkles that were treated for global aesthetic improvement using the following scale (one composite score for both the left and right NLF and for any other facial wrinkle treated (eg, cheeks or marionette lines):

+3 – Much improved
+2 – Moderately improved
+1 – Slightly improved
0 – No change
-1 – Slightly worse
-2 – Moderately worse
-3 – Much worse

9.2.3 Subject global evaluation

Subject global evaluations will be collected at the Month 6, Month 13, and Year 2, 3, 4, 5 visits after the initial injection of study treatment (see Section 2, Flowchart of Study Procedures). Assessments will be made in comparison to baseline (pre-treatment) using the Visit 1 center profile photograph as reference.

The study coordinator will ask the subject to rate their NLFs and other facial wrinkles that were initially treated for global aesthetic improvement compared to baseline using the following scale (one composite score for both the left and right NLF and for any other facial wrinkle treated (eg, cheeks or marionette lines):

+3 – Much improved
+2 – Moderately improved
+1 – Slightly improved
0 – No change
-1 – Slightly worse
-2 – Moderately worse
-3 – Much worse

10 SUBJECT SAFETY

10.1 ADVERSE EVENTS MONITORING

Adverse events will be documented at each treatment and follow up visit, monthly safety contacts, and any unscheduled visits.

All adverse events will be managed and reported in compliance with all applicable regulations and will be included in the final clinical study report.

10.2 DEFINITIONS OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENT

An **adverse event** is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

In this study (additionally to other adverse events), any occurrence of a nodule, papule, granulomas (confirmed by a biopsy), skin necrosis, hypersensitivity reactions, hypertrophic scarring, keloid formation, changes in the skin pigmentation compared to adjacent skin, or unexpected change in wrinkle contour in the Sculptra® Aesthetic injection site and compared to adjacent skin is to be reported as an adverse event.

A **Serious Adverse Device Event (SADE)** an adverse event that:

- results in death;
- is life-threatening;
- results in permanent impairment of a body function;
- results in permanent damage to a body structure; or,
- necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

10.3 SEVERITY OF ADVERSE EVENTS

The **severity** of an adverse event is to be indicated by the investigator according to the following scale:

Mild	does not interfere with routine activities, can perform daily functions
Moderate	Interferes with routine activities, can perform daily functions, but with concerted efforts
Severe	Unable to perform routine activities

10.4 RELATEDNESS OF ADVERSE EVENT (AE)

The Investigator is to classify the relationship of an AE to the procedure or device according to the following definitions:

Study procedure caused or contributed to the event. The Investigator is to evaluate the adverse event as to whether it was contributed to or caused by the injection procedure according to the definitions outlined in the table below.

Study device caused or contributed to the event. The Investigator is to evaluate the AE as to whether it was contributed to or caused by the device according to the definitions outlined in the following table.

Association	Definition
Not related	The event can be readily explained by other factors, does not follow a known response pattern to the device and no temporal relationship exists with the device.
Related	The AE follows a reasonable temporal sequence related to treatment by the device, follows a known or suspected response pattern and a plausible alternative etiology cannot be identified.

10.5 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

Adverse events

All adverse events regardless of seriousness or relationship to Sculptra® Aesthetic, spanning from the first visit planned in the clinical trial protocol/signature of the informed consent form (ie, occurring during the enrollment period even in the absence of any administration of Sculptra® Aesthetic), up to the last visit planned in the clinical trial protocol, are to be recorded on the corresponding page(s) included in the CRF. The adverse event CRF must be completed at each visit. The sites will be provided a CRF completion Guideline with detailed instructions on when and how to complete all aspects of the CRF, including the relevant adverse event forms for each follow-up visit.

For **Serious Adverse Device Events (SADEs)**, in addition to completing the appropriate CRF pages, a SADE Reporting Form should be completed for any reported SADEs. The sites will be provided a SADE Reporting Form completion guideline with detailed instructions on when and how to complete all aspects of the SADE Reporting Form.

The SADE Reporting Form should be completed and forwarded within 24 hours of the investigator or any site staff becoming aware of the SADE:

Contact For SADE Reporting:

This protocol will be supplemented with a Safety Management Plan (SMP) which will further explain the SADE reporting process.

Whenever possible, symptoms should be grouped as a single syndrome or diagnosis. The Investigator should specify the date of onset, date of resolution, intensity, action taken with respect to Sculptra® Aesthetic, corrective treatment/therapy given, additional investigations performed, outcome and his/her opinion as to whether there is a reasonable possibility that the adverse event was caused by the Sculptra® Aesthetic.

Laboratory, vital signs, or ECG abnormalities are to be recorded as adverse events only if they are deemed to be medically relevant (ie, symptomatic, requiring corrective treatment, leading to discontinuation and/or fulfilling a seriousness criterion).

Follow-up

- The Investigator should take all appropriate measures to ensure the safety of the subjects, notably he/she should follow up the outcome of any adverse event (clinical signs, laboratory values or other, etc) until the return to normal or consolidation of the subject's condition;
- In case of any SADE, the subject must be followed up until clinical recovery is complete, laboratory results have returned to normal, or until progression has been stabilized. This may imply that follow-up will continue after the subject has left the clinical trial and that additional investigations may be requested by the monitoring team;
- In case of any SADE brought to the attention of the Investigator at any time after cessation of Sculptra® Aesthetic and considered by him/her to be caused by the Sculptra® Aesthetic with a reasonable possibility, this should be reported to the monitoring team.

10.6 ADVERSE EVENTS AS PRODUCT TECHNICAL COMPLAINTS

As Sculptra® Aesthetic is considered a medical device all adverse events related to the device and all SADEs are also considered PTCs (Section 8.11).

10.7 PREGNANCY

- Pregnancy will be recorded as an adverse event in all cases. It will be reported following the same procedure as for adverse events related to Sculptra® Aesthetic.
- In the event of pregnancy during the study, Sculptra® Aesthetic should be discontinued and the Sponsor/designee should be informed by contacting the representative of the monitoring team within 24 hours of knowledge.
- In the event of pregnancy, the pregnancy reporting form along with the SAE Reporting Form should be filled out and sent to the representative of the monitoring team within 24 hours of knowledge (see Section 10.3).
- Follow-up of the pregnancy (mother and fetus/child) will be mandatory through delivery or other end of the pregnancy (eg, abortion) and during the 5 year follow-up, whichever is the latest.

11 HANDLING OF SUBJECT TEMPORARY OR DEFINITIVE TREATMENT DISCONTINUATION AND OF SUBJECT STUDY DISCONTINUATION

Sculptra® Aesthetic should be continued whenever possible. In case Sculptra® Aesthetic is stopped, it should be determined if the stop can be made temporarily; permanent Sculptra® Aesthetic discontinuation should be a last resort. Any Sculptra® Aesthetic discontinuation should be fully documented in the CRF. In any case, the subject should remain in the study as long as possible.

11.1 TEMPORARY TREATMENT DISCONTINUATION WITH INVESTIGATIONAL PRODUCT

Sculptra® Aesthetic 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. This deferral will include the entire facial treatment (versus only the specific site with an active inflammatory process or infection).

11.2 DEFINITIVE TREATMENT DISCONTINUATION WITH INVESTIGATIONAL PRODUCT

11.2.1 Criteria for definitive treatment discontinuation with investigational product

Subjects must be withdrawn from receiving any further Sculptra® Aesthetic for the following reasons:

- *At their own request* : In case the subject wishes to discontinue treatment the Investigator must inquire and document in the medical record whether:
  - the subject decides to discontinue study treatment but agrees to follow-up procedures required by the clinical trial protocol,
  - the subject decides to discontinue study treatment and all follow-up procedures,
  - the subject decides to revoke the consent to collect and process further data.
- If, *in the Investigator's opinion*, continuation in the study would be detrimental to the subject's well-being (eg, serious adverse events*)*
- *Pregnancy:* Pregnancy will lead to definitive discontinuation of any further Sculptra® Aesthetic treatment in all cases.

The Investigator may withdraw the subject from any further Sculptra® Aesthetic treatment due to the following reasons:

- Use of prohibited concomitant medications that will interfere with the analysis of the study
- Use of another investigational drug or device

11.2.2 Handling of subjects after definitive treatment discontinuation

Subjects will be followed up, unless he/she withdraws consent for follow-up, according to the study procedures as specified in this protocol up to the scheduled date of study completion (ie, 5 years after the initial treatment), or up to recovery or stabilization of a followed-up adverse event, whichever comes last.

As far as possible, after the permanent discontinuation of Sculptra® Aesthetic treatment, all examinations scheduled for the final study day must be performed on all subjects who receive the Sculptra® Aesthetic but do not complete the study according to clinical trial protocol.

For all definitive treatment discontinuations, when considered as confirmed, the reason for and date of withdrawal must be recorded by the Investigator in the appropriate pages of the CRF and in the subject's medical records.

11.3 PROCEDURE FOR WITHDRAWAL OF SUBJECTS FROM STUDY FOLLOW-UP SCHEDULE

The subjects may withdraw from the study follow-up schedule, before study completion if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision (eg, noncompliance with clinical trial protocol requirements):

- All study withdrawals should be recorded by the Investigator in the appropriate CRF pages when considered as confirmed.
- If possible, the subjects are assessed using the procedure normally planned for the end-of- study.

In the event that a subject is lost to follow-up, the Investigator should make every effort to contact the subject, to identify the reason why he/she failed to attend the visit, and to determine his/her health status, including at least his/her vital status. Attempts to contact such a subject using the information provided by the subject during the study, will include 3 attempts to contact the subject's telephone number(s) of record, followed by 2 certified letters to the mailing address provided by the subject. These must be documented in the subject's records (eg, times and dates of attempted telephone contact, receipt for certified letters that were sent).

The statistical analysis plan will specify how these subjects without primary endpoints will be considered.

11.4 CONSEQUENCE

Subjects who have been withdrawn from the study cannot be reincluded in the study. Their subject number must not be reused. In specific situations to be discussed between Investigator and Sponsor or designee, subjects who have not yet been treated can be reincluded in the study with a new number.

12 STUDY PROCEDURES

12.1 VISIT SCHEDULE

The purpose of the study, benefits, risks, study visit schedule, and the main aspects of the study design will be discussed individually with each subject by the study site personnel. The subject will have the opportunity to ask the Investigator any questions prior to enrolling in the study.

Subjects will be recruited from the outpatient population seeking treatment for contour dermal deformities of the NLF area and other facial areas.

12.1.1 Visit 1 (Day 1) – Screening/initial treatment

The following procedures will be performed during Visit 1 (listed in recommended order):

CCI

- The subject must sign the informed consent form, initial and date "A Patient's Guide to Treatment with Sculptra® Aesthetic," HIPAA authorization, and photographic consent for the study.
- Assign a unique subject number to the subject. This number will be entered in a CRF used to identify that subject over the course of the clinical trial.
- Review inclusion/exclusion criteria.
- Review the subject's medical history and prior/concomitant medications and treatment procedures.
- Perform physical examination (overall subject assessment and skin assessment, particularly the facial area; height and weight)
- Collect vital signs (sitting heart rate and blood pressure)
- Collect urine and perform a pregnancy test on the specimen (females of childbearing potential only). Results must be negative to continue into the study.
- The clinical Investigator will visually inspect the subject's NLFs and determine severity based on the photo-numeric wrinkle assessment scale (see Appendix II). These will be recorded as the baseline measurements.

  NOTE: The subject must have a grade of ≥2 and ≤4 on the photo-numeric wrinkle assessment scale (see Appendix II) of the left and right NLFs to continue the screening process and be enrolled into the study.
- The clinical Investigator will measure the length of the subject's NLFs. This will be recorded as the baseline measurement.
- Assess Fitzpatrick skin type (see Appendix I)
- The clinical Investigator will visually inspect the subject's other facial wrinkles that are planned to be treated and determine severity based on the Assessment Scale for Other Facial Wrinkles (see Appendix III). These will be recorded as the baseline measurements.
- The clinical Investigator will measure the length of the subject's other facial wrinkles that are planned to be treated. These will be recorded as the baseline measurements.
- If the subject meets all of the study requirements, take photographs of each area that will be treated (see the manual of photographic procedures). Standardized photographs must be taken prior to administration of any injection. This photo will serve as the baseline photograph.
- The clinical Investigator will measure the grid (length and width) corresponding to the area of each wrinkle to be treated.
- Perform initial treatment in accordance with instructions for use (see the Sculptra® Aesthetic package insert). If a local anesthetic is injected, then the WAS must be assessed, after administration of local anesthetic (prior to injection of Sculptra® Aesthetic), and after injection of Sculptra® Aesthetic. A maximum of 10 mL (5 mL per side of the face), 2 vials of Sculptra® Aesthetic, is allowed at each injection session and is up to the discretion of the Investigator.
- Take post-treatment photographs (see the manual of photographic procedures).
- Distribute diary card.

- Schedule the subject's next visit in 3 weeks (±3 days).
- Review subject contact information.

12.1.2 Visit 2 (Week 3) – second treatment, *if needed*

The following procedures will be performed (listed in recommended order):

- All adverse events will be collected including, but not limited to:
  - Adverse events of interest: nodule, papule, hypertrophic scarring, keloid formation, granuloma (confirmed by a biopsy), changes in skin pigmentation, skin necrosis, hypersensitivity reaction, and unexpected changes in wrinkle contour
  - Adverse events reported in more than 1% of subjects during clinical trials regardless of relationship to the device/procedure: injection-site edema, injection-site tenderness, injection-site erythema, injection-site pain, injection-site bleeding, injection-site itching, injection-site bruising, injection-site inflammation, injection-site discomfort, injection-site infection, injection-site acne, injection-site dermatitis, and injection-site skin dryness; nasopharyngitis, headache, hypertension, fracture, urinary tract infection, tooth abscess, syncope, and cough
  - Adverse events reported in less than 1% of subjects during clinical trials regardless of relationship to the device/procedure: sinusitis, influenza, bronchitis, 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, rheumatoid arthritis, gastroenteritis, skin burning sensation, spider vein, staphylococcal infection, stress symptoms, tooth infection, toothache, and vaginal infection
  - Adverse events reported during postmarketing surveillance regardless of relationship to the device/procedure: allergic reaction, angioedema (Quincke's edema), application site discharge, fatigue, hypersensitivity reaction, hypertrophy of skin, injection-site abscess, injection-site atrophy, injection-site fat atrophy, injection-site granuloma (including ectropion), injection-site induration, lack of effectiveness, malaise, periorbital nodules, photosensitivity reaction, scar and skin discoloration, skin infection, skin rash, skin roughness, skin sarcoidosis, telangiectasias, and urticarial
- Collect and review the diary card. Record relevant medication use that have occurred since the last visit.
- Subject contact information should be reviewed and updated if needed, at each study visit and monthly safety contact.
- Take standardized photographs (see the manual of photographic procedures).
- The clinical Investigator will visually inspect the subject's NLFs and determine severity based on the photo-numeric wrinkle assessment scale (see Appendix II).
- The clinical Investigator will measure the length of the subject's NLFs.

- The clinical Investigator will visually inspect the subject's other facial wrinkles and determine severity based on the Assessment Scale for Other Facial Wrinkles (see Appendix III).
- The clinical Investigator will measure the length of the subject's other facial wrinkles that are planned to be treated.
- Based on the WAS, the Investigator will determine if further injections of Sculptra® Aesthetic are needed;

A treatment session to correct WAS 2 to 4 NLF contour deficiencies consists of multiple deep dermal threading or tunneling injection of 0.1 mL to 0.2 mL of Sculptra® Aesthetic in grid pattern to a maximum of 2.5 mL per NLF per session. Sculptra® Aesthetic **injections should be stopped when both NLFs and other facial folds have reached a grade of 0 to 1 on the wrinkle assessment scale (see Appendix II and Appendix III). Correction should be limited to no more than 100% of the defect.** [If only one wrinkle has reached the target grade of 0 to 1 the other side should continue to be treated until the target grade is achieved (or a maximum of 4 injection sessions and a maximum of 2.5 mL per NLF per session).] A maximum of 10 mL (5 mL per side of the face), 2 vials of Sculptra® Aesthetic, is allowed at each injection session and is up to the discretion of the Investigator.

If the subject DOES NOTrequire further injections:

- Schedule the three (3) month (±2 weeks) follow-up visit from the date of the INITIAL treatment (Note: not 3 months from this visit date).
- Distribute diary card.

If subject DOES require further injections:

- Note: Only NLFs and other facial wrinkles treated at Visit 1 may be treated at this visit.
- The clinical Investigator will measure the grid (length and width) corresponding to the area of each of the wrinkles to be treated.
- Perform additional injections with Sculptra® Aesthetic in accordance with instructions for use. NOTE: Photographs must be taken of each area that is treated **prior** to any injection and **after** administration of Sculptra® Aesthetic (see the manual of photographic procedures), but not between administration of a local anesthetic and Sculptra® Aesthetic. If a local anesthetic is injected, then the WAS must be assessed, after administration of local anesthetic (prior to injection of Sculptra® Aesthetic), and after injection of Sculptra® Aesthetic.
- Distribute diary card.
- Subjects will be scheduled for next visit in three (3) weeks (±3 days).

12.1.3 Visit 3 (Week 6) – third treatment, *if needed*

The following procedures will be performed (listed in recommended order):

- All adverse events will be collected including, but not limited to:

- Adverse events of interest: nodule, papule, hypertrophic scarring, keloid formation, granuloma (confirmed by a biopsy), changes in skin pigmentation, skin necrosis, hypersensitivity reaction, and unexpected changes in wrinkle contour
- Adverse events reported in more than 1% of subjects during clinical trials regardless of relationship to the device/procedure: injection-site edema, injection-site tenderness, injection-site erythema, injection-site pain, injection-site bleeding, injection-site itching, injection-site bruising, injection-site inflammation, injection-site discomfort, injection-site infection, injection-site acne, injection-site dermatitis, and injection-site skin dryness; nasopharyngitis, headache, hypertension, fracture, urinary tract infection, tooth abscess, syncope, and cough
- Adverse events reported in less than 1% of subjects during clinical trials regardless of relationship to the device/procedure: sinusitis, influenza, bronchitis, 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, rheumatoid arthritis, gastroenteritis, skin burning sensation, spider vein, staphylococcal infection, stress symptoms, tooth infection, toothache, and vaginal infection
- Adverse events reported during postmarketing surveillance regardless of relationship to the device/procedure: allergic reaction, angioedema (Quincke's edema), application site discharge, fatigue, hypersensitivity reaction, hypertrophy of skin, injection-site abscess, injection-site atrophy, injection-site fat atrophy, injection-site granuloma (including ectropion), injection-site induration, lack of effectiveness, malaise, periorbital nodules, photosensitivity reaction, scar and skin discoloration, skin infection, skin rash, skin roughness, skin sarcoidosis, telangiectasias, and urticaria

- Collect and review the diary card. Record relevant medication use that have occurred since the last visit.
- Subject contact information should be reviewed and updated if needed, at each study visit and monthly safety contact.
- Take standardized photographs (see the manual of photographic procedures).
- The clinical Investigator will visually inspect the subject's NLFs and determine severity based on the photo-numeric wrinkle assessment scale (see Appendix II).
- The clinical Investigator will measure the length of the subject's NLFs.
- The clinical Investigator will visually inspect the subject's other facial wrinkles and determine severity based on the Assessment Scale for Other Facial Wrinkles (see Appendix III).
- The clinical Investigator will measure the length of the subject's other facial wrinkles that are planned to be treated.
- Based on the WAS, the Investigator will determine if further injections of Sculptra® Aesthetic are needed;

A treatment session to correct WAS 2 to 4 NLF contour deficiencies consists of multiple deep dermal threading or tunneling injection of 0.1 mL to 0.2 mL of Sculptra® Aesthetic in grid pattern to a maximum of 2.5 mL per NLF per session. Sculptra® Aesthetic **injections should be stopped when both NLFs and or other facial folds have reached a grade of 0 to 1 on the wrinkle assessment scale (see Appendix II and Appendix III). Correction should be limited to no more than 100% of the defect.** [If only one wrinkle has reached the target grade of 0 to 1 the other side should continue to be treated until the target grade is achieved (or a maximum of 4 injection sessions and a maximum of 2.5 mL per NLF per session).] A maximum of 10 mL (5 mL per side of the face), 2 vials of Sculptra® Aesthetic, is allowed at each injection session and is up to the discretion of the Investigator.

If the subject DOES NOT require further injections:

- Schedule the three (3) month (±2 weeks) follow-up visit from the date of the INITIAL treatment (Note: not 3 months from this visit date).
- Distribute diary card.

If subject DOES require further injections:

- Note: Only NLFs and other facial wrinkles treated at Visit 1 may be treated at this visit.
- The clinical Investigator will measure the grid (length and width) corresponding to the area of each of the wrinkles to be treated.
- Perform additional injections with Sculptra® Aesthetic in accordance with instructions for use. NOTE: Photographs must be taken of each area that is treated **prior** to any injection and **after** administration of Sculptra® Aesthetic (see the manual of photographic procedures), but not between administration of a local anesthetic and Sculptra® Aesthetic. If a local anesthetic is injected, then the WAS must be assessed, after administration of local anesthetic (prior to injection of Sculptra® Aesthetic), and after injection of Sculptra® Aesthetic.
- Distribute diary card.
- Subjects will be scheduled for next visit in three (3) weeks (±3 days).

12.1.4 Visit 4 (Week 9) – fourth treatment, *if needed*

The following procedures will be performed (listed in recommended order):

- All adverse events will be collected including, but not limited to:
  - Adverse events of interest: nodule, papule, hypertrophic scarring, keloid formation, granuloma (confirmed by a biopsy), changes in skin pigmentation, skin necrosis, hypersensitivity reaction, and unexpected changes in wrinkle contour
  - Adverse events reported in more than 1% of subjects during clinical trials regardless of relationship to the device/procedure: injection-site edema, injection-site tenderness, injection-site erythema, injection-site pain, injection-site bleeding, injection-site itching, injection-site bruising, injection-site inflammation, injection-

site discomfort, injection-site infection, injection-site acne, injection-site dermatitis, and injection-site skin dryness; nasopharyngitis, headache, hypertension, fracture, urinary tract infection, tooth abscess, syncope, and cough

- Adverse events reported in less than 1% of subjects during clinical trials regardless of relationship to the device/procedure: sinusitis, influenza, bronchitis, 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, rheumatoid arthritis, gastroenteritis, skin burning sensation, spider vein, staphylococcal infection, stress symptoms, tooth infection, toothache, and vaginal infection
- Adverse events reported during postmarketing surveillance regardless of relationship to the device/procedure: allergic reaction, angioedema (Quincke's edema), application site discharge, fatigue, hypersensitivity reaction, hypertrophy of skin, injection-site abscess, injection-site atrophy, injection-site fat atrophy, injection-site granuloma (including ectropion), injection-site induration, lack of effectiveness, malaise, periorbital nodules, photosensitivity reaction, scar and skin discoloration, skin infection, skin rash, skin roughness, skin sarcoidosis, telangiectasias, and urticaria

- Collect and review the diary card. Record relevant medication use that have occurred since the last visit.
- Subject contact information should be reviewed and updated if needed, at each study visit and monthly safety contact.
- Take standardized photographs (see the manual of photographic procedures).
- The clinical Investigator will visually inspect the subject's NLFs and determine severity based on the photo-numeric wrinkle assessment scale (see Appendix II).
- The clinical Investigator will measure the length of the subject's NLFs.
- The clinical Investigator will visually inspect the subject's other facial wrinkles and determine severity based on the Assessment Scale for Other Facial Wrinkles (see Appendix III).
- The clinical Investigator will measure the length of the subject's other facial wrinkles that are planned to be treated.
- Based on the WAS, the Investigator will determine if further injections of Sculptra® Aesthetic are needed;

  A treatment session to correct WAS 2 to 4 NLF contour deficiencies consists of multiple deep dermal threading or tunneling injection of 0.1 mL to 0.2 mL of Sculptra® Aesthetic in grid pattern to a maximum of 2.5 mL per NLF per session. Sculptra® Aesthetic **injections should be stopped when both NLFs and or other facial folds have reached a grade of 0 to 1 on the wrinkle assessment scale (see Appendix II and Appendix III). Correction should be limited to no more than 100% of the defect.** [If only one wrinkle has reached the target grade of 0 to 1 the other side should continue to be treated until the target grade is achieved (or a

maximum of 4 injection sessions and a maximum of 2.5 mL per NLF per session).] A maximum of 10 mL (5 mL per side of the face), 2 vials of Sculptra® Aesthetic, is allowed at each injection session and is up to the discretion of the Investigator.

If the subject DOES NOT require further injections:

- Schedule the three (3) month (±2 weeks) follow-up visit from the date of the INITIAL treatment (Note: not 3 months from this visit date).
- Distribute diary card.

If subject DOES require further injections:

- Note: Only NLFs and other facial wrinkles treated at Visit 1 may be treated at this visit.
- The clinical Investigator will measure the grid (length and width) corresponding to the area of each of the wrinkles to be treated.
- Perform additional Sculptra® Aesthetic injections in accordance with instructions for use. NOTE: Photographs must be taken of each area that is treated **prior** to any injection and **after** administration of Sculptra® Aesthetic (see the manual of photographic procedures), but not between administration of a local anesthetic and Sculptra® Aesthetic. If a local anesthetic is injected, then the WAS must be assessed, after administration of local anesthetic (prior to injection of Sculptra® Aesthetic), and after injection of Sculptra® Aesthetic.
- Distribute diary card.
- Schedule the three (3) month (±2 weeks) follow-up visit from the date of the INITIAL treatment (Note: not 3 months from this visit date).

12.1.5 Follow-up phase

All subjects will be scheduled to visit the study site at Months 3, 6, 9, 13 (±2 weeks) and Years 2, 3, 4, 5 (±4 weeks) after the initial treatment. In addition, there will be monthly safety contacts between each follow-up visit. Subject contact information will be reviewed and updated as needed. Three contact attempts followed by 2 certified letters will be sent as a reminder contact to the subject starting 3 months before an annual follow-up visit (ie, Years 2, 3, 4, and 5).

All follow-up visit times are relative to the date of the INITIAL treatment.

12.1.5.1 Follow-up visits at Month 3, 6, 9, and 13

The following procedures will be performed at the Month 3, 6, 9, and 13 follow-up visits, unless specified otherwise:

- All adverse events will be collected including, but not limited to:
  - Adverse events of interest: nodule, papule, hypertrophic scarring, keloid formation, granuloma (confirmed by a biopsy), changes in skin pigmentation, skin necrosis, hypersensitivity reaction, and unexpected changes in wrinkle contour

- Adverse events reported in more than 1% of subjects during clinical trials regardless of relationship to the device/procedure: injection-site edema, injection-site tenderness, injection-site erythema, injection-site pain, injection-site bleeding, injection-site itching, injection-site bruising, injection-site inflammation, injection-site discomfort, injection-site infection, injection-site acne, injection-site dermatitis, and injection-site skin dryness; nasopharyngitis, headache, hypertension, fracture, urinary tract infection, tooth abscess, syncope, and cough
- Adverse events reported in less than 1% of subjects during clinical trials regardless of relationship to the device/procedure: sinusitis, influenza, bronchitis, 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, rheumatoid arthritis, gastroenteritis, skin burning sensation, spider vein, staphylococcal infection, stress symptoms, tooth infection, toothache, and vaginal infection
- Adverse events reported during postmarketing surveillance regardless of relationship to the device/procedure: allergic reaction, angioedema (Quincke's edema), application site discharge, fatigue, hypersensitivity reaction, hypertrophy of skin, injection-site abscess, injection-site atrophy, injection-site fat atrophy, injection-site granuloma (including ectropion), injection-site induration, lack of effectiveness, malaise, periorbital nodules, photosensitivity reaction, scar and skin discoloration, skin infection, skin rash, skin roughness, skin sarcoidosis, telangiectasias, and urticaria

- Examine the subject, collect and review diary cards, and review/record relevant medication use that has occurred since the last visit (all visits)
- Take standardized photographs (see the manual of photographic procedures) (Months 6 and 13).
- The clinical Investigator will visually inspect the subject's NLFs and determine severity based on the photo-numeric wrinkle assessment scale (see Appendix II) (Months 6 and 13).
- The clinical Investigator will measure the length of the subject's NLFs (Months 6 and 13).
- The clinical Investigator will visually inspect the subject's other facial wrinkles and determine severity based on the Assessment Scale for Other Facial Wrinkles (Months 6 and 13) (see Appendix III).
- The clinical Investigator will measure the length of the subject's other facial wrinkles (Months 6 and 13).
- Perform Investigator/subject global evaluation assessments (Months 6 and 13).
- Subject contact information should be reviewed and updated if needed, at each study visit and monthly safety contact.
- Distribute diary card.
- At Months 3, 6, and 9, schedule next visit (± 2 weeks); at Month 13, schedule the Year 2 annual visit (± 4 weeks).
- For the Months 3, 6, 9, and 13, at least 1 contact attempt will be made approximately 1 month prior to the scheduled visit as a reminder appointment call (can coincide with the

monthly safety contact) to help ensure compliance. [For the Year 2 annual visit, 3 contact attempts followed by 2 certified letters will be sent as a reminder contact to the subject starting 3 months before the Year 2 annual visit to help ensure compliance (see Section 12.1.5.2).]

- Schedule the monthly safety contact calls with the subject.

12.1.5.2 Follow-up visits at Years 2, 3, and 4

The following procedures will be performed at the Year 2, 3, and 4 follow-up visits:

- All adverse events will be collected including, but not limited to:
  - Adverse events of interest: nodule, papule, hypertrophic scarring, keloid formation, granuloma (confirmed by a biopsy), changes in skin pigmentation, skin necrosis, hypersensitivity reaction, and unexpected changes in wrinkle contour
  - Adverse events reported in more than 1% of subjects during clinical trials regardless of relationship to the device/procedure: injection-site edema, injection-site tenderness, injection-site erythema, injection-site pain, injection-site bleeding, injection-site itching, injection-site bruising, injection-site inflammation, injection-site discomfort, injection-site infection, injection-site acne, injection-site dermatitis, and injection-site skin dryness; nasopharyngitis, headache, hypertension, fracture, urinary tract infection, tooth abscess, syncope, and cough
  - Adverse events reported in less than 1% of subjects during clinical trials regardless of relationship to the device/procedure: sinusitis, influenza, bronchitis, 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, rheumatoid arthritis, gastroenteritis, skin burning sensation, spider vein, staphylococcal infection, stress symptoms, tooth infection, toothache, and vaginal infection
  - Adverse events reported during postmarketing surveillance regardless of relationship to the device/procedure: allergic reaction, angioedema (Quincke's edema), application site discharge, fatigue, hypersensitivity reaction, hypertrophy of skin, injection-site abscess, injection-site atrophy, injection-site fat atrophy, injection-site granuloma (including ectropion), injection-site induration, lack of effectiveness, malaise, periorbital nodules, photosensitivity reaction, scar and skin discoloration, skin infection, skin rash, skin roughness, skin sarcoidosis, telangiectasias, and urticaria
- Examine the subject, collect and review diary card, and review/record relevant medication use that have occurred since the last visit (all visits).
- Take standardized photographs (see the manual of photographic procedures).
- The clinical Investigator will visually inspect the subject's NLFs and determine severity based on the photo-numeric wrinkle assessment scale (see Appendix II).

- The clinical Investigator will measure the length of the Subject's NLFs.
- The clinical Investigator will visually inspect the subject's other facial wrinkles and determine severity based on the Assessment Scale for Other Facial Wrinkles (see Appendix III).
- The clinical Investigator will measure the length of the subject's other facial wrinkles.
- Perform Investigator/subject global evaluation assessments (all visits).
- Subject contact information should be reviewed and updated if needed, at each study visit and monthly safety contact.
- Distribute diary cards.
- Schedule the next annual visit (±4 weeks) from the date of the initial treatment. Three contact attempts followed by 2 certified letters will be sent as a reminder contact to the subject starting 3 months before an annual follow-up visit to help ensure compliance. These can coincide with the monthly safety contact.
- Schedule the monthly safety contacts with the subject.

12.1.5.3 End of study or early termination visit (Year 5)

The following procedures will be performed at Year 5, end of study or early termination visit:

- All adverse events will be collected including, but not limited to:
  - Adverse events of interest: nodule, papule, hypertrophic scarring, keloid formation, granuloma (confirmed by a biopsy), changes in skin pigmentation, skin necrosis, hypersensitivity reaction, and unexpected changes in wrinkle contour
  - Adverse events reported in more than 1% of subjects during clinical trials regardless of relationship to the device/procedure: injection-site edema, injection-site tenderness, injection-site erythema, injection-site pain, injection-site bleeding, injection-site itching, injection-site bruising, injection-site inflammation, injection-site discomfort, injection-site infection, injection-site acne, injection-site dermatitis, and injection-site skin dryness; nasopharyngitis, headache, hypertension, fracture, urinary tract infection, tooth abscess, syncope, and cough
  - Adverse events reported in less than 1% of subjects during clinical trials regardless of relationship to the device/procedure: sinusitis, influenza, bronchitis, 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, rheumatoid arthritis, gastroenteritis, skin burning sensation, spider vein, staphylococcal infection, stress symptoms, tooth infection, toothache, and vaginal infection
  - Adverse events reported during postmarketing surveillance regardless of relationship to the device/procedure: allergic reaction, angioedema (Quincke's

edema), application site discharge, fatigue, hypersensitivity reaction, hypertrophy of skin, injection-site abscess, injection-site atrophy, injection-site fat atrophy, injection-site granuloma (including ectropion), injection-site induration, lack of effectiveness, malaise, periorbital nodules, photosensitivity reaction, scar and skin discoloration, skin infection, skin rash, skin roughness, skin sarcoidosis, telangiectasias, and urticaria

- Examine the subject, collect and review diary card, and review/record relevant medication use that have occurred since the last visit.
- Take standardized photographs (see the manual of photographic procedures).
- The clinical Investigator will visually inspect the subject's NLFs and determine severity based on the photo-numeric wrinkle assessment scale (see Appendix II).
- The clinical Investigator will measure the length of the subject's NLFs.
- The clinical Investigator will visually inspect the subject's other facial wrinkles and determine severity based on the Assessment Scale for Other Facial Wrinkles (see Appendix III).
- The clinical Investigator will measure the length of the subject's other facial wrinkles.
- Perform Investigator/subject global evaluation assessments (all visits).
- Final subject study status information is collected and all necessary study related documentation is completed.
- The subject will be discharged from the study.

12.2 MONTHLY SAFETY CONTACTS

During the follow-up phase (Month 3 through Year 5), the site personnel will contact each subject monthly to review/record adverse events that have occurred and relevant medication that were taken since the last site visit, as well as confirm the next follow-up visit. The monthly safety contact and reminder contact will occur at the same time, whenever possible. In the event an adverse event is recorded that is listed in Section 9.1.1 (Primary safety criteria), the subject will be brought in for an unscheduled visit.

Subject contact information should be reviewed and updated if needed. If the site is unable to contact the subject directly within 3 months before each of their annual follow-up visits, the site will attempt to make 3 attempts to contact the subject, followed by 2 certified letters.

12.3 UNSCHEDULED VISITS

In the event that an adverse event listed in Section 9.1.1 (Primary safety criteria) occurs, the subject will be brought in for an unscheduled visit, a photograph will be taken (see the manual of photographic procedures), and the subject will then receive monthly safety contacts until resolution or stabilization (no further changes expected) of the adverse event. Upon resolution or stabilization of the adverse event, the subject will return for a follow-up unscheduled visit for verification of the resolution or stabilization of the effect by the Investigator. The resolution of the adverse event will be documented on the source documents and on the adverse event CRF.

12.4 EARLY TERMINATION

If a subject is withdrawn before the end of the study the following procedures, in addition to those listed in Section 12.1.5.3, will be performed during an early termination visit (listed in recommended order):

- Determine and record reason for early termination and initiate plan for follow-up (see Section 11.2.2 Handling of subjects after definitive treatment discontinuation and Section 11.3 Procedures for withdrawal of subjects from study follow-up schedule).
- Complete all necessary study documentation as well as end of study completion page of the CRF.

12.5 DEFINITION OF SOURCE DATA

The data source for the analyses of the primary and secondary endpoints will be medical records and the study specific source documents for the study. Source data will be where the information is first recorded at the investigative site.

13 STATISTICAL CONSIDERATIONS

13.1 STATISTICAL AND ANALYTICAL PLANS

The material of Section 13 of the clinical trial protocol is the basis for the statistical analysis plan for the study. This plan may be revised during the study to accommodate clinical trial protocol amendments and to make changes to adapt to unexpected issues in study execution and data that affects planned analysis. These revisions will be based on a review of the study data, and a final plan will be issued before database lock. Complete details of the statistical analyses and methods, including data conventions, will be contained in a separate and final statistical analysis plan.

13.2 DETERMINATION OF SAMPLE SIZE

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13.3 ANALYSIS VARIABLES

13.3.1 Demographic and baseline characteristics

Demographic and baseline characteristics include subjects' sex, race/ethnicity, age, height, weight, medical history, prior and concomitant medications, length of NLFs and other facial wrinkles, and vital signs (sitting heart rate and blood pressure).

13.3.2 Safety variables

13.3.2.1 Adverse events

The co-primary safety endpoints are:

1. The percentage (incidence rate) of subjects with any injection site nodule and/or papule over 5 years.
2. The percentage (incidence rate) of subjects with any of the following injection site events over 5 years:
   - Hypertrophic scarring
   - Keloid formation
   - Changes in the skin pigmentation at the site of injection compared to adjacent skin
   - Granuloma (confirmed by a biopsy)
   - Skin necrosis
   - Hypersensitivity reactions
   - Unexpected change in wrinkle contour

The injection site adverse events listed above are defined as adverse events of interest in this study.

The secondary safety endpoints are the percentages (incidence rate) of subjects with any injection site nodule and/or papule, the percentage of subjects who experienced any adverse events of interest other than nodule or papule over 2 years; location and intervention for any adverse events of interest; adverse event severity, duration, time to onset of adverse event, relationship to Sculptra® Aesthetic and relationship to injection procedure during the course of the study.

13.3.2.2 Laboratory safety variables

A urine pregnancy test for women of child-bearing potential will be collected at Visit 1.

13.3.2.3 Vital signs and physical exam

Vitals signs (sitting heart rate and blood pressure) and physical examination (overall subject assessment and facial assessment) will only be collected at Visit 1 and considered as the baseline characteristics for each subject (see Section 13.3.1).

13.3.2.4 Other safety variables

None.

13.3.3 Efficacy variables

13.3.3.1 Primary efficacy variables

None.

13.3.3.2 Secondary efficacy variables

The secondary efficacy endpoints are:

- Change from baseline to post-treatment follow-up time points in the WAS at Month 6, Month 13, and Years 2, 3, 4, and 5.
- Investigator/Subject Global Assessments Scores at Month 6, Month 13, and Years 2, 3, 4, and 5.

13.4 ANALYSIS POPULATIONS

The intent-to-treat (ITT) population, per protocol (PP) population, and Completer2 and Completer5 populations are defined as follows:

13.4.1 Efficacy populations

The analysis populations for efficacy will be the ITT population that consists of all subjects who receive at least one Sculptra® Aesthetic injection; the PP population will consist of all subjects who receive at least 1 Sculptra® Aesthetic injection and are without any major protocol deviation.

13.4.2 Safety populations

The analysis population for safety will also include the ITT population and the PP population. The ITT population is the primary population for hypothesis testing.

13.4.3 Other analysis populations

The Completer2 population consists of all subjects who receive at least 1 Sculptra® Aesthetic injection and finish the second year visit.

The Completer5 population consists of all subjects who receive at least 1 Sculptra® Aesthetic injection and finish the fifth year visit.

13.4.4 Disposition of subjects

The general disposition of subjects during the study will be defined as follows: (a) **screened** subjects are those who have a written informed consent document; (b) **treated** subjects are those screened subjects who received at least 1 dose of Sculptra® Aesthetic; and (c) **completed** subjects are those treated subjects who complete all clinical trial protocol required visits.

13.5 STATISTICAL METHODS

CCI

[redacted]

13.5.1 Demographics and baseline characteristics

Demographics and baseline characteristics will be summarized by descriptive statistics, which consist of mean, standard deviation, median, minimum and maximum for continuous variables or frequency count and percentage for categorical variables.

13.5.2 Extent of study treatment exposure and compliance

Extent of treatment exposure and compliance will be determined by the number of injection sessions, duration of treatment period (days), the total amount of Sculptra® Aesthetic used, the total amount of Sculptra® Aesthetic used per injection site and the amount of Sculptra® Aesthetic used per surface area per WAS. They will all be summarized by descriptive statistics.

13.5.4 Analysis of safety data

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[redacted]

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[redacted]

13.5.4.2 Other analyses of adverse events

All adverse events will be collected and summarized with the number of subjects reporting adverse events by number of injections, system organ class, preferred term, severity, and relationship to the Sculptra® Aesthetic or injection procedure as well. Time to onset of the first adverse event of interest and the duration of adverse event of interest (maximum duration if there are multiple adverse events of interest with a subject) will be summarized by Kaplan-Meier plots.

Treatment-emergent adverse events (TEAEs) are defined as adverse events that develop or worsen during the on-treatment period (time from first dose of Sculptra® Aesthetic to the end of the study). All adverse events will be coded using the current version of MedDRA.

The following frequency distributions of adverse events (incidence tables) will be provided:

- Overview of adverse events
- All TEAEs by number of injections
- All TEAEs by system organ class and preferred term
- All TEAEs by system organ class and preferred term by decreasing frequency
- All TEAEs by preferred term by decreasing frequency
- All TEAEs by system organ class, preferred term and intensity
- Possibly related TEAEs by system organ class, preferred term and intensity

The following listings will be provided for the ITT population:

- All adverse events
- Serious adverse events

- adverse events that resulted in death
- adverse events that lead to discontinuation of Sculptra® Aesthetic
- Nodules and papules
- adverse events of interest, other than nodule and papule

13.5.4.3 Laboratory variables analysis

Not applicable.

13.5.4.4 Analysis of vital sign variables

Not applicable.

13.5.4.5 Analysis of other safety variables

Not applicable.

13.5.4.6 Analysis of pharmacokinetic and pharmacodynamic variables

Not applicable.

13.5.4.7 Analysis of health economics variables

Not applicable.

13.6 INTERIM ANALYSIS

Interim analyses will be conducted on all study variables at 4 time points:

- Following completion of all subjects Month 13 follow-up visits;
- Following completion of all subjects Year 2 follow-up visits;
- Following completion of all subjects Year 3 follow-up visits; and
- Following completion of all subjects Year 4 follow-up visits.

For each interim analysis the method of analysis will be the same as described above in Section 13.5. CCI [redacted]

13.7 MISSING DATA

The following rules will be applied to handle missing data in the safety analyses:

- If a subject discontinues the study before 5 years, all his/her safety information before discontinuation will be used in the safety analysis, and the subject will be assumed to have no adverse events between the date of discontinuation and the 5-year timepoint. Sensitivity analyses for primary and secondary hypotheses will be conducted as described in Section 13.5.4.1.
- If the timing of an adverse event cannot be identified because of missing data and the subject is treated, the adverse event will be considered as a TEAE.
- If the assessment of the intensity is missing, the most severe case will be assumed in the frequency tables of adverse event intensity.
- If the assessment of the relationship to the Sculptra® Aesthetic or injection procedure is missing, a possible relationship to the Sculptra® Aesthetic will be assumed in the frequency tables of possibly related adverse events.

Detailed plans for handling missing data will be contained in the statistical analysis plan.

14 ETHICAL AND REGULATORY STANDARDS

14.1 ETHICAL PRINCIPLES

This clinical trial will be conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies and the International Conference on Harmonization (ICH) guidelines for Good Clinical Practice.

14.2 LAWS AND REGULATIONS

This clinical trial will be conducted in compliance with all international laws and regulations, and national laws and regulations of the country in which the clinical trial is performed, as well as any applicable guidelines.

14.3 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the subject of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the IRB. All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a subject's participation in the clinical trial, the written informed consent form and any other local applicable documents in accordance with local laws and regulations, should be signed, name filled in and personally dated by the subject and by the person who conducted the informed consent discussion. Copies of the signed and dated written informed consent form will be provided to the subject.

The informed consent form used by the Investigator for obtaining the subject's informed consent must be reviewed and approved by the Sponsor or designee prior to submission to the appropriate IRB for approval/favorable opinion.

To encourage continued participation, subjects may be provided with a modest financial compensation to help defray the associated expenses (eg, transportation to the trial site).

14.4 INSTITUTIONAL REVIEW BOARD (IRB)

The Investigator or the Sponsor/designee must submit this clinical trial protocol to the appropriate IRB, and is required to forward to the Sponsor/designee a copy of the written and dated approval/favorable opinion signed by the chairman with IRB composition.

The clinical trial (study code, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form, package insert, Investigator's curriculum vitae, etc.), the list of voting members and their qualifications, and the date of the review should be clearly stated on the written IRB approval/favorable opinion.

Sculptra® Aesthetic and SWFI will not be released to the study site and the clinical trial will not start until a copy of this written and dated approval/favorable opinion has been received by the Sponsor or designee.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the IRB. It should also be informed of any effect likely to affect the safety of subjects or the continued conduct of the clinical trial, in particular any change in safety. All updates to the package insert will be sent to the IRB.

If requested, a progress report will be sent to the IRB annually and a summary of the clinical trial's outcome at the end of the clinical trial.

15 STUDY MONITORING

15.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator(s) undertake(s) to perform the clinical trial in accordance with this clinical trial protocol, ICH guidelines for Good Clinical Practice and the applicable regulatory requirements. The Investigator will ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor/designee in the CRFs and in all required reports, as per ICH-E6.

The Investigator may provide each subject with "A Patient's Guide to Treatment with Sculptra® Aesthetic," to resolve any subject questions after the subject has read this guide and to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the CRF, discrepancy resolution form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided, and to ensure direct access to source documents by Sponsor representatives.

The Investigator may appoint a designee or such other individuals as he/she may deem appropriate as subinvestigators to assist in the conduct of the clinical trial, including transcription of source data, in accordance with the clinical trial protocol. All subinvestigators shall be appointed and listed in a timely manner. The subinvestigators will be supervised by and under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

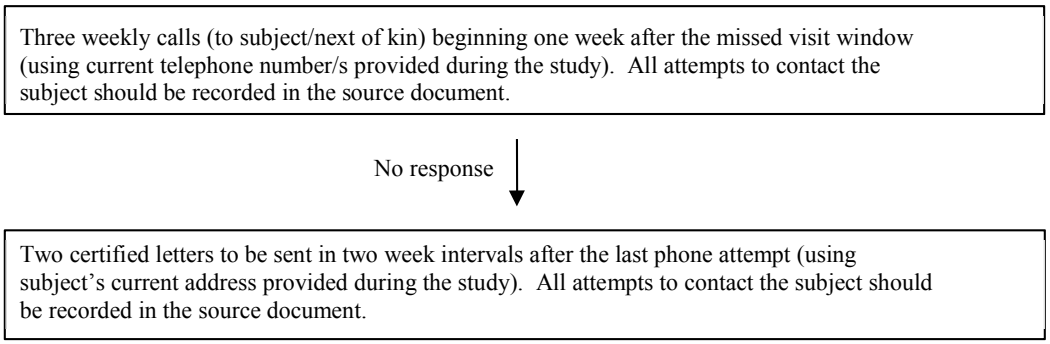
The Investigator must maintain the clinical trial documents as required by the applicable regulatory requirements (see Section 16.2). The Investigator must take measures to prevent accidental or premature destruction of these documents (see Sections 15.3 and 16.2).

Contact prior to annual visits

Before a subject is considered lost-to-follow-up, the Investigator will attempt to contact the subject 3 times followed by 2 certified letters starting 3 months before an annual follow-up visit (ie, Years 2, 3, 4, and 5) (see Sections 12.1.5 and Section 12.2). If still unable to contact the subject, the site will contact the subject's relative/next of kin or search National databases (ie, those at the time of signing informed consent) as shown in the Figure 2.

Figure 2 - Steps to be taken before a subject is considered to be lost-to-follow-up

Subject contact information should be reviewed and updated if needed, at each study visit and monthly safety contact.



Note: If permitted by subject and by local laws and regulations, a national database could be searched to determine survival status.

15.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical trial is responsible to health authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial protocol as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the CRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical, and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters, and/or contacts, by a representative of the monitoring team to review study progress, Investigator and subject compliance with clinical trial protocol requirements and any emergent problems. During these monitoring visits, the following, but not exhaustive, list of points will be scrutinized with the Investigator: subject informed consent, subject eligibility, subject recruitment and follow-up, serious adverse event documentation and reporting, Sculptra® Aesthetic and SWFI allocation, subject compliance with the clinical trial protocol and the Sculptra® Aesthetic /SWFI regimen, Sculptra® Aesthetic and SWFI accountability, concomitant therapy use, and quality of data.

The Sponsor will ensure that all participating Investigators are successfully trained on the use of Sculptra® Aesthetic, which includes WAS use, grid (cross-hatch) and a description of injection technique for NLFs and other facial wrinkles, as allowed by this protocol, and for which grid (cross-hatch) injection is clinically appropriate.

15.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH guidelines for Good Clinical Practice, the monitoring team must check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The informed consent form will include a statement by which the subject allows the Sponsor's duly authorized personnel, the IRB, and the regulatory authorities to have direct access to source data which support the data on the CRFs (eg, subject's medical file, appointment books, original laboratory records, etc.). Such personnel, bound by professional secrecy, must keep confidential all personal identity or personal medical information (according to confidentiality rules).

15.4 USE AND COMPLETION OF CASE REPORT FORMS AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate CRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation. The sites will be provided a CRF Completion Guideline with detailed instructions on when and how to complete all aspects

of the CRF. Data can be entered into the electronic CRFs by any member of the site staff who is clearly identified on the Delegation of Duties form, and who:

- Has successfully completed CRF training provided by the Sponsor, and
- Has an individual access code and password.

15.5 USE OF COMPUTERIZED SYSTEMS

SAS will be used for statistical analysis. The data management system will be determined once the data management vendor has been identified.

16 ADMINISTRATIVE RULES

16.1 CURRICULUM VITAE

An updated copy of the curriculum vitae limited to the experience, qualifications, and training for each Investigator and subinvestigator will be provided to the Sponsor or designee prior to the beginning of the clinical trial.

16.2 RECORD RETENTION IN STUDY SITE(S)

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Sponsor will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, Sponsor standard operating procedures, and/or institutional requirements.

The Investigator must notify the Sponsor prior to destroying any essential study documents following completion or discontinuation of the clinical trial.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

17 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial

protocol, the CRFs, the Package insert and the results obtained during the course of the Clinical Trial, is confidential. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the IRB is expressly permitted, the IRB members having the same obligation of confidentiality.

The subinvestigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the subinvestigators of the confidential nature of the clinical trial.

The Investigator and the subinvestigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

18 PROPERTY RIGHTS

All information, documents, and Sculptra® Aesthetic provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not mention any information or the Sculptra® Aesthetic in any application for a patent or for any other intellectual property rights.

All the results, documents and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical trial.

19 DATA PROTECTION

Each subject's personal data and Investigator's personal data which may be included in the Sponsor database shall be treated in compliance with all applicable laws and regulations.

When archiving or processing personal data pertaining to the Investigator and/or to the subjects, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

20 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, Good Clinical Practice and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by applicable regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that their personnel are bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a future inspection by the authorities, he/she will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the subjects should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

21 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

21.1 DECIDED BY THE SPONSOR IN THE FOLLOWING CASES

- If the information on the product leads to doubt as to the benefit/risk ratio;
- If the Investigator has received from the Sponsor all Sculptra® Aesthetic and SWFI, means and information necessary to perform the clinical trial and has not included any subject after a reasonable period of time mutually agreed upon;
- In the event the results of the clinical trial do not appear to be scientifically convincing to the Sponsor (for example, based on the results of a planned futility analysis);
- If the aim of the clinical trial has become outdated or is no longer of interest;
- In the event of breach by the Investigator of a fundamental obligation under this agreement, including but not limited to breach of the clinical trial protocol, breach of the applicable laws and regulations or breach of the ICH guidelines for Good Clinical Practice;
- If the total number of subjects are included earlier than expected.

- In any case the Sponsor will notify the Investigator of its decision by written notice.

21.2 DECIDED BY THE INVESTIGATOR

The Investigator must notify (at least 30 days prior to discontinuation) the Sponsor of his/her decision and give the reason in writing.

In all cases (decided by the Sponsor or by the Investigator), the appropriate IRB and health authorities should be informed.

22 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a clinical study report.

When the data from all investigational sites have been fully analyzed by the Sponsor, the latter will communicate the results of the clinical trial to the Investigator(s).

Regardless of the study outcome, the Sponsor is committed to publishing the results.

23 PUBLICATIONS AND COMMUNICATIONS

23.1 PUBLICATION/COMMUNICATION OF STUDY RESULTS

The Sponsor recognizes the Investigator's right to utilize data derived from the clinical trial for teaching purposes, communication at congresses and scientific publications. Nevertheless, in order to ensure the accuracy and scientific value of the information, while preserving the independence and accountability of the Investigator, and the confidentiality of the information, only checked and validated data will be used. To that effect, it is essential that the parties exchange and discuss, prior to any publication or communication, any draft publication or communication made by the Investigator.

The Investigator shall send to the Sponsor a copy of the manuscript for review and possible comments at least forty-five (45) calendar days in advance of the date of submission to the journal and at least twenty (20) days in advance for abstracts. The publication shall be delayed until a written response is received by the Sponsor, not to exceed ninety (90) days. The Sponsor can delay publication or communication for a limited time in order to protect the confidentiality or proprietary nature of any information contained therein, it being understood that the Sponsor cannot refuse its consent without reasonable cause. The Investigator agrees to include the modifications requested by the Sponsor, provided they do not jeopardize the accuracy and/or the scientific value of the publication.

All study Investigators and committee members give full authority to the Steering Committee, if applicable, for primary presentation and/or primary publication of results. However, in the

absence of primary publication within 12 months of the termination of the clinical trial at all other sites, the Sponsor or the Steering Committee, if applicable, may consider the Investigator's request for independent publication. The Investigator agrees not to publish the results of the clinical trial pertaining to his/her center prior to the publication of the overall clinical trial results. If no publication has occurred within twelve (12) months of the termination of the clinical trial at all other sites, the Investigator shall have the right to publish independently the results of this clinical trial, subject to the review procedure set forth herein. If the clinical trial is conducted with the support of a Steering Committee, the latter may define specific rules for publication.

No other publication is allowed before the primary publication. Any subsequent presentation or publication by a study participant (including for sub studies) must be reviewed by the Sponsor and make reference to the study and the primary publication.

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the clinical trial.

23.2 PUBLIC DISCLOSURE OF CLINICAL TRIALS

Regarding clinical trial registries, the Sponsor will comply with the following:

- This clinical trial will be recorded in a registry accessible to the public free of charge; the Sponsor has decided to register its clinical trials on the following Web site: www.clinicaltrials.gov.
    - The registry will contain basic information about each trial sufficient to inform interested subjects (and their healthcare practitioners) how to enroll in the trial;
    - The trial will be registered under a unique identification number to ensure transparency of clinical trial results;
    - As a general rule, clinical trial information will be published within 21 days following enrollment of the first subject.
    - If trial results are published in a peer-reviewed medical journal, the database will contain a citation to or link to the journal article and/or a summary of the results in a standard format, such as the ICH E-3 summary format, that includes a description of the trial design and methodology, results of primary and secondary outcome measures, and safety results. Study results will be recorded in a database in the ICH E-3 format if they are not published in a medical journal within the required time frame.

- Results will include the unique identification number used to register the corresponding trial.
- As a general rule, results will be published within one year of trial completion, unless such publication would compromise publication in a peer-reviewed medical journal or contravene national laws or regulations.

In case of local requirement, additional registration at local registries may also be done by the Sponsor.

24 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol. The Investigator should not implement any deviation from, or changes in, the clinical trial protocol without agreement by the Sponsor, approval by the FDA and prior review and documented approval/favorable opinion from the IRB of an amendment, except where necessary to eliminate an immediate hazard(s) to clinical trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor, and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the FDA and the IRB prior to its implementation, unless there are overriding safety reasons.

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB approval/favorable opinion concerning the revised informed consent form prior to implementation of the change.

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26 APPENDICES

APPENDIX I – FITZPATRICK SKIN TYPE

TYPE I: Pale white skin color that burns easily, strongly; never tans

TYPE II: White skin color that burns easily; tans minimally with difficulty

TYPE III: White skin color that burns moderately; tans moderately, and uniformly

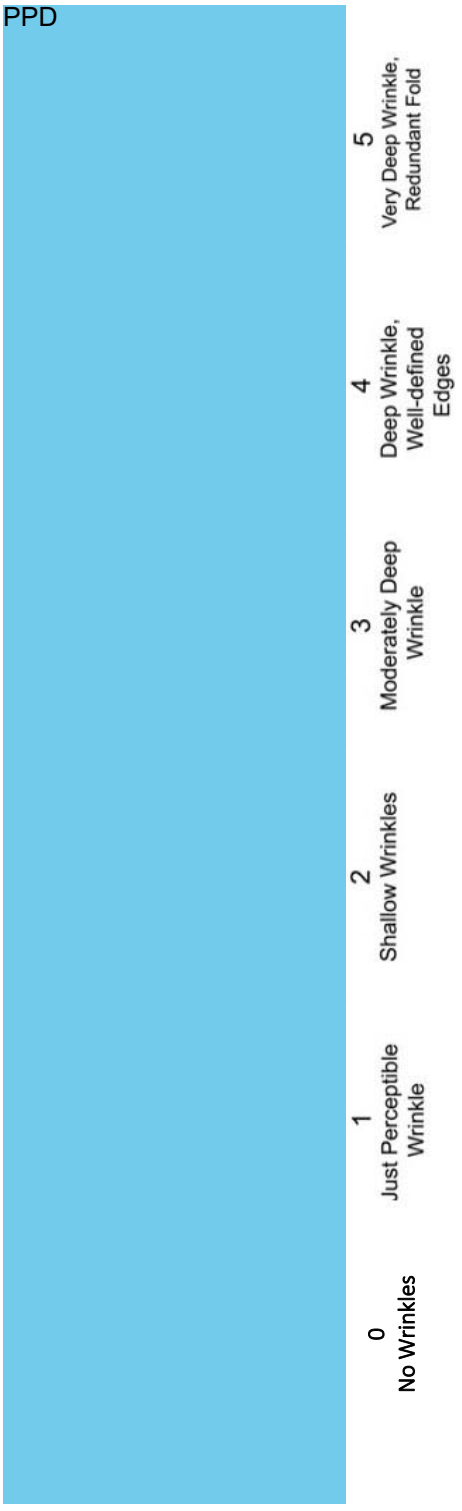
TYPE IV: Beige or lightly tanned skin color that burns minimally; trans easily, and moderately

TYPE V: Moderate brown or tanned skin color that rarely burns; tans profusely (dark brown)

TYPE VI: Dark brown or black skin color that never burns; tans profusely (deep brown or black)

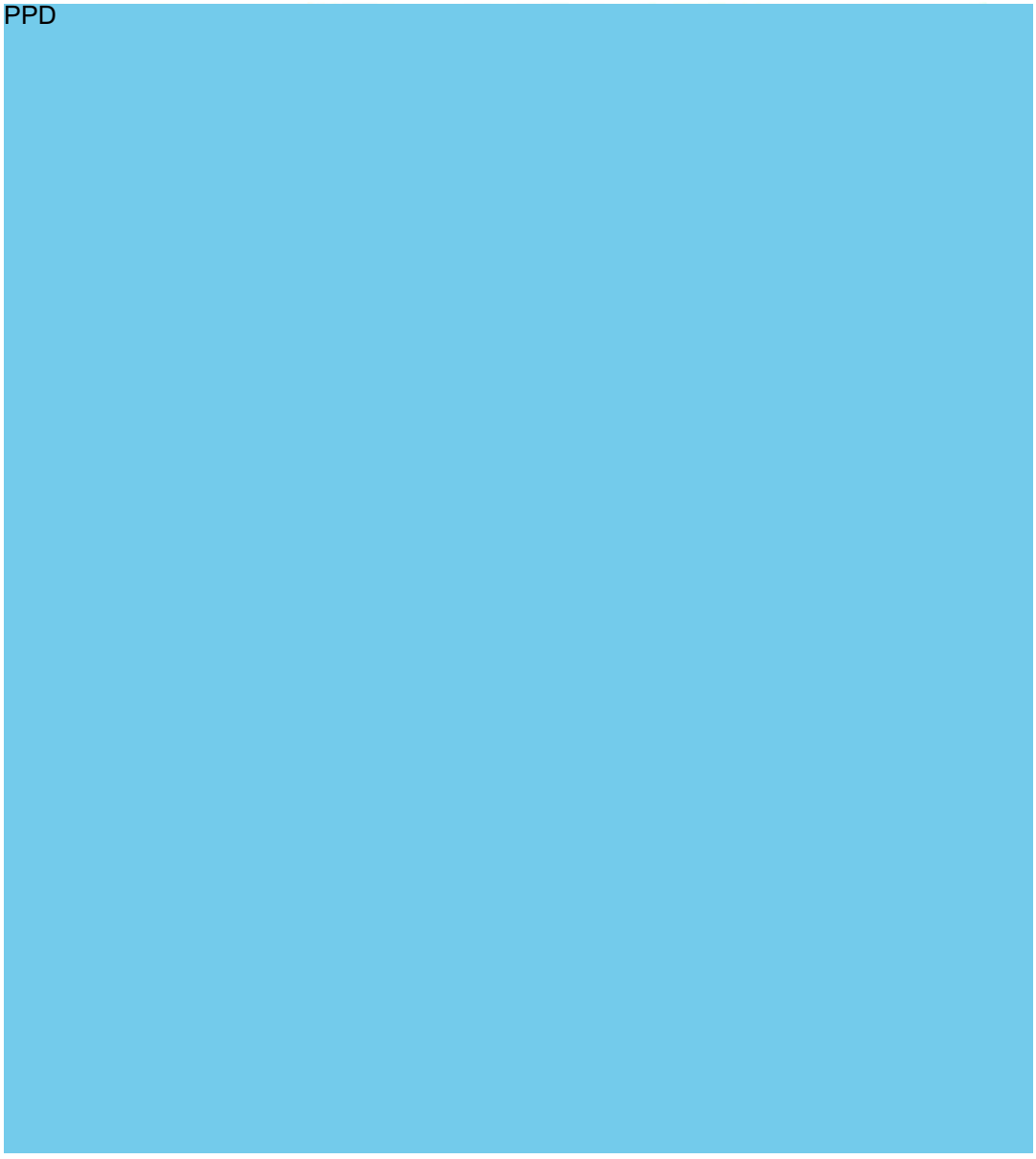
From: Fitzpatrick TB. The validity and practicality of sun-reactive skin Types I through VI [editorial]. Arch Dermatol. 1988;124(6):869-871.

APPENDIX II – NASOLABIAL FOLD WRINKLE ASSESSMENT SCALE



APPENDIX III – ASSESSMENT SCALE FOR OTHER FACIAL WRINKLES

Cheek Folds



0 = No Wrinkles
1 = Just perceptible wrinkle
2 = Shallow wrinkles
3 = Moderately deep wrinkle
4 = Deep wrinkle, well defined edges
5 = Very deep wrinkle, redundant fold

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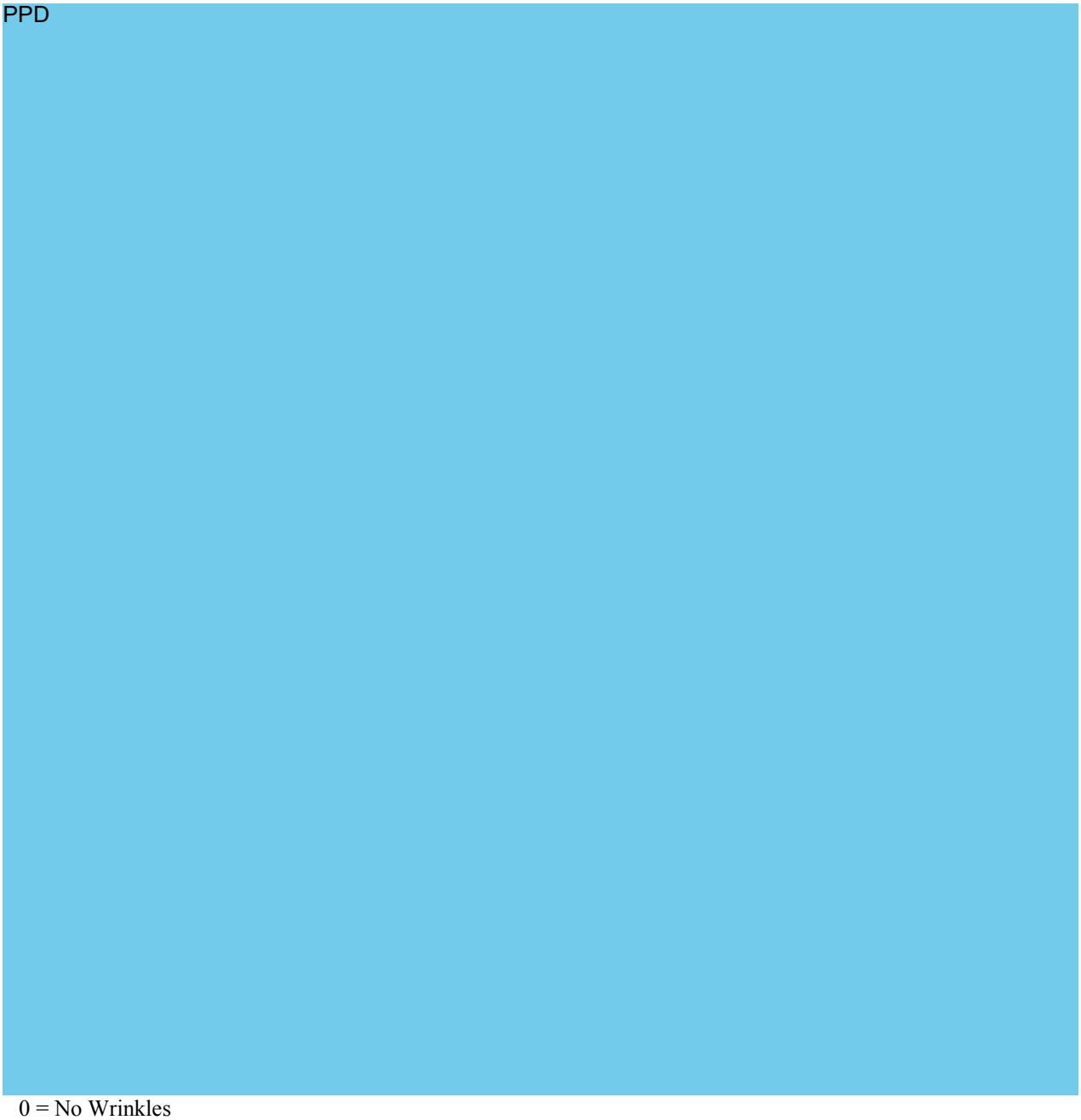
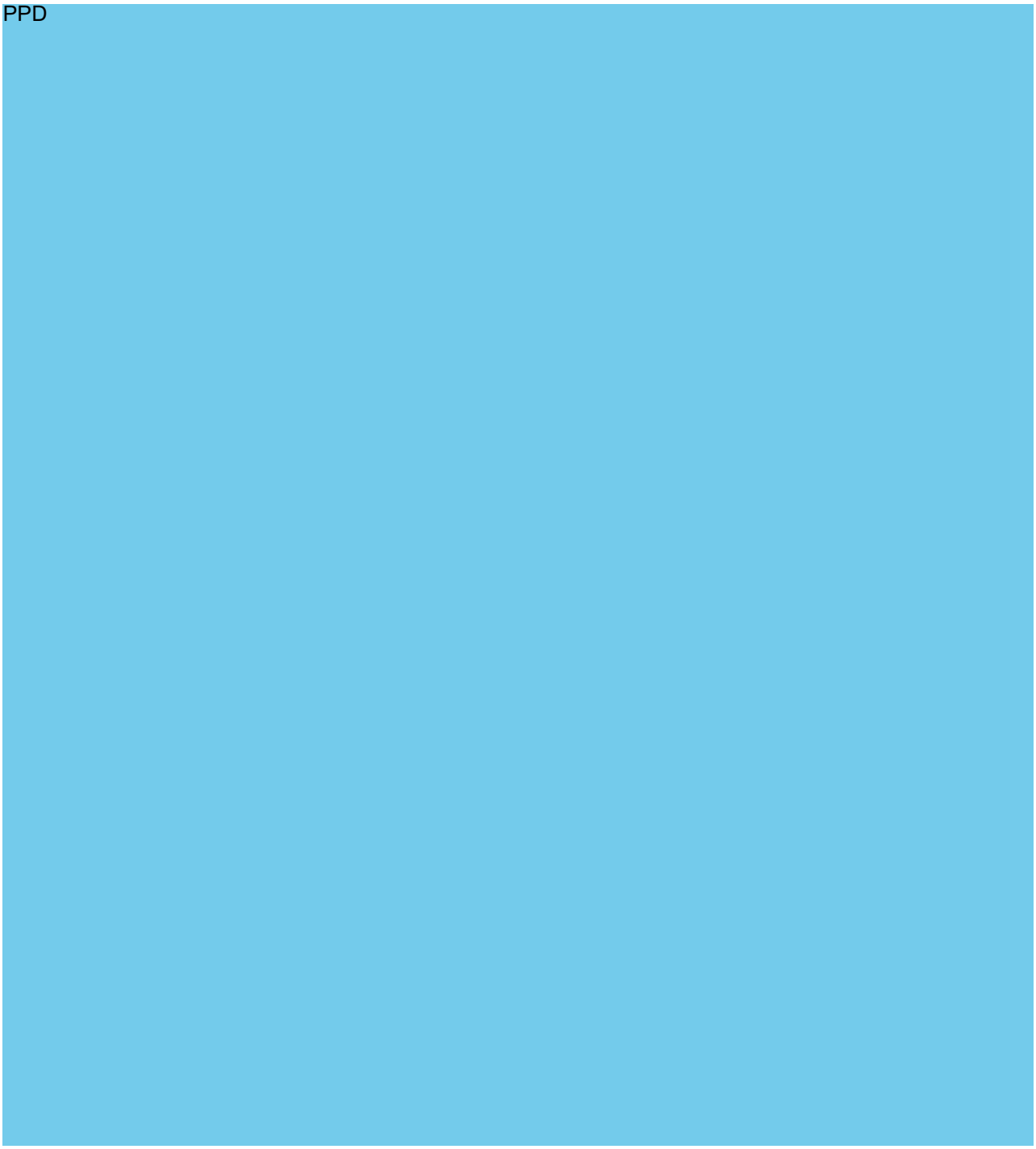
Marionette Lines



0 = No Wrinkles
1 = Just perceptible wrinkle
2 = Shallow wrinkles
3 = Moderately deep wrinkle
4 = Deep wrinkle, well defined edges
5 = Very deep wrinkle, redundant fold

Used with permission of Gottfried Lemperle

Chin Crease



0 =No Wrinkles
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4 =Deep wrinkle, well defined edges
5 =Very deep wrinkle, redundant fold

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APPENDIX IV – AMERICAN SOCIETY OF ANESTHESIOLOGISTS' PHYSICAL STATUS CLASSIFICATION SYSTEM

P1	A normal healthy patient
P2	A patient with mild systemic disease
P3	A patient with severe systemic disease
P4	A patient with severe systemic disease that is a constant threat to life
P5	A moribund patient who is not expected to survive without the operation
P6	A declared brain-dead patient whose organs are being removed for donor purposes

Signature History

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