Statistical Analysis Plan

Clinical Trial Number: **43CHSA1803**

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1 Study Information

1.1 Background

1.1.1 Study design

This is a randomized, multi-center, evaluator-blinded, no-treatment controlled study of Sculptra for correction of Midface Volume Deficit and/or Midface Contour Deficiency in subjects of Chinese origin, men or women aged 18 years or older.

For Group A, after screening, eligible subjects will be treated from day 1 and followed up for 24 months.

For Group B, the study includes two phases as follows:

Main study phase: It is randomized, evaluator-blinded and no-treatment controlled. After screening, all eligible subjects will be randomized either to the Treatment Group or the Control Group in a 2:1 ratio. All the subjects will be followed up for 12 months.

Extension study phase: After the main study phase, the Treatment Group and Group A will be followed up for additional 12 months.

Each Treating Investigator will enroll 1 or 2 subjects as Group A. Before start of enrolment into Group B, the injection technique will be evaluated by the Sponsor or designee of Sponsor and performed after the subjects in Group A for each investigator have received their first treatment and second treatment. If treatments are found to be correctly performed, no further training is needed, there are no outstanding questions regarding the injection technique and no other corrective actions are identified, the enrolment in Group B can start for that investigator.

Each subject assigned to Group A and Treatment Group will receive up to 4 injection sessions with 5 (±1) weeks intervals. Study treatments should be stopped if optimal midface augmentation has been obtained or a maximum of 4 injection sessions completed. Optimal midface augmentation is defined as the best possible aesthetic result that can be obtained for an individual study participant, as agreed upon by the treating investigator and subject.

Subjects assigned to the Control Group will not receive treatment during the study.

For more details regarding the study, and references, see the Clinical Study Protocol (MA-39381).

1.1.2 Number of subjects and randomization

The study will be performed at approximately 8 sites in China and approximately 32 subjects in Group A and 189 subjects in group B will be enrolled. Approximately 189 subjects in group B will be randomized in a 2:1 ratio to treatment with Sculptra (Treatment Group) or to no treatment (Control Group). The randomization list will be stratified by site.

1.2 Study objectives

- To evaluate the effectiveness of Sculptra in the treatment of Midface Volume Deficit and/or Midface Contour Deficiency.
- To evaluate the safety of Sculptra in the treatment of Midface Volume Deficit and/or Midface Contour Deficiency.

1.3 Effectiveness assessments

For all assessments regarding subjects in Group A and subjects in Treatment Group in Group B, baseline will be defined as the observation that is closest to but prior to study treatment on Day 1. Likewise, change from baseline will be calculated as the value at a given time point minus the baseline value. For the Control Group baseline is defined as the observation that is closest to but prior to randomization.

1.3.1 Medicis Midface Volume Scale (MMVS)

MMVS is a four-point scale assesses the fullness of the midface from Fairly Full (1) to Substantial Loss of Fullness (4) as described below. The blinded evaluator will rate the subject's right and left midface for severity of volume deficiency using the MMVS at screening, baseline, 6, 9, 12, 18 and 24 months in Group A and Treatment Group, and at screening, baseline 6, 9 and 12 months in Control Group. The treating investigator will do the MMVS evaluation at all visits in each group. The blinded evaluator and treating investigator will conduct their MMVS assessments using a photographic scale.

Table 1. Medicis Midface Volume Scale

MMVS	
1	Fairly full midface; cheek prominence projected beyond the infraorbital rim at 45-degree view.
2	Mild loss of fullness in midface area; flatness of midface; cheek prominence at or behind infraorbital rim. May have slight presence of tear trough but not extending past mideye. Can start to see minimum volume loss of anterior cheek.
3	Moderate loss of fullness with slight hollowing below malar prominence; presence of the nasojugal groove extending past mideye.
4	Substantial loss of fullness in the midface area, clearly apparent hollowing below malar prominence; evidenced by significant indentation in the midface area.

1.3.2 3D Digital Imaging Analysis

The measurement of volume change in the midface (right and left combined) from baseline will be calculated by 3D digital image analysis at 6, 9, 12, 18 and 24 months in Group A and Treatment Group, and at 6, 9 and 12 months in Control Group.

1.3.3 Global Aesthetic Improvement Scale (GAIS)

The 5-graded Global Aesthetic Improvement Scale (GAIS) will be used to assess the aesthetic improvement of the midface fullness of both sides of the live subject as compared to photographs taken before treatment. Each midface side will be rated separately. The treating investigator and the subject will, independently of each other, respond to the question: "How would you describe the aesthetic improvement of the midface fullness for each side today compared to the photos taken before treatment?" GAIS will be assessed by treating investigator and subjects at each follow up visit.

Table 2. Global Aesthetic Improvement Scale

Rating	Definition (for treating investigator)
Very much improved	Optimal cosmetic result for the implant in this subject.
Much improved	Marked improvement in appearance from the original condition, but not completely optimal for this subject.
Improved	Obvious improvement in appearance from the original condition.
No change	The appearance is essentially the same as original condition.
Worse	The appearance is worse than the original condition.

1.3.4 Subject satisfaction questionnaire

Subjects will be asked about their satisfaction with the treatment outcome using a questionnaire at 6, 9, 12, 18 and 24 months in Group A and Treatment Group.

1). Do you think your Cheek Volume Deficit and/or Contour Deficiency has been improved with the treatment? Yes/No

2). Do you think that the overall result of the treatment looks natural? Yes/No

3). Would you say that the study treatment?

- ☐ Surpass your expectations
- ☐ Meet your expectations
- ☐ Do not meet your expectations
- ☐ You did not have any specific expectations before the injections

4). Do you think that the treatment brings you more? *(tick all boxes that apply)*

- ☐ Youth
- ☐ Beauty
- ☐ Harmony
- ☐ Symmetrical appearance
- ☐ Pep/Liveliness/Freshened look
- ☐ Self esteem /confidence

5). Would you say that you feel more attractive? Yes/No

6). How do you feel about yourself since the treatment was performed?

- ☐ Very much better
- ☐ Much better
- ☐ Somewhat better
- ☐ The Same
- ☐ Worse; if worse, please explain why:

7). Overall, how satisfied are you with the treatment result?

- ☐ Very satisfied
- ☐ Satisfied

- ☐ Somewhat satisfied
- ☐ Not satisfied

8). Did you get any feedback about your look from your family, friends, colleagues?

- ☐ Positive feedback
- ☐ Negative feedback
- ☐ No feedback

9). Would you recommend this treatment to friends? Yes/No

10). Would you like to receive the same treatment again? Yes (exactly the same)/No

1.4 Effectiveness endpoints

1.4.1 Primary effectiveness endpoint

Percentage of responders, defined by at least 1 point improvement from baseline on the MMVS on both sides of the face concurrently, as measured by the blinded evaluator at 12 months in both Treatment Group and Control group.

1.4.2 Secondary effectiveness endpoints

- Percentage of responders, defined by at least 1 point improvement from baseline on the MMVS on both sides of the face concurrently, as measured by the blinded evaluator at 6, 9, 18 and 24 months in Treatment Group, and at 6 and 9 months in Control Group.
- Percentage of responders, defined by at least 1 point improvement from baseline on the MMVS on both sides of the face concurrently, as measured by the treating investigator at 6, 9, 12, 18 and 24 months in Treatment Group, and at 6, 9 and 12 months in Control Group.
- Volume change from baseline over time of the right and left midface areas combined, as measured by digital 3D photography at 6, 9, 12, 18 and 24 months in Treatment Group, and at 6, 9 and 12 months in Control Group.
- Percentage of responders, defined by having “Improved”, “Much improved” or “Very much improved” according to the Global Aesthetic Improvement Scale (GAIS) on both sides of the face combined, as assessed by the subject and the treating investigator at 6, 9, 12, 18 and 24 months in Treatment Group, and at 6, 9 and 12 months in Control Group.
- Percentage of subjects in each response category of each question in the subject satisfaction questionnaire in Treatment Group at 6, 9, 12, 18 and 24 months.

Note: Time of the Follow up visits at 6, 9, 12, 18 and 24 months is calculated from baseline/randomization.

1.5 Safety assessments

The methods for collecting safety data are described in Section 8 of the Clinical Study Protocol (MA-39381) and include assessments of anticipated injection related reactions as collected in Subject Diary, Adverse Events (AE) and Serious Adverse Events (SAE). Laboratory assessments will be performed at screening for all subjects. In Group A and Treatment Group, it will also be taken at 12 months visit or at early termination if termination occurs before 12 months visit.

A two-point scale (“Yes” or “No” response) will be used for the causality assessments of AE and SAE. The Treating Investigator should be asked to indicate a response to each of the following questions in the eCRF:

“Do you consider that there is a reasonable possibility that the event may have been caused by the study product?”

“Do you consider that there is a reasonable possibility that the event may have been caused by the study product injection procedure?”

If any of these questions is answered with a ‘Yes’, the AE will be considered related. These assessments will also be reviewed by the Sponsor. In the case of a disagreement, the AE will be classified as “Related”.

1.6 Safety endpoints

- Incidence, intensity, duration, and onset of adverse events (AEs) collected throughout the study.
- Incidence, intensity, and number of days of anticipated injection related reactions, collected using 4-week subject diaries after each treatment session for the Treatment Group.

2 Statistical Methods

2.1 General methods

All summaries for Group A and B will be done separately. The analyses described in the following sections primarily concern Group B. However, Group A will be analyzed in the same way, except that no hypothesis testing will be performed for Group A (there is only one treatment group in Group A), and the analyses will be done based on observed cases (i.e. no imputation of missing values will be done).

All statistical analyses, including summary tables and data listings, will be performed using the SAS® system (version 9.4 or later).

In general, effectiveness, safety, demography, subject characteristics, and treatment related variables will be presented using descriptive statistics. Continuous data will be summarized using n (number of observations), mean, standard deviation, median, minimum and maximum value, while categorical data will be presented by frequency and percentage. Graphs may be used as appropriate.

All statistical testing will be two-sided and performed at a significance level of 5%. Confidence intervals will be 2-sided and constructed using 95% confidence level.

If any SAP changes are needed before database lock (DBL), the SAP will be amended. Changes after DBL will be documented in the Clinical Study Report (CSR). If additional supportive or exploratory analyses are requested after SAP approval, this will not require amendment of the SAP, but these additional analyses will be described in the CSR. Some of the analyses detailed here may be more explicit or in some aspects different from those stated in the protocol. In case of differences, this SAP supersedes the statistical sections in the protocol.

All study data from the CRFs as well as derived variables will be provided in subject data listings.

2.2 Analysis Populations

The following populations will be defined:

- Safety
  - Includes all subjects in Group B who were treated with Sculptra or randomized to no-treatment group. Subjects are analyzed based on the as treated principle.
- Full Analysis Set (FAS)
  - Includes all subjects in Group B who were treated with Sculptra or randomized to no-treatment group. Subjects are analyzed according to the randomisation assignment.
- Per Protocol (PP)
  - Includes all subjects in FAS that comply to the protocol procedures with no deviations that can affect the evaluation of the primary variable.

The FAS population is the primary population for all effectiveness analyses. All safety analyses will be based on the Safety population.

For Group A, all analyses will be performed based on all subjects.

2.3 Study subjects

2.3.1 Subject disposition

The number of subjects in each study population (i.e. FAS, PP, and Safety) will be summarized by site and in total.

The disposition of subjects (including reasons for screening failures and withdrawals) will be presented by treatment group and in total. Subject accountability will be presented by treatment and visit.

2.3.2 Withdrawals and Protocol deviations

All withdrawn subjects will be listed individually, including at least subject number, date and reason for withdrawal, and last visit performed. Subjects with CSP deviations will be listed individually, including subject number and observed deviation. Depending on the seriousness of the deviation, Group B subjects might be excluded from the PP population, which shall be documented prior to database lock.

For this study, the protocol deviations that will exclude Group B subjects from PP are identified (but not limited to) in Table 3 below.

Table 3. Protocol deviations

		Deviation
GENERAL		
		Visit out-of-window
	*	Follow-up at Month 12 after baseline performed earlier than 2 weeks before or later than 4 weeks after the scheduled visit for the treatment and control group
EFFECTIVENESS		
		Primary effectiveness endpoint
	*	No baseline MMVS by blinded evaluator available
	*	MMVS by blinded evaluator missing at Month 12 after baseline
		Treatment
	*	Treatment not performed according to randomization
OTHER		
		Inclusion/exclusion criteria
	*	Violate any inclusion or exclusion criteria considered to have substantial effect on the primary effectiveness endpoint
		Concomitant medication/procedures
	*	Take any prohibited concomitant medication/procedures considered to have substantial effect on the primary effectiveness endpoint

Deviations from the SAP will be documented in the CSR.

2.3.3 Demographic characteristics

Subject demographic and baseline characteristics data will be summarized for the FAS population by treatment group and in total.

2.3.4 Medical and surgical history, concomitant medication/procedures

All summaries will be done by treatment group based on the FAS population. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. Medical History will be coded according to MedDRA.

The number and percent of subjects reporting medical history, and the number of events will be summarized by system organ class (SOC), in total and for ongoing events.

The number and percentage of subjects reporting concomitant medications will be summarized by treatment. In addition, the number and percent of subjects reporting concomitant medication, and the number of drugs (total number and the number of ongoing drugs), will be summarized by reason. The same summary will be done for concomitant procedures/treatments. Also, the number and percent of subjects, and the number of drugs, will be summarized by ATC code. Concomitant medications that started due to an AE will be summarized separately.

2.4 Effectiveness analysis

2.4.1 Datasets analyzed

All effectiveness variables will be analyzed using the FAS population. The primary analysis will be repeated using the PP population. If it is deemed necessary, other analyses will be repeated using the PP population.

2.4.2 Handling of missing data

Different assumptions regarding the missing data will be used. For the primary effectiveness analysis, missing values in the FAS will be assumed to be missing due to lack of effect. Therefore missing data up to the Month 12 visit will be imputed using the baseline observation carried forward (BOCF) method. As an alternative approach, missing data will be assumed to be unrelated to treatment effect. To impute data under this assumption, missing data up to the Month 12 visit will be imputed using the hot deck method. Both of these alternatives will estimate the effectiveness of the treatment policy (irrespective of use of not allowed treatments, procedures, or medications) rather than the true, clinical treatment effect.

To obtain an estimate of the true, clinical treatment effect, the primary effectiveness analysis will be performed using the PP population.

All other endpoints will be analysed on available data (observed cases - OC), i.e. no imputations will be done.

Use of Hot Deck

Each missing value in MMVS at Month 12 visit (recipient) will be imputed with a non-missing (observed) value from a subject randomly selected from the same imputation class (donor). Imputation classes will be defined based on treatment group (Sculptra or Control group), baseline MMVS value (2, 3 or 4 as assessed by the blinded evaluator) and age group (<55 vs. ≥55). Alternative imputation classes may be used if deemed necessary.

2.4.3 Primary effectiveness analysis

The percentage of responders (a responder will be defined as a subject with at least 1 point improvement from baseline MMVS on both sides of the face concurrently) will be calculated at 12 months after baseline both in Treatment Group (denoted as $\pi_{12M\ Sculptra}$) and Control Group (denoted as $\pi_{12M\ Control}$) based on the blinded evaluator's assessment.
The null hypothesis H_0: $\pi_{12M\ Sculptra} = \pi_{12M\ Control}$ will be tested against the alternative hypothesis H_1: $\pi_{12M\ Sculptra} \neq \pi_{12M\ Control}$ by using a Fisher's exact test at a significance level of 5%. In addition, for each group and also for the difference between the two groups the two-sided 95% confidence intervals around the estimates of the percentage of responders will also be calculated. The treatment will be deemed a success if the p-value for the treatment difference on the primary endpoint is less than 0.05 (i.e. the proportion of responders is statistically significantly larger in the Treatment Group compared to the Control Group).

Subgroup analyses by site will be performed for the primary analysis. The difference in responder rates along with the 95% confidence intervals will be presented for each each site. No formal statistical testing will be carried out for the subgroup analysis.

In addition, to obtain an estimate of the true clinical treatment effect, the primary analysis will be re-run using the PP analysis set.

2.4.4 Secondary effectiveness analysis

The percentage of responders based on the MMVS on both sides of the face concurrently will also be derived at all applicable follow-up visits for both the blinded evaluator's assessment and the treating investigator's assessment respectively. The response rates and their 95% confidence interval will be presented by visit and group.

Fisher's exact test will be used to compare the response rates in the Treatment group versus the Control group based on the blinded evaluator's assessment and the treating investigator's assessment respectively. In other words, the null hypothesis
H_0: $\pi_{t,Sculptra} = \pi_{t,\ Control}$ will be tested against the alternative hypothesis
H_1: $\pi_{t,Sculptra} \neq \pi_{t,\ Control}$ for each of the timepoints t = Month 6 and Month 9 for the blinded evaluator's assessment, and t = Month 6, Month 9 and Month 12 for the treating investigator's assessment.

The volume change in the midface area as compared with baseline (right and left sides combined) obtained by 3D imaging will be presented descriptively by treatment for all applicable follow-up visits.

GAIS (by treating investigator and subject) and satisfaction with the treatment outcome will be analyzed descriptively.

2.5 Safety Analysis

For Group B all safety variables will be summarized descriptively based on the safety population.
For Group A all safety variables will be summarized descriptively based on all subjects.

2.5.1 Extent of exposure

Data of extent of exposure and treatment procedure will be summarized per treatment session and also in total. Other relevant injection parameters, such as injection depth, injection method will be presented in a similar way.

2.5.2 Subjects Diary

Number and percentage of subjects reporting anticipated injection related reactions, as collected in diaries will be presented in total and by maximum intensity for each treatment session (only Sculptra treated subjects). Graphs will be generated to illustrate the incidence over time. Number of days with the event will be summarized using mean, SD, min, max and median.

2.5.3 Adverse events

All AEs will be coded according to MedDRA.

A summary of all AEs, by Treatment Group, will be provided, which will include:

- Number of subjects with at least one AE and number of events (in total as well as serious AEs)
- Number of subjects with at least one related AE and number of events (in total as well as serious AEs)
- Number of subjects with at least one unrelated AE and number of events (in total as well as serious AEs)
- Number of subjects who did not have an AE.

Related AEs as well as number of subjects with related AEs will be summarised by SOC, PT and intensity. In addition, for related AEs the number of days to onset and the duration of event will be summarised by SOC and PT using mean, SD, min, max and median. Action taken for related AEs will also be summarized. Related AEs will be summarized per treatment session.

Serious AEs will be listed.

Late onset (>21 days) AEs will be listed.

Related AEs with late onset (>21 days after most recent treatment) will be listed, if any.

Non-related AEs will be summarised by SOC, PT, and intensity and by Treatment Group.

Time to onset of an AE will be derived as the start date minus the date of most recent treatment. For the Control group date of randomization will be used instead of most recent treatment. If the start date is missing, it will be assumed that the AE started on the day of most recent treatment. If the start month is available but not the day, it will be assumed that the AE started on the first day of the month.

Duration of an AE will be derived as the stop date minus the start date + 1. If the start date is missing, it will be assumed that the AE started on the day of most recent treatment or date of randomization for the Control group. If the start month is available but not the day, it will be assumed that the AE started on the first day of the month. If the stop month is available but not the day, it will be assumed that the AE stopped on the last day of the month. Completely missing stop dates will not be imputed and therefore no duration will be calculated in these cases. Instead, the number of AEs that were ongoing at the end of the study will be given.

2.6 Interim Analysis

An interim analysis will be performed when the month 12 visit is completed for all the subjects (main study phase).

2.7 Determination of Sample Size

There are no available clinical data for Sculptra studied under conditions similar to the current study. However, based on what is seen in clinical studies of injectable fillers in the facial areas, it is

reasonable to assume a response rate of at least 60% in the Sculptra Treatment Group at Month 12. For the no treatment Control Group, response rate of 25.8% has been observed in an ongoing clinical trial in China. Based on this, it was assumed that the response rate will be maximum 30% in the no-treatment Control Group at Month 12.

With a sample size of 100 subjects treated with Sculptra and 50 subjects in the no-treatment control group, Fisher's Exact test will have approximately 90% power to detect difference between the anticipated percentage of responders at a 5% significance level (two-sided). To account for 20% drop-outs, approximately 126 will be randomized to the Sculptra group and approximately 63 to the control group.

2.8 Changes in the Analysis Planned in the Protocol

3 Planned Tables and Figures

Group B:

Table 3-1 Analysis populations, by site

Site	Subject Id	Safety		FAS		PP	
		n	%	n	%	n	%
Site 1							
Site 2							
…							
Total (N)							

% = (n/N)*100

Table 3-2 Group A, by site

Site	Subject Id	Group A	
		n	%
Site 1			
Site 2			
…			
Total (N)			

% = (n/N)*100

Table 3-3 – Subject disposition, Group B

Number of subjects		Sculptra	Control	Total
Screened		-	-	
Screening failures		-	-	
Randomized				
Treated			-	
Completed primary endpoint				
Completed				
Withdrawn				
Reason for withdrawal	Withdrawn consent			
	Lost to follow-up			
	Medical reason			
	Other			

% screening failures is based on total number of screened subjects.
In all other cases: % is based on the number of randomized subjects in each treatment group

Table 3-4 – Subject disposition, Group A

Number of subjects		Group A
Treated		
Completed		
Withdrawn		
Reason for withdrawal	Withdrawn consent	
	Lost to follow-up	
	Medical reason	
	Other	

Table 3-5 Subject accountability, Group B

Number of subjects	Sculptra				Control			
	Expected	Performed	Missed	Withdrawn	Expected	Performed	Missed	Withdrawn
Baseline / Treatment 1								
Treatment 2 (optional)								
Treatment 3 (optional)								
Treatment 4 (optional)								
Week 5 after last treatment								
Month 6 after baseline								
Month 9 after baseline								
Month 12 after baseline								
Month 18 after baseline								
Month 24 after baseline								

Note: The main study consists of visits up to 12 months

Table 3-6 Subject accountability, Group A

Number of subjects	Expected	Performed	Missed	Withdrawn
Baseline / Treatment 1				
Treatment 2 (optional)				
Treatment 3 (optional)				
Treatment 4 (optional)				
Week 5 after last treatment				
Month 6 after baseline				
Month 9 after baseline				
Month 12 after baseline				
Month 18 after baseline				
Month 24 after baseline				

Note: The main study consists of visits up to 12 months

Table 3-7 Withdrawals, Group B

Subject Number	Treatment/Control	Date of withdrawal	Reason for withdrawal	Last visit	Date of last visit

Table 3-8 Withdrawals, Group A

Subject Number	Date of withdrawal	Reason for withdrawal	Last visit	Date of last visit

Table 3-9 – Protocol deviations affecting Per Protocol population (PP)

Protocol deviation	Subject Number(s)	Number of deviations

Table 3-10 – Protocol deviations not affecting Per Protocol population (PP), Group B

Protocol deviation	Number of subjects

Table 3-11 – Protocol deviations, Group A

Protocol deviation	Number of subjects

Group B

Table 3-12 Summary of demographics and baseline characteristics, FAS

Characteristics		Parameter	Group B		
			Sculptra	Control	Total
Age (years)		n			
		Mean (SD)			
		Median			
		Range			
Gender					
	Female	n (%)			
	Male	n (%)			
	Total	N			
Ethnic origin					
	Han Chinese	n (%)			
	Other[1)]	n (%)			
	Total	N			
Baseline BMI		n			
		Mean (SD)			
		Median			
		Range			
MMVS Blinded	Right side				
	Score 2	n (%)			
	Score 3	n (%)			
	Score 4	n (%)			
	Total	N			
MMVS Blinded	Left side				
	Score 2	n (%)			
	Score 3	n (%)			
	Score 4	n (%)			
	Total	N			

Table 3-13: Subjects reporting medical history/concurrent diseases and number of conditions by MedDRA System Organ Class (SOC), FAS

Primary SOC	Sculptra N = XX						Control N = XX					
	Total			Whereof ongoing at study start			Total			Whereof ongoing at study start		
	Subjects		Number of conditions	Subjects		Number of conditions	Subjects		Number of conditions	Subjects		Number of conditions
	n	%		n	%		n	%		n	%	
Vascular disorders												
Total												

% = (n/N)*100

Note: A single subject may have reported medical history/concurrent diseases by more than one primary SOC category

Table 3-14: Prior use of facial fillers or implants, FAS

	Sculptra N = XX			Control N = XX		
	Subjects		Number of procedures	Subjects		Number of procedures
	n	%		n	%	
Total						

% = (n/N)*100

Note: A single subject may have had several fillers or implants

Table 3-15: Prior use of other facial dermatological procedures, FAS

	Sculptra N = XX			Control N = XX		
	Subjects		Number of procedures	Subjects		Number of procedures
	n	%		n	%	
Total						

% = (n/N)*100

Note: A single subject may have had several facial dermatological procedures

Table 3-16: Subjects reporting concomitant medication, FAS

	Sculptra N = XX				Control N = XX			
	No		Yes		No		Yes	
	n	%	n	%	n	%	n	%
Ongoing at study start								
Initiated during study								
Total								

% = (n/N)*100

Note: A single subject might have had concomitant medication ongoing at study start and initiated during study

Table 3-17: Subjects reporting concomitant medication and number of medications by reason, FAS

Reason for concomitant medication	Sculptra N = XX				Control N = XX			
	Subjects		Number of medications		Subjects		Number of medications	
	n	%	Total	Ongoing at study end	n	%	Total	Ongoing at study end
Related Adverse Event								
Unrelated Adverse Event								
Medical History								
Other								
Total								

% = (n/N)*100

Note: A single subject might have reported concomitant medication for several reasons

Table 3-18: Subjects reporting concomitant medication and number of medications by ATC code, FAS

ATC code	ATC text	Sculptra N = XX			Control N = XX		
		Subjects		Number of medications	Subjects		Number of medications
		n	%		n	%	
Total							

% = (n/N)*100
Note: A single subject may have reported several types of concomitant medication

Concomitant procedures

In a similar way as for conmed

Efficacy

Table 3-19: MMVS responder rate at Month 12 by treatment (both sides of the face combined), Blinded Evaluator

Population	Visit	Treatment	Subjects	Responders		95% Confidence interval			p-value
			N	n	%				
FAS[1)]	Month 12	Sculptra							
		Control							
		Difference							
PP[2)]	Month 12	Sculptra							
		Control							
		Difference							
FAS[3)]	Month 12	Sculptra							
		Control							
		Difference							

1) Note: Missing values at Month 12 are imputed using the BOCF method.
2) No imputation is used for PP analysis. Only subjects with complete data are included.
3) Note: Missing values at Month 12 are imputed using the Hot deck imputation method.
Note: Responder is defined as a subject with an improvement of at least one grade on the MMVS from baseline
Note: Responder rate (%) = (n/N)*100
Note: P-values for the difference in proportions are based on the Fisher's Exact test.
Note: 95% confidence intervals are two-sided and calculated using the exact interval. For the difference, asymptotic confidence limits are used.

Table 3-20: MMVS responder rate over time (both sides of the face combined), Blinded Evaluator, FAS, OC

Visit	Treatment	Subjects	Responders		95% Confidence interval			p-value
		N	n	%				
Month 6	Sculptra							
	Control							
	Difference							
Month 9	Sculptra							
	Control							
	Difference							
Month 12	Sculptra							
	Control							
	Difference							
Month 18	Sculptra							
Month 24	Sculptra							

Note: Responder is defined as a subject with an improvement of at least one grade on the MMVS from baseline.
Note: Responder rate (%) = (n/N)*100
Note: P-values for the difference in proportions are based on the Fisher's Exact test.
Note: 95% confidence intervals are two-sided and calculated using the exact interval. For the difference, asymptotic confidence limits are used.
Note: The main study consists of visits up to 12 months

Figure 3-1: MMVS responder rate over time (both sides of the face combined), Blinded Evaluator, FAS, OC

Table 3-21: MMVS over time, Blinded Evaluator, FAS, OC

			MMVS								
Visit / Treatment		Side	1 – Fairly full		2 – Mild loss		3 – Moderate loss		4 – Substantial loss		Total
			n	%	n	%	n	%	n	%	N
Baseline	Sculptra	Left									
		Right									
	Control	Left									
		Right									
Month 6	Sculptra	Left									
		Right									
	Control	Left									
		Right									
Month 9	Sculptra	Left									
		Right									
	Control	Left									
		Right									
Month 12	Sculptra	Left									
		Right									
	Control	Left									
		Right									
Month 18	Sculptra	Left									
		Right									
Month 24	Sculptra	Left									
		Right									

% = (n/N)*100

Note: The main study consists of visits up to 12 months

Table 3-22: MMVS responder rate over time (both sides of the face combined), Treating Investigator, FAS, OC

Same as for Blinded Evaluator

Figure 3-2: MMVS responder rate over time (both sides of the face combined), Blinded Evaluator, FAS, OC

Table 3-23: MMVS over time, Treating Investigator, FAS, OC

Same as for Blinded Evaluator

Table 3-24: Volume change (mL) over time (both sides of the face combined) as measured by digital 3D photography, FAS

Visit / Treatment		N	Mean	SD	Median	Minimum	Maximum
Month 6	Sculptra						
	Control						
Month 9	Sculptra						
	Control						
Month 12	Sculptra						
	Control						
Month 18	Sculptra						
Month 24	Sculptra						

Note: The main study consists of visits up to 12 months

Table 3-25: GAIS responder rate over time, (both sides of the face combined), Treating Investigator, FAS, OC

Visit	Treatment	Subjects	Responders		95% Confidence interval		
		N	n	%			
Month 6	Sculptra						
	Control						
Month 9	Sculptra						
	Control						
Month 12	Sculptra						
	Control						
Month 18	Sculptra						
Month 24	Sculptra						

Note: Subjects with a GAIS rating of 'Very much improved', 'Much improved', or 'Improved' are defined as responders.
Note: Responder rate (%) = (n/N)*100
Note: 95% Confidence Intervals are two-sided confidence intervals calculated using the exact interval.
Note: The main study consists of visits up to 12 months

Figure 3-3: GAIS responder rate over time, (both sides of the face combined), Treating Investigator, FAS, OC

Table 3-26: GAIS over time, Treating Investigator, FAS, OC

		GAIS										
Visit / Treatment	Side	Very much improved		Much improved		Improved		No change		Worse		Total
		n	%	n	%	n	%	n	%	n	%	N
Month 6 Sculptra	Left											
	Right											
Control	Left											
	Right											
Month 9 Sculptra	Left											
	Right											
Control	Left											
	Right											
Month 12 Sculptra	Left											
	Right											
Control	Left											
	Right											
Month 18 Sculptra	Left											
	Right											
Month 24 Sculptra	Left											
	Right											

% = (n/N)*100

Note: The main study consists of visits up to 12 months

Table 3-27: GAIS responder rate over time (both sides of the face combined), Subject assessment, FAS, OC

Same as for Treating Investigator

Figure 3-4: GAIS responder rate over time, (both sides of the face combined), Subject assessment, FAS, OC

Table 3-28: GAIS over time, Subject assessment, FAS, OC

Same as for Treating Investigator

Table 3-29: Subject Satisfaction Questionnaire, Question 1), Subjects randomized to Sculptra, FAS, OC

Do you think your Cheek Volume deficit and/or Contour Deficiency has been improved with the treatment?					
Visit (after baseline)	Yes		No		Total
	n	%	n	%	N
Month 6					
Month 9					
Month 12					
Month 18					
Month 24					

% = (n/N)*100

Note: The main study consists of visits up to 12 months

Table 3-30: Subject Satisfaction Questionnaire, Question 2), Subjects randomized to Sculptra, FAS, OC

Do you think that the overall result of the treatment looks natural?					
Visit (after baseline)	Yes		No		Total
	n	%	n	%	N
Month 6					
Month 9					
Month 12					
Month 18					
Month 24					

% = (n/N)*100

Note: The main study consists of visits up to 12 months

Table 3-31: Subject Satisfaction Questionnaire, Question 3), Subjects randomized to Sculptra, FAS, OC

Would you say that the study treatment:									
Visit (after baseline)	Surpass your expectations		Meet your expectations		Do not meet your expectations		You did not have any specific expectations before the injections		Total
	n	%	n	%	n	%	n	%	N
Month 6									
Month 9									
Month 12									
Month 18									
Month 24									

% = (n/N)*100

Note: The main study consists of visits up to 12 months

Table 3-32: Subject Satisfaction Questionnaire, Question 4), Subjects randomized to Sculptra, FAS, OC

Do you think that the treatment brings you more:												
Visit (after baseline)	Youth		Beauty		Harmony		Symmetrical appearance		Pep/Liveliness / Freshened look		Self-esteem/ confidence	
	n	%	n	%	n	%	n	%	n	%	n	%
Month 6												
Month 9												
Month 12												
Month 18												
Month 24												

% = (n/N)*100 where N=number of filled in questionnaires
Note: All that applies are ticked
Note: The main study consists of visits up to 12 months

Table 3-33: Subject Satisfaction Questionnaire, Question 5), Subjects randomized to Sculptra, FAS, OC

Would you say that you feel more attractive?					
Visit (after baseline)	Yes		No		Total
	n	%	n	%	N
Month 6					
Month 9					
Month 12					
Month 18					
Month 24					

% = (n/N)*100
Note: The main study consists of visits up to 12 months

Table 3-34: Subject Satisfaction Questionnaire, Question 6), Subjects randomized to Sculptra, FAS, OC

How do you feel about yourself since the treatment was performed?											
Visit (after baseline)	Very much better		Much better		Somewhat better		The same		Worse		Total
	n	%	n	%	n	%	n	%	n	%	N
Month 6											
Month 9											
Month 12											
Month 18											
Month 24											

% = (n/N)*100
Note: The main study consists of visits up to 12 months

Table 3-35: Subject Satisfaction Questionnaire, Question 7), Subjects randomized to Sculptra, FAS, OC

Overall, how satisfied are you with the treatment result?									
Visit (after baseline)	Very satisfied		Satisfied		Somewhat satisfied		Not satisfied		Total
	n	%	n	%	n	%	n	%	N
Month 6									
Month 9									
Month 12									
Month 18									
Month 24									

% = (n/N)*100
Note: The main study consists of visits up to 12 months

Table 3-36: Subject Satisfaction Questionnaire, Question 8), Subjects randomized to Sculptra, FAS, OC

Did you get any feedback about your look from your family, friends and colleagues?							
Visit (after baseline)	Positive feedback		Negative feedback		No feedback		Total
	n	%	n	%	n	%	N
Month 6							
Month 9							
Month 12							
Month 18							
Month 24							

% = (n/N)*100
Note: The main study consists of visits up to 12 months

Table 3-37: Subject Satisfaction Questionnaire, Question 9), Subjects randomized to Sculptra, FAS, OC

Would you recommend this treatment to friends?					
Visit (after baseline)	Yes		No		Total
	n	%	n	%	N
Month 6					
Month 9					
Month 12					
Month 18					
Month 24					

% = (n/N)*100
Note: The main study consists of visits up to 12 months

Table 3-38: Subject Satisfaction Questionnaire, Question 10), Subjects randomized to Sculptra, FAS, OC

Would you like to receive the same treatment again?					
Visit (after baseline)	Yes		No		Total
	n	%	n	%	N
Month 6					
Month 9					
Month 12					
Month 18					
Month 24					

% = (n/N)*100
Note: The main study consists of visits up to 12 months

Treatment procedure

Table 3-39: Volume injected (both cheeks combined), Subjects randomized to Sculptra, Safety population

Volume injected (mL)						
Visit	N	Mean	SD	Median	Minimum	Maximum
Baseline / Treatment 1						
Treatment 2 (optional)						
Treatment 3 (optional)						
Treatment 4 (optional)						
Total exposure						

Table 3-40: Treatment procedure (both cheeks combined, all treatments combined), Subjects randomized to Sculptra, Safety population

Characteristic	Answer	Statistic	Result
Was 1 ml of lidocaine added to the vial before treatment?	Yes	n (%)	
	No	n (%)	
Local anaesthesia used?	Yes	n (%)	
	No	n (%)	
If local anaesthesia used	Topical cream	n (%)	
	Local infiltration	n (%)	
Needle gauge	25 G	n (%)	
	26 G	n (%)	
Depth of injection	Deep dermis	n (%)	
	Subcutaneous layer	n (%)	
	Supraperiosteal layer	n (%)	
	Other	n (%)	
Primary injection method	Linear Retrograde	n (%)	
	Serial Puncture	n (%)	
	Fanning	n (%)	
	Other	n (%)	
Post-treatment care (ice and massage) according to study protocol?	Yes	n (%)	
	No	n (%)	
Any deviation from the treatment procedure as	Yes	n (%)	

Characteristic	Answer	Statistic	Result
described in the study protocol?			
	No	n (%)	

List deviations:…

Table 3-41: Treatment procedure (both cheeks combined), Subjects randomized to Sculptra, Safety population

Characteristic	Visit	Statistic	Answer	Result
Was 1 ml of lidocaine added to the vial before treatment?	Baseline / Treatment 1	n (%)	Yes	
		n (%)	No	
	Treatment 2 (optional)	n (%)	Yes	
		n (%)	No	
	Treatment 3 (optional)	n (%)	Yes	
		n (%)	No	
	Treatment 4 (optional)	n (%)	Yes	
		n (%)	No	
Local anaesthesia used?	Baseline / Treatment 1	n (%)	Yes	
		n (%)	No	
	Treatment 2 (optional)	n (%)	Yes	
		n (%)	No	
	Treatment 3 (optional)	n (%)	Yes	
		n (%)	No	
	Treatment 4 (optional)	n (%)	Yes	
		n (%)	No	
If local anaesthesia used	Baseline / Treatment 1	n (%)	Topical cream	
		n (%)	Local infiltration	
	Treatment 2 (optional)	n (%)	Topical cream	
		n (%)	Local infiltration	
	Treatment 3 (optional)	n (%)	Topical cream	
		n (%)	Local infiltration	
	Treatment 4 (optional)	n (%)	Topical cream	
		n (%)	Local infiltration	
Needle gauge	Baseline / Treatment 1	n (%)	25 G	
		n (%)	26 G	

Characteristic	Visit	Statistic	Answer	Result
	Treatment 2 (optional)	n (%)	25 G	
		n (%)	26 G	
	Treatment 3 (optional)	n (%)	25 G	
		n (%)	26 G	
	Treatment 4 (optional)	n (%)	25 G	
		n (%)	26 G	
Depth of injection	Baseline / Treatment 1	n (%)	Deep dermis	
		n (%)	Subcutaneous layer	
		n (%)	Supraperiosteal layer	
		n (%)	Other	
	Treatment 2 (optional)	n (%)	Deep dermis	
		n (%)	Subcutaneous layer	
		n (%)	Supraperiosteal layer	
		n (%)	Other	
	Treatment 3 (optional)	n (%)	Deep dermis	
		n (%)	Subcutaneous layer	
		n (%)	Supraperiosteal layer	
		n (%)	Other	
	Treatment 4 (optional)	n (%)	Deep dermis	
		n (%)	Subcutaneous layer	
		n (%)	Supraperiosteal layer	
		n (%)	Other	
Primary injection method	Baseline / Treatment 1	n (%)	Linear Retrograde	
		n (%)	Serial Puncture	
		n (%)	Fanning	
		n (%)	Other	
	Treatment 2 (optional)	n (%)	Linear Retrograde	
		n (%)	Serial Puncture	
		n (%)	Fanning	
		n (%)	Other	
	Treatment 3 (optional)	n (%)	Linear Retrograde	
		n (%)	Serial Puncture	

Characteristic	Visit	Statistic	Answer	Result
		n (%)	Fanning	
		n (%)	Other	
	Treatment 4 (optional)	n (%)	Linear Retrograde	
		n (%)	Serial Puncture	
		n (%)	Fanning	
		n (%)	Other	
Post-treatment care (ice and massage) according to study protocol?	Baseline / Treatment 1	n (%)	Yes	
		n (%)	No	
	Treatment 2 (optional)	n (%)	Yes	
		n (%)	No	
	Treatment 3 (optional)	n (%)	Yes	
		n (%)	No	
	Treatment 4 (optional)	n (%)	Yes	
		n (%)	No	
Any deviation from the treatment procedure as described in the study protocol?	Baseline / Treatment 1	n (%)	Yes	
		n (%)	No	
	Treatment 2 (optional)	n (%)	Yes	
		n (%)	No	
	Treatment 3 (optional)	n (%)	Yes	
		n (%)	No	
	Treatment 4 (optional)	n (%)	Yes	
		n (%)	No	

List deviations:…

Safety

Table 3-42: Anticipated injection related reactions recorded in the subject diary after first treatment (both sides of the face combined), Safety population

Event	Treatment with Sculptra N=XX							
	Subjects		Maximum intensity					
			Mild		Moderate		Severe	
	n	%	n	%	n	%	n	%
Pain								
Tenderness								
Localized redness								
Bruising								
Hematoma								
Edema								
Other								
No diary events								

% = (n/N)*100

Note: Percentages for intensity categories are based on the number of subjects reporting the symptom.

Table 3-43: Number of days anticipated injection related reactions recorded in subject diary after first treatment (both sides of the face combined), Safety population

Event	Treatment with Sculptra N=XX					
	n	Mean	SD	Minimum	Median	Maximum
Pain						
Tenderness						
Localized redness						
Bruising						
Hematoma						
Edema						
Other						

Figure 3-5: Proportion of subjects with observed anticipated injection related reactions (to any intensity level) after first treatment with Sculptra (both sides of the face combined), Safety population

Same tables and figure for treatment sessions two, three and four

Table 3-44: Brief summary of all AEs, Main study, Safety population

	Sculptra, N=XX			Control, N=YY		
	Subjects n	%	Events #	Subjects n	%	Events #
Adverse Events reported, total						
Total, serious						
Total, non-serious						
AEs related to injection procedure and/or product, total						
Serious						
Non-serious						
Unrelated AEs, total						
Serious						
Non-serious						
Subjects with no AE reported						

% = (n/N)*100

Table 3-45: Related Adverse Events by MedDRA SOC and preferred term, Main study, subjects randomized to Sculptra, Safety population

Primary SOC	Preferred Term	Subjects n	%	Events #	Maximal Intensity		
					Mild	Moderate	Severe
Total							

% = (n/number of subjects in the Safety population)*100

Table 3-46: Related Adverse Events by MedDRA SOC and preferred term, by treatment session, Main study, subjects randomized to Sculptra, Safety population

Visit	Primary SOC	Preferred Term	Subjects n	Subjects %	Events #	Maximal Intensity Mild	Maximal Intensity Moderate	Maximal Intensity Severe
Baseline / Treatment 1								
Treatment 2 (optional)								
Treatment 3 (optional)								
Treatment 4 (optional)								

% = (n/number of subjects in the Safety population)*100

Table 3-47: Time to onset from last treatment of related AEs,
Main study, subjects randomized to Sculptra, Safety population

Preferred term	Time to onset (days)					
	n	Mean	SD	Min	Median	Max
Total						

NA = Not Applicable

Table 3-48: Duration of related AEs,
Main study, subjects randomized to Sculptra, Safety population

Preferred term	Duration (days)					
	n	Mean	SD	Min	Median	Max
Total						

NA = Not Applicable

Table 3-49: Action taken of related AEs,
Main study, subjects randomized to Sculptra, Safety population

Preferred term	Action taken			
	None	Medication treatment	Non-pharmacological treatment or other procedures / tests	Withdrawn
Total				

Table 3-50: Unrelated Adverse Events by MedDRA SOC and preferred term,
Main study, Subjects randomized to Sculptra, Safety population

Primary SOC	Preferred Term	Subjects		Events	Maximal Intensity		
		n	%	#	Mild	Moderate	Severe
Total							

% = (n/number of subjects in the Safety population)*100

Table 3-51: Unrelated Adverse Events by MedDRA SOC and preferred term, Main study, Subjects randomized to no-treatment control, Safety population

Primary SOC	Preferred Term	Subjects n	Subjects %	Events #	Maximal Intensity Mild	Maximal Intensity Moderate	Maximal Intensity Severe
Total							

% = (n/number of subjects in the Safety population)*100

AE tables for Extension phase

Same tables as above when applicable

AE tables for Combined phases

Same tables as above when applicable

Group A

The same tables as for Group B, when applicable

GALDERMA	Title **43CHSA1803 Statistical Analysis Plan - Sculptra China**	Doc id **MA-40407**

SIGNATURES PAGE

Date	Signed by
2019-10-23 07:15	[redacted]
Justification	Approved by Owner

2019-10-23 08:02	[redacted]
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