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Statistical Analysis Plan

Clinical Trial Number: 43CH1508

A randomized, multi-center, evaluator-blinded study to evaluate the efficacy and safety of Restylane Defyne compared to Restylane for correction of moderate to severe nasolabial folds

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1 Study Information

1.1.1 Study design

This is a randomized, evaluator-blinded study to evaluate the efficacy and safety of Restylane Defyne (with lidocaine) compared to Restylane (without lidocaine) for correction of moderate to severe nasolabial folds (NLFs) in subjects of Chinese origin, men or women aged 18 years or older.

The study will be conducted at 4 sites located in China, and subjects with a Wrinkle Severity Rating Scale (WSRS) score of either 3 or 4 on both sides, as assessed by the Blinded Evaluator, will be enrolled. The subjects will be followed for up to 14.5 months.

Blinding will be accomplished by a Blinded Evaluator, to whom randomization and treatment are concealed, to evaluate the WSRS score. The treating Investigator will not be blinded. To minimize inter-observer variability, a subject should preferably be assessed by the same individual at the initial Baseline determinations and all follow-up evaluations.

For more details regarding the study, and references, please see the Clinical Study Protocol (CSP), MA-29708.

1.1.2 Number of subjects and randomization

Approximately 175 subjects will be enrolled and treated with Restylane Defyne in one NLF and Restylane in the opposite NLF, as randomly assigned to one of the two possible treatment sequences:

- Restylane Defyne in the subject's right NLF followed by Restylane in the subject's left NLF, or
- Restylane in the subject's right NLF followed by Restylane Defyne in the subject's left NLF.

1.2 Study Objectives

1.2.1 Primary Objective

The primary objective is to evaluate the efficacy of Restylane Defyne compared to Restylane in correction of NLFs by comparing the response rates based on the WSRS score, as assessed by the Blinded Evaluator at 6 months after last treatment.

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1.2.3 Safety objectives

The safety objectives are:

- To evaluate the safety of Restylane Defyne and Restylane during the whole study by collecting adverse events (AEs).

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1.3 Efficacy Assessments

1.3.1 Wrinkle Severity Rating Scale (WSRS)

WSRS is a 5-grade validated photograph-based scale designed for quantifying facial folds. Scoring of fold severity is based on a visual assessment of the length and depth of the NLF at a certain time point, not in comparison to the Baseline or pre-treatment appearance, see Table 1-1. Each score in the WSRS is exemplified by a photograph of NLFs.

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Table 1-1: Wrinkle Severity Rating Scale (WSRS)

Grade	Description
1	**Absent:** No visible fold; continuous skin line.
2	**Mild:** Shallow but visible fold with a slight indentation; minor facial feature. Implant is expected to produce a slight improvement in appearance.
3	**Moderate:** Moderately deep fold; clear facial feature visible at normal appearance but not when stretched. Excellent correction is expected from injectable implant.
4	**Severe:** Very long and deep fold; prominent facial feature; less than 2 mm visible fold when stretched. Significant improvement is expected from injectable implant.
5	**Extreme:** Extremely deep and long fold; detrimental to facial appearance; 2 to 4 mm V-shaped fold when stretched. Unlikely to have satisfactory correction with injectable implant alone.

The Blinded Evaluator will perform assessment of each NLF using the WSRS at Screening, Baseline, and each follow-up visit.

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1.3.4 Photography

Digital photographs, taken of each subject pre-treatment at visits when treatment is performed, CCI

1.4 Efficacy Endpoints

1.4.1 Primary efficacy endpoint

The primary efficacy endpoint is the response rate based on the WSRS score, as assessed by the Blinded Evaluator at 6 months after last treatment.

Response rate is defined as the percentage of subjects with at least one ($\geq$ 1) grade improvement on the WSRS.

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1.5 Safety Assessments

The methods for collecting the safety data are described in Section 8 of the CSP and include assessments of CCI [redacted] laboratory assessments, ECG-screening, adverse events (AEs), serious adverse events (SAEs), and device deficiency.

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A two-point scale ('*Yes*' or '*No*') will be used to assess causality of AEs, serious as well as non-serious. The investigator shall be asked to indicate a response to each of the following questions in the electronic case report form (eCRF):

- *"Do you consider that there is a reasonable possibility that the event may have been caused by the study product?"* and
- *"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 are answered with a '*Yes*', the AE will be considered related.

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Each AE will also be assessed for causal relationship and seriousness by the Sponsor, in order to fulfill regulatory requirements. In case of a disagreement, the AE will be considered '*Related*'.

Digital photographs, taken at all follow-up visits, will be used to document AEs in the treated area. If necessary, the photo should be taken when AEs occur. Note that no covering make-up should be used on the photographs.

Any device deficiencies discovered in relation to treatment at Baseline and Week 4 follow-up visits will be recorded.

1.6 Safety Endpoints

Safety endpoints include:

(i) Incidence, intensity, duration and time to onset of related treatment emergent AEs collected during the whole study

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2 Statistical Methods

2.1 General Methods

All statistical analyses, including summary tables and data listings, will be performed using the SAS® system (version 9). Confidence intervals will be two-sided and constructed at the 95% confidence level.

Continuous endpoints will be summarized using descriptive statistics, e.g., mean, median, standard deviation, minimum, and maximum values. Categorical endpoints will be presented in frequency tables with number and percentage of observations for each level.

Table/graph shells of data summaries are provided in Appendix A-F and are referenced to in the text. All graphs are only examples and will be updated in the Statistical Analysis Report (SAR) to reflect the study data. Any change made to the finalized Statistical Analysis Plan (SAP) will be documented in the Clinical Study Report (CSR).

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2.2 Analysis Populations

The following populations will be defined:

- Full Analysis Set (FAS) — Includes all subjects who were injected in both NLFs. Subjects are analyzed according to the randomization assignment.
- Per protocol (PP) — Includes all FAS subjects who completed the Month 6 follow-up visit without any major deviations.
- Safety — Includes all subjects who were injected in at least one NLF, based on the as treated principle.

The FAS population is the primary population for all efficacy analyses. If there are any CSP deviations considered to have substantial impact on the efficacy outcome at the Month 6 follow-up visit, a PP population excluding those subjects will be defined. As this is a non-inferiority trial, non-inferiority will need to be shown in both FAS and PP analyses. Safety analysis will be performed based on the Safety population set.

2.3 Study Subjects

2.3.1 Subject disposition

The number and percentage of subjects in each study population (FAS, PP, and Safety) will be summarized by site (including subject number) and in total (Table 4-1). Study population variables will also be presented in a data listing.

The disposition of subjects (Table 4-4) will be presented by site, and in total, including number and percentage of subjects that were

- screened
- treated,
- completed,
- withdrawn.

The number of completed and withdrawn subjects will also be accounted for by visit, along with number of expected subjects, number of screening failures, number of treated subjects, and subjects with performed WSRS assessment (Table 4-5).

Reasons for screening failures and withdrawals, if applicable, will be summarized. All withdrawn subjects will be listed individually, including site and subject number, date of treatment, last visit performed, date and reason for withdrawal (Table 4-7). Screening failures

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will be listed by site number, subject screening number, date of screening, and reason for screening failure (Table 4-6).

2.3.2 Protocol deviations

Subjects with CSP deviations will be listed individually, including subject number and observed deviation, and visit number if applicable (Table 4-3). Depending on the seriousness of the deviation, the subject might be excluded from the PP population (Table 4-2), which shall be documented prior to database lock (DBL).

Definition of protocol deviations that will exclude subjects from the PP are defined (but not limited to) in Table 2-1 below.

Table 2-1: Protocol deviations

		Deviation
GENERAL		
		Visit out-of-window
	*	Follow-up at 6 months after last treatment performed earlier than 1 week before the scheduled visit or later than 2 weeks after the scheduled visit.
		Visit not done
	*	Follow-up at 6 months not done.
EFFICACY		
		WSRS assessed by Blinded Evaluator
	*	Not done for both NLFs at 6 months after last treatment.
	*	Pre-treatment WSRS not available for both NLFs.
OTHER		
		Inclusion/exclusion criteria
	*	Any inclusion criteria affecting primary efficacy evaluation not met.
	*	Any exclusion criteria affecting primary efficacy evaluation met.
		Treatment
	*	Same product administered in both NLFs at initial treatment or touch-up.
	*	Products administered in the wrong sides at initial treatment or touch-up.

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2.3.3 *Demographics and Baseline characteristics*

Demographic endpoints and subject baseline characteristics will be presented overall (Table 5-1) using descriptive statistics. Gender, ethnic origin, and Baseline WSRS score will be analyzed as categorical end points using number and percentage of subjects. Age and vital sign tests will be summarized by number of subjects, mean, standard deviation, minimum, median, and maximum values. Pre-treatment procedures will be summarized as categorical endpoints by treatment visit (Table 5-2).

2.3.4 *Medical history, and concomitant medication and procedures/treatments*

All summaries will be 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 medical dictionary for regulatory activities (MedDRA).

Medical history/concurrent disease

The number and percentage of subjects reporting any medical history/concurrent disease (relevant or major illness), (Table 5-3), and any previous cosmetic/aesthetic procedures or implants (Table 5-5) will be presented in total.

The number and percentage of subjects reporting medical history/concurrent disease (relevant or major illness), and the number of events will be summarized by System Organ Class (SOC) and in total, for all medical history during the whole study and ongoing at study start (Table 5-4).

Previous cosmetic/aesthetic or implant procedures will be summarized by procedure/product name and procedure/product location using number and percentage of subjects (Table 5-6).

Concomitant medication and procedures/treatments

The number and percentage of subjects reporting concomitant medication ongoing at study start, initiated during study and in total (Table 6-1) will be summarized. In addition, the number and percentage of subjects reporting concomitant medication, and the number of medications (all during study and the number of ongoing medications at study end), will be summarized by reason and in total (Table 6-2). Also, the number and percentage of subjects, and the number of medications, will be summarized by ATC code and in total, along with an ATC text description for medication ongoing at study start (Table 6-3) and initiated during study (Table 6-4).

Concomitant medication taken due to an AE will be summarized by ATC code (along with an ATC text description) and in total using number and percentage of subjects and number of medications, and by MedDRA coded AE and whether the AE is related or not (Table 6-5).

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Concomitant procedures/treatments will be presented using number and percentage of subjects (Table 6-6), as well as by reason and in total using number and percentage of subjects and number of procedures/treatments (Table 6-7).

2.3.5 Extent of exposure

Injection volume (mL), for each treatment visit and in total will be presented by treatment (Table 7-1) using number of subjects, mean, standard deviation, minimum, median, and maximum values. The same summary will also be generated by site and in total (Table 7-4). Within-subject difference (Restylane minus Restylane Defyne) of injected volume (mL) will be presented by treatment visit and in total by number of subjects, mean, standard deviation, minimum, median, and maximum values (Table 7-2).

Injection time (minutes) for each treatment and within-subject difference (Restylane minus Restylane Defyne) in injection time (minutes) will be summarized using number of subjects, mean, standard deviation, minimum, median, and maximum values (Table 7-3).

Optional touch-up treatment eligibility evaluation (*No/Yes*) after initial treatment will be summarized by 3 eligibility questions using number and percentage of subjects (Table 7-5). In addition, number and percentage of subjects receiving touch-up treatment will be presented.

Number and percentage of subjects in each category and in total for injection method (Table 7-6), injection depth (Table 7-7), topical/local anesthesia used (Table 7-8), post-treatment care (Table 7-9), technical problems/device deficiencies (Table 7-10), deviations from the treatment procedure (Table 7-11), and directly observed AEs associated with the injection (Table 7-12) will be presented by treatment visit and treatment.

2.4 Efficacy Analysis

2.4.1 Data sets analyzed

All efficacy 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

As the study design is intra-individual, in which the outcome of both treatments to be compared is available on each subject, it is expected that when a data is missing, it will be missing for both NLFs in most of the cases. A majority of the deviations from the protocol can be expected to affect both NLFs and evaluations of the same subject the same way.

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FAS analyses of WSRS scores in the primary analysis will use multiple imputation method (MI) as the primary method for imputing missing values. Rather than imputing each missing observation by a single value, this approach represents a random sample of the missing values, and therefore accounts for the prediction uncertainty of the unknown missing values. Last observation carried forward (LOCF) will be used as an alternative imputation method.

Safety and PP analyses will be presented based on observed cases, i.e., no imputation of missing values will be performed.

(i) Use of MI

The imputation using MI will assume a Missing Completely at Random (MAR) mechanism. The MI procedure of the SAS® system will be used to generate five sets of data with missing values imputed from observed data. It is expected that the pattern of missing data will be monotonic, with slight deviations being corrected by the Markov Chain Monte Carlo (MCMC) method of the MI procedure. Linear regression will be employed to model the missing WSRS score, with the following covariates included in the imputation model: treatment and non-missing data from earlier time points (Baseline, Week 2, and Month 3). The imputed datasets will be analyzed using the methodology described for the primary analysis of response rates at Month 6. The results from the analysis of the multiple imputed datasets will be presented as appropriate. The seed number to be used will be 431508.

2.4.3 Primary analysis

Non-inferiority testing of Restylane Defyne relative to Restylane will be assessed on the 95% confidence interval approach with a non-inferiority margin of 15%. The confidence interval will be constructed for the difference (Restylane minus Restylane Defyne) in response rates at the 6 months follow-up visit (Table 8-1 and Table 8-2). Non-inferiority will be declared if the two-sided 95% interval is fully below 15%, i.e., the upper bound of the interval is less than 15% in both the FAS and PP populations.

To assess the robustness of the results using the MI method, LOCF will be used as an alternative imputation method. The same summary of primary analysis results will also be presented for observed cases (OC), (Table 8-1).

2.4.4 Subgroup analysis of primary endpoint

Graphical presentation, such as blobbogram, will be used to explore the differences in WSRS response rates between treatments by site, with corresponding 95% confidence intervals (Graph 8-1 and Graph 8-2).

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2.5 Safety Analysis

All safety variables will be summarized descriptively based on the safety population.

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2.5.2 Adverse events

All AEs will be coded according to MedDRA. Treatment emergent adverse events (TEAEs) will be summarized by System Organ Class (SOC) and Preferred Term (PT). The same summaries will be generated for treatment emergent related AEs, severe AEs, AEs leading to discontinuation, and serious AEs (SAEs). An overall summary of number and percentage of subjects with TEAEs reported in total, no TEAEs reported, related and unrelated TEAEs, and the number of events will be compiled (Table 9-5).

For related TEAEs, intensity of the AE will be summarized (Table 9-6). The number of days to onset (Table 9-8) and duration of event (Table 9-7) will be summarized by SOC and PT using number of events, mean, standard deviation, minimum, median, and maximum statistics. Action taken due to a related TEAE will be summarized by SOC, PT, and treatment (Table 9-9) using number of events.

Number and percentage of subjects with unrelated TEAEs and number of events will be presented by SOC, PT and intensity (Table 9-10).

Time to onset of a TEAE will be derived as the start date minus Day 1. If the start date is missing, it will be assumed that the AE started on Day 1.

Duration of a TEAE 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 Day 1. Missing stop date will not be imputed and therefore no duration will be calculated in these cases. Instead, the number of TEAEs that were ongoing at the end of the study will be given.

2.6 Interim Analysis

No interim analysis is planned.

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2.7 Determination of Sample Size

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2.8 Changes in the Analysis Planned in the Protocol

Regarding statistical analysis in general (CSP Section 10.1), no *p*-values will be presented since no actual statistical testing will be performed.

In SAP Section 2.3, a list of protocol deviations disqualifying subjects from PP has been added.

Summaries of demographics and baseline characteristics (CSP Section 10.3) will not be summarized by study product since the same subject will be treated with both products.

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Safety analysis of AEs (CSP Section 10.5) has been clarified.

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3 Reference List

1 Taylor SC, Burgess CM, Callender VD. Efficacy of Variable-Particle Hyaluronic Acid Dermal Fillers in Patients with Skin of Color: A Randomized, Evaluator-Blinded Comparative Trial. Dermatol Surg. 2010 May; 36 Suppl 1:741-749.

2 Weiss R, Bank R, Brandt F. Randomized, Double-Blind, Split-Face Study of Small-Gel-Particle Hyaluronic Acid with and without Lidocaine During Correction of Nasolabial Folds, Dermatol Surg 2010;36:750–759.

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4 Appendix A: Study Subjects

4.1 Analysis Populations

Table 4-1: Analysis populations

Site	Subject number	FAS		PP		Safety	
		n	%	*n*	%	*n*	%
Site 1	1xx-1xx						
Site 2	2xx-2xx						
Site 3	3xx-3xx						
Site 4	4xx-4xx						
Total (N)							

% = *n*/N*100

4.2 Protocol Deviations

Table 4-2: Protocol deviations affecting PP population

Protocol deviation	Subject number	Visit

Table 4-3: Protocol deviations not affecting PP population

Protocol deviation	Subject number	Visit

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4.3 Disposition of subjects

Table 4–4: Disposition of subjects: screened, treated, completed, and withdrawn subjects by site

Site	Screened subjects		Treated subjects		Completed subjects		Withdrawn subjects	
	n	%	*n*	%	*n*	%	*n*	%
Site 1								
Site 2								
Site 3								
Site 4								
Total (N)								

% = *n*/N*100

Table 4–5: Subject accountability by visit

Visit	Expected subjects	Screening failures	Treated subjects	WSRS performed	Completed subjects	Withdrawn subjects
	n	*n*	*n*	*n*	*n*	*n*
Screening						
Baseline (Initial treatment)						
Week 4 follow-up / Optional touch-up treatment						
Week 4 follow-up after touch-up treatment						
Month 3 after last treatment						
Month 6 after last treatment						
Month 9 after last treatment						
Month 12 after last treatment						

% = *n*/N*100

Table 4-6: Summary of screening failures

Site	Subject screening number	Date of screening	Reason for screening failure

Any extra comments here …

Table 4-7: Withdrawn subjects

Site	Subject number	Date of treatment		Last visit performed	Date of withdrawal	Reason for withdrawal
		Initial treatment	Optional touch-up treatment			

Any extra comments here …

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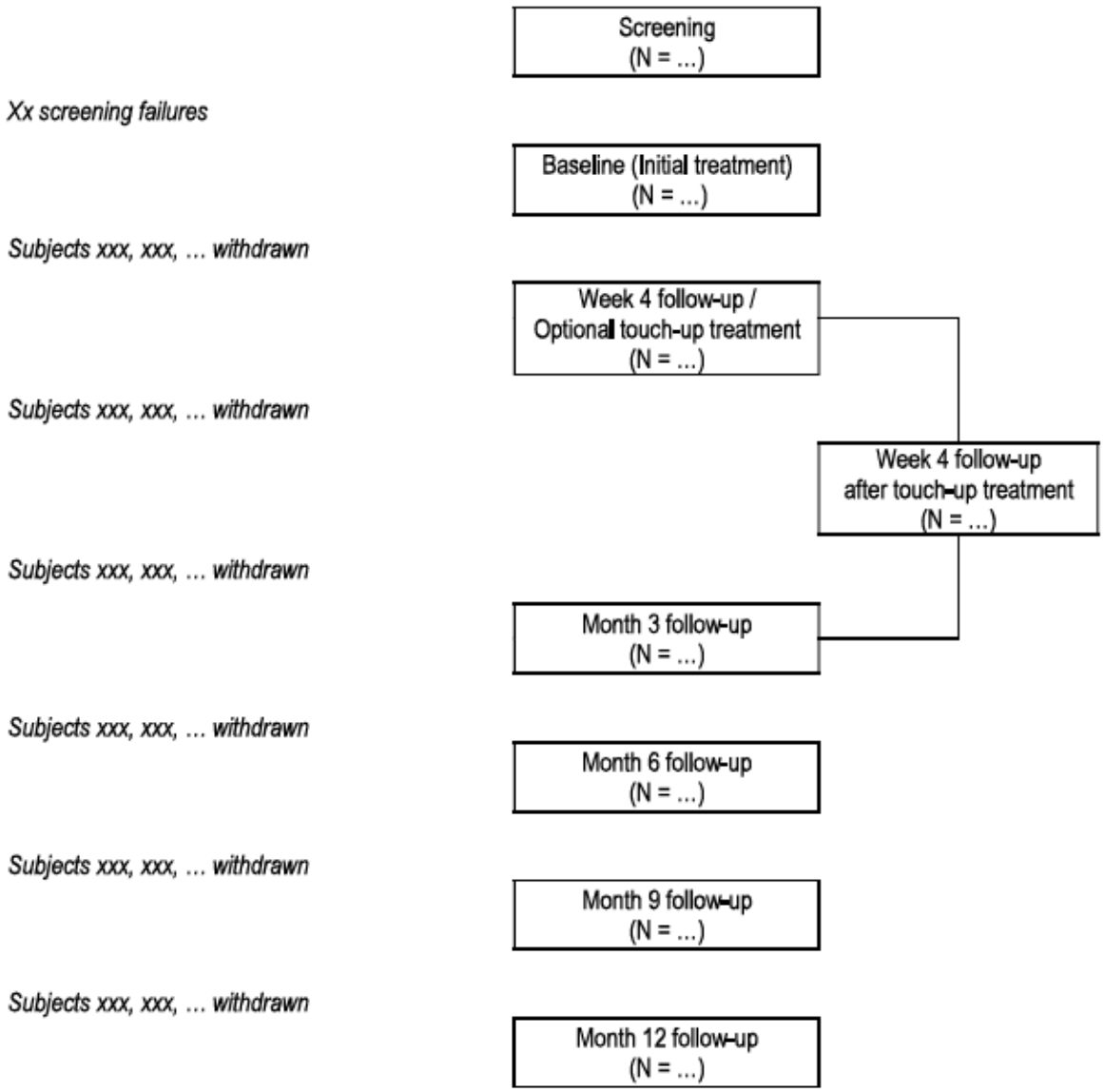
Figure 4-1: Flowchart of study visits and subject accountability



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5 Appendix B: Demographics

5.1 Demographics and Baseline characteristics

Table 5-1: Summary of demographics and Baseline characteristics, all subjects

Treated subjects: N = xxx	
Characteristics	*Result*
Age (years)	
n	
Mean	
SD	
Minimum	
Median	
Maximum	
	n (%)
Gender	
Female	
Male	
Ethnic origin	
Han Chinese	
Other[1)]	
Baseline WSRS score	
Score 3	
Score 4	

% = *n*/N*100

1) Specification of Other: …, …, …..

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Treated subjects: N = xxx	
Vital signs	*Result*
Pulse rate (beats/min)	
n	
Mean	
SD	
Minimum	
Median	
Maximum	
Blood pressure (Systolic mmHG / Diastolic mmHG)	
n	
Mean	
SD	
Minimum	
Median	
Maximum	
Respiratory rate (breaths/min)	
n	
Mean	
SD	
Minimum	
Median	
Maximum	
Temperature (Axillary) (°C)	
n	
Mean	
SD	
Minimum	
Median	
Maximum	

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5.2 Pre-treatment procedures

Table 5-2: Pre-treatment procedures by treatment visit, FAS

	Initial treatment Subjects: N = xxx	Optional touch-up treatment Subjects: N = xxx
Procedure	*n (%)*	*n (%)*
Urine pregnancy test[1]		
Negative		
Positive		
Pre-treatment photography[2]		
No		
Yes		

% = *n*/**N***100

1) If urine pregnancy test wasn't done for some subjects, note the subject number and treatment here.

2) If pre-treatment photography wasn't done for some subjects, note the subject number and treatment here.

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5.3 Medical history

Table 5-3: Subjects reporting medical history/concurrent disease (relevant or major illness), FAS

Any medical history / concurrent disease	No		Yes		Total (N)	
	n	%	*n*	%	*n*	%

% = *n*/N*100

Table 5-4: Subjects reporting medical history/concurrent disease (relevant or major illness) and number of events by MedDRA System Organ Class (SOC), FAS

Primary SOC	All			Ongoing at study start		
	Events	Subjects		Events	Subjects	
	n	*n*	%	*n*	*n*	%
Total[1)]						

% = *n* / number of subjects in FAS (N = xxx) * 100

1) A single subject may have reported medical history (relevant or major illness) by more than one primary SOC category.

Table 5-5: Subjects reporting previous cosmetic/aesthetic procedures or implants, FAS

Any previous cosmetic/aesthetic procedures or implants	No		Yes		Total (N)	
	n	%	*n*	%	*n*	%

% = *n*/N*100

Table 5-6: All previous cosmetic/aesthetic procedures or implants by procedure/product name and procedure/product location, FAS

Procedure/Product name	Procedure/Product location	Subjects	
		n	%

% = *n* / number of subjects in FAS (N = xxx) * 100

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6 Appendix C: Concomitant medication and procedures / treatments

6.1 Concomitant medication

Table 6-1: Subjects reporting concomitant medication, FAS

Concomitant medication	Any concomitant medication?					
	No		Yes		Total (N)	
	n	%	*n*	%	*n*	%
Ongoing at study start						
Initiated during study						
Total						

% = *n*/N*100

Table 6-2: Subjects reporting concomitant medication and number of medications by reason, FAS

Reason for concomitant medication	Subjects		Medications	
			All	Ongoing at study end
	n	%	*n*	*n*
Adverse Event				
Medical History				
Other				
Total[1)]				

% = *n* / number of subjects in FAS (N = xxx) * 100

1) A single subject may have reported concomitant medication for several reasons.

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Table 6–3: Subjects reporting concomitant medication ongoing at study start and number of medications by ATC code, FAS

ATC code	ATC text	Subjects		Medications
		n	%	*n*
Total[1)]				

% = *n* / number of subjects in FAS (N = xxx) * 100

1) A single subject may have reported several types of concomitant medication.

Table 6–4: Subjects reporting concomitant medication initiated during study and number of medications by ATC code, FAS

ATC code	ATC text	Subjects		Medications
		n	%	*n*
Total[1)]				

% = *n* / number of subjects in FAS (N = xxx) * 100

1) A single subject may have reported several types of concomitant medication.

Table 6–5: Subjects reporting concomitant medication taken due to an AE and number of medications, AE by MedDRA Preferred Term (PT) and relatedness, by ATC code, FAS

Concomitant medication				Adverse Event	
ATC code	ATC text	Subjects	Medications	PT	Related AE
		n	*n*		
Total[1)]					

% = *n* / number of subjects in FAS (N = xxx) * 100

1) A single subject may have reported several types of concomitant medication.

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6.2 Concomitant procedures/treatments

Table 6-6: Subjects reporting concomitant procedures/treatments, FAS

Any concomitant procedures/treatments	No		Yes		Total (N)	
	n	%	*n*	%	*n*	%

% = *n*/N*100

Table 6-7: Subjects reporting concomitant procedures/treatments and number of procedures/treatments by reason, FAS

Reason for concomitant procedure/treatment	Subjects		Procedures/treatments
	n	%	*n*
Adverse Event			
Medical History			
Other			
Total[1)]			

% = *n* / number of subjects in FAS (N = xxx) * 100

1) A single subject may have reported procedures/treatments for several reasons.

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7 Appendix D: Treatment procedure

Table 7-1: Volume (mL) injected per subject by treatment visit and treatment, FAS

Treatment visit	Restylane Defyne						Restylane					
	n	*Mean*	*SD*	*Min*	*Median*	*Max*	*n*	*Mean*	*SD*	*Min*	*Median*	*Max*
Initial treatment												
Optional touch-up treatment												
Total												

Table 7-2: Difference within subject (Restylane - Restylane Defyne) of injected volume (mL) by treatment visit, FAS

Treatment visit	Difference within subject					
	n	*Mean*	*SD*	*Min*	*Median*	*Max*
Initial treatment						
Optional touch-up treatment						
Total						

Table 7-3: Injection time (minutes) at initial treatment by treatment, FAS

Treatment visit	Initial treatment					
	n	*Mean*	*SD*	*Min*	*Median*	*Max*
Restylane Defyne						
Restylane						
Difference within subject (Restylane – Restylane Defyne)						

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Table 7-4: Volume (mL) injected per subject by site, treatment visit and treatment, FAS

Site	Restylane Defyne						Restylane					
	n	*Mean*	*SD*	*Min*	*Median*	*Max*	*n*	*Mean*	*SD*	*Min*	*Median*	*Max*
Volume (mL) injected at initial treatment												
Site 1												
Site 2												
Site 3												
Site 4												
Total												
Volume (mL) injected at optional touch-up treatment												
Site 1												
Site 2												
Site 3												
Site 4												
Total												
Total volume (mL) injected												
Site 1												
Site 2												
Site 3												
Site 4												
Total												

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Table 7-5: Optional touch-up treatment eligibility evaluation after initial treatment, FAS

Optional touch-up treatment eligibility	No		Yes		Total (N)	
	n	%	*n*	%	*n*	%
Was optimal correction achieved?[1)]						
Is the subject unwilling to receive a touch-up?						
Does the subject have any ongoing treatment-related Adverse Events?						
Subject received touch-up treatment						

% = *n*/N*100

1) If optimal correction assessment wasn't performed, note it here.

Table 7-6: Injection method used by treatment visit and treatment, FAS

Injection method	Initial treatment				Optional touch-up treatment			
	Restylane Defyne		Restylane		Restylane Defyne		Restylane	
	n	%	*n*	%	*n*	%	*n*	%
Linear threading								
Other[1)]								
Total (N)[2)]								

% = *n*/N*100

1) Specification of Other: …, …, …..

2) A single subject may have been treated by several injection methods.

Table 7-7: Injection depth by treatment visit and treatment, FAS

Injection depth	Initial treatment				Optional touch-up treatment			
	Restylane Defyne		Restylane		Restylane Defyne		Restylane	
	n	%	*n*	%	*n*	%	*n*	%
Middle part of dermis								
Deep layer of dermis								
Other[1)]								
Total (N)[2)]								

% = *n*/N*100

1) Specification of Other: …, …, …..

2) A single subject may have been treated at several depths of the skin layer.

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Table 7-8: Topical or local anesthesia used before optional touch-up treatment injection, FAS

Topical or local anesthesia used[1]	Optional touch-up treatment			
	Restylane Defyne		Restylane	
	n	%	*n*	%
No				
Yes				
Total (N)				

% = *n*/N*100

1) No topical or local anesthesia was used before initial treatment in order to assess pain associated with the injection by VAS.

Table 7-9: Post-treatment care by treatment visit and treatment, FAS

Post-treatment care	Initial treatment				Optional touch-up treatment			
	Restylane Defyne		Restylane		Restylane Defyne		Restylane	
	n	%	*n*	%	*n*	%	*n*	%
None								
Massage								
Ice-pack								
Other[1]								
Total (N)[2]								

% = *n*/N*100

1) Specification of Other: …, …, …..

2) A single subject may have received several types of post-treatment care.

Table 7-10: Technical problems (device deficiencies) associated with injection by treatment visit and treatment, FAS

Any technical problems (device deficiencies)	Initial treatment[1]				Optional touch-up treatment[2]			
	Restylane Defyne		Restylane		Restylane Defyne		Restylane	
	n	%	*n*	%	*n*	%	*n*	%
No								
Yes								
Total (N)								

% = *n*/N*100

1) List technical problems (device deficiencies) for the initial treatment here.

2) List technical problems (device deficiencies) for the touch-up treatment here.

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Table 7-11: Deviations from the treatment procedure as described in the study protocol by treatment visit and treatment, FAS

Any deviations from the treatment procedure	Initial treatment[1]				Optional touch-up treatment[2]			
	Restylane Defyne		Restylane		Restylane Defyne		Restylane	
	n	%	*n*	%	*n*	%	*n*	%
No								
Yes								
Total (N)								

% = *n*/N*100

1) List deviations from the treatment procedure for the initial treatment here.

2) List deviations from the treatment procedure for the touch-up treatment here.

Table 7-12: Directly observed AEs or clinical complications associated with the injection by treatment visit and treatment, FAS

AEs associated with the injection	Initial treatment[1]				Optional touch-up treatment[2]			
	Restylane Defyne		Restylane		Restylane Defyne		Restylane	
	n	%	*n*	%	*n*	%	*n*	%
No								
Yes								
Total (N)								

% = *n*/N*100

1) List directly observed AEs associated with the injection for the initial treatment here.

2) List directly observed AEs associated with the injection for the touch-up treatment here.

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8 Appendix E: Efficacy Evaluation

8.1 Primary analysis

8.1.1 WSRS response rate at 6 months

Table 8-1: Difference in WSRS response rates (Restylane – Restylane Defyne) at 6 months after last treatment, FAS

Analysis	Method	Treatment	N	Improved subjects	RR	$RR_{Restylane} - RR_{Restylane\ Defyne}$		
				n	%	Δ	*95% LCL*	*95% UCL*
Primary	MI[1)]	Restylane Defyne						
		Restylane						
Sensitivity	LOCF	Restylane Defyne						
		Restylane						
Sensitivity	OC	Restylane Defyne						
		Restylane						

% = *n*/N*100
RR = response rate
Δ = difference
LCL = lower confidence level
UCL = upper confidence level
1) See the 95% confidence interval for respective treatment response rate in Table 8-3.

Table 8-2: Difference in WSRS response rate (Restylane – Restylane Defyne) at 6 months after last treatment, PP

Analysis	Method	Treatment	N	Improved subjects	RR	$RR_{Restylane} - RR_{Restylane\ Defyne}$		
				n	%	Δ	*95% LCL*	*95% UCL*
Sensitivity	OC[1)]	Restylane Defyne						
		Restylane						

% = *n*/N*100
RR = response rate
Δ = difference
LCL = lower confidence level
UCL = upper confidence level
1) See the 95% confidence interval for respective treatment response rate in Table 8-4.

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Table 8-3: WSRS response rate at 6 months after last treatment, Blinded Evaluator's assessment, FAS

Treatment	N	Improved subjects	Response rate		
		n	%	*95% LCL*	*95% UCL*
Resylane Defyne					
Restylane					

% = *n*/N*100
LCL = lower confidence level
UCL = upper confidence level

Table 8-4: WSRS response rate at 6 months after last treatment, Blinded Evaluator's assessment, PP

Treatment	N	Improved subjects	Response rate		
		n	%	*95% LCL*	*95% UCL*
Resylane Defyne					
Restylane					

% = *n*/N*100
LCL = lower confidence level
UCL = upper confidence level

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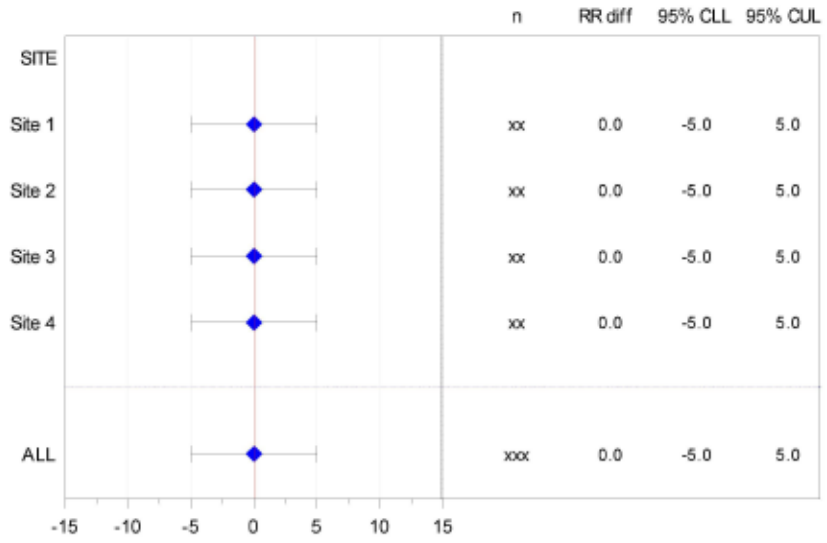
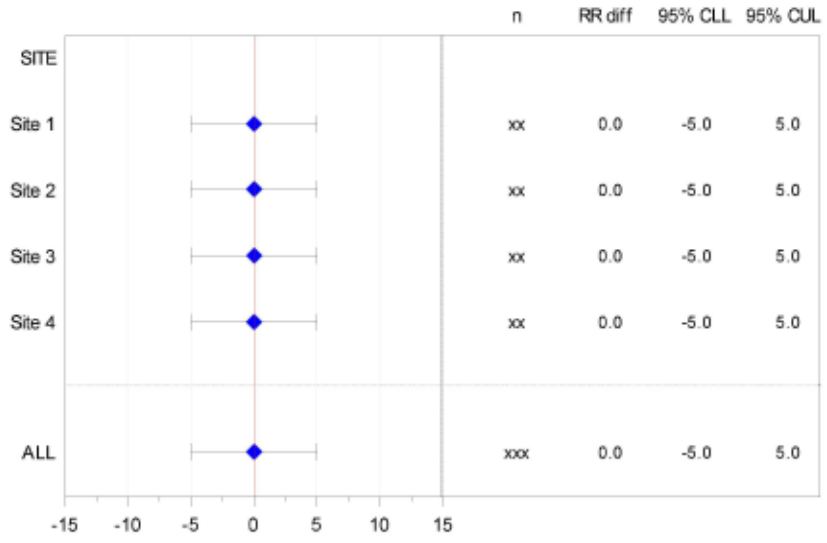
8.1.2 Subgroup analysis of WSRS response rate at 6 months

Graph 8-1: Difference in WSRS response rates (Restylane - Restylane Defyne) at 6 months after last treatment by site, FAS



RR diff = difference in response rates
LCL = lower confidence level
UCL = upper confidence level

Graph 8-2: Difference in WSRS response rates (Restylane - Restylane Defyne) at 6 months after last treatment by site, PP



RR diff = difference in response rates
LCL = lower confidence level
UCL = upper confidence level

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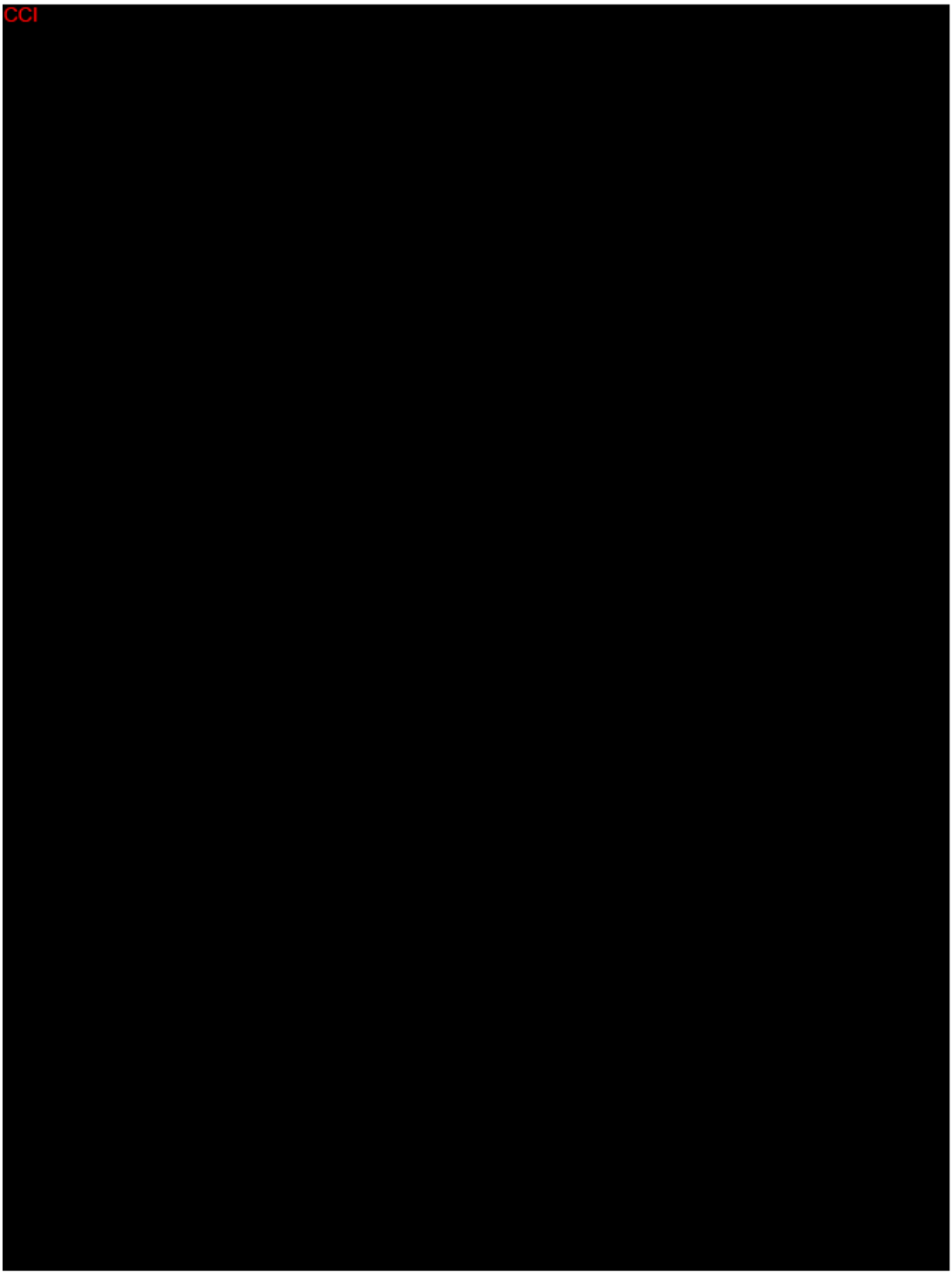

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9 Appendix F: Safety evaluation

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GALDERMA	Title **SAP, 43CH1508, Restylane Defyne NLF**	Doc id **MA-31549**

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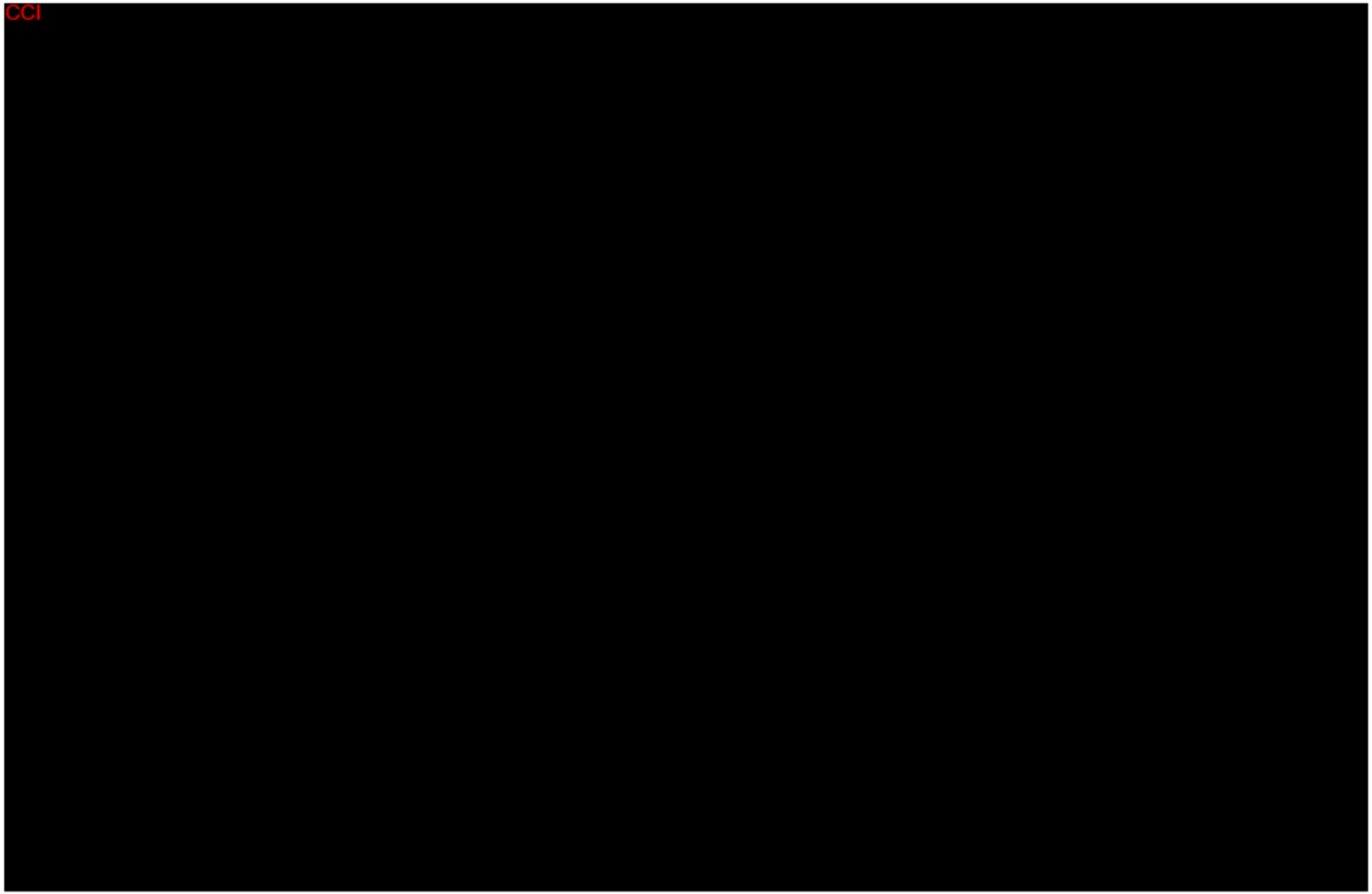

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9.3 Adverse Events

9.3.1 Summary of treatment emergent Adverse Events (TEAEs)

Table 9-5: Brief summary of all TEAEs, Safety population

	Events	Subjects	
	n	*n*	%
Any AEs reported, total			
of which were serious			
AEs related to product and/or injection procedure			
of which were serious			
Restylane Defyne			
Restylane			
AEs unrelated to product and/or injection procedure			
of which were serious			
No AEs reported			

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

9.3.2 Related TEAEs

Table 9-6: Related TEAEs by MedDRA System Organ Class, Preferred Term, and intensity, Safety population

Primary System Organ Class / *Preferred Term*	Restylane Defyne									Restylane									Total		
	Events	Subjects		Intensity						Events	Subjects		Intensity						Events	Subjects	
				Mild		Moderate		Severe					Mild		Moderate		Severe				
	n	*n*	%	*n*	%	*n*	%	*n*	%	*n*	*n*	%	*n*	%	*n*	%	*n*	%	*n*	*n*	%
SOC																					
PT																					
PT																					
...																					
SOC																					
PT																					
PT																					
...																					
All[1)]																					

% = *n* / number of subjects in Safety population (N = xxx) * 100
1) A single subject may have reported several related TEAEs.

Table 9-7: Duration (number of days days) of related TEAEs by MedDRA System Organ Class and Preferred Term, Safety population

Primary System Organ Class *Preferred Term*	**Restylane Defyne**						**Restylane**					
	Events *n*	*Mean*	*SD*	*Min*	*Median*	*Max*	*n*	*Mean*	*SD*	*Min*	*Median*	*Max*
SOC												
PT												
PT												
...												
SOC												
PT												
PT												
...												
All												

If applicable, list TEAEs ongoing at study end here, alternatively create a summary table.

Table 9-8: Time to onset (number of days) from treatment for related TEAEs by MedDRA System Organ Class and Preferred Term, Safety population

Primary System Organ Class *Preferred Term*	Restylane Defyne						Restylane					
	Events *n*	*Mean*	*SD*	*Min*	*Median*	*Max*	*n*	*Mean*	*SD*	*Min*	*Median*	*Max*
SOC												
PT												
PT												
...												
SOC												
PT												
PT												
...												
All												

Any extra comments here…

Table 9-9: Action taken due to related TEAEs by MedDRA System Organ Class and Preferred Term, Safety population

Primary System Organ Class *Preferred Term*	Action Taken							
	Restylane Defyne				Restylane			
	None	Medication treatment	Non-pharmacological treatment or other procedures/tests	Subject withdrawn	None	Medication treatment	Non-pharmacological treatment or other procedures/tests	Subject withdrawn
SOC								
PT								
PT								
...								
SOC								
PT								
PT								
...								
All								

9.3.3 Unrelated TEAEs

Table 9-10: Unrelated TEAEs by MedDRA System Organ Class, Preferred Term, and intensity, Safety population

Primary System Organ Class *Preferred Term*	Restylane Defyne									Restylane									Total		
	Events	Subjects		Intensity						Events	Subjects		Intensity						Events	Subjects	
				Mild		Moderate		Severe					Mild		Moderate		Severe				
	n	*n*	%	*n*	%	*n*	%	*n*	%	*n*	*n*	%	*n*	%	*n*	%	*n*	%	*n*	*n*	%
SOC																					
PT																					
PT																					
…																					
SOC																					
PT																					
PT																					
…																					
All[1)]																					

% = *n* / number of subjects in Safety population (N = xxx) * 100
1) A single subject may have reported several unrelated TEAEs.

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Date	Signed by
2017-02-09 08:54	PPD
Justification	Approved by Owner
2017-02-09 14:10	PPD
Justification	Approved by Technical Expert
2017-02-09 15:03	PPD
Justification	Approved by Technical Expert
2017-02-10 03:01	PPD
Justification	Approved by Project Manager
2017-02-13 08:27	PPD
Justification	Approved by Technical Expert

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