Statistical Analysis Plan

Clinical Trial Number: **43CH1627**

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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 Restylane Defyne for correction of Chin Retrusion. Eligible subjects will be randomized either to the Treatment group or the Control Group in a 3:1 ratio.

Each subject assigned to the Treatment Group will receive an initial treatment on Day 1. A touch-up treatment may be performed 4 weeks after the initial treatment if optimal chin augmentation has not been obtained.

Subjects assigned to the Control Group will not receive treatment at baseline but will return for routine follow-up. At month 6 visit after randomization the subjects in the Control Group will be offered a treatment and an optional touch-up treatment 4 weeks later.

1.1.2 Number of subjects and randomization

Approximately 148 subjects will be randomized in a 3:1 ratio to treatment with Restylane Defyne or to no-treatment Control Group. The randomization will be stratified by center.

1.2 Study objectives

1.2.1 Primary effectiveness objective

The primary objective is to measure the effectiveness of Restylane Defyne versus a no-treatment control in the treatment of Chin Retrusion by comparing the percentage of responders, defined by at least 1 point improvement from baseline on the Galderma Chin Retrusion Scale (GCRS), as measured by the Blinded Evaluator at 6 months (after last treatment in Treatment Group, and after randomization in Control Group).

1.2.2 Secondary effectiveness objectives

The secondary objectives are:

- Percentage of responders, defined by at least 1 point improvement from baseline on the GCRS, as measured by the Blinded Evaluator at 3, 9 and 12 months after last treatment in Treatment Group, and at 3 months after randomization as well as 3, 6, 9 and 12 months after the last treatment in Control Group.

- Percentage of responders, defined by at least 1 point improvement from baseline on the GCRS, as measured by the Treating Investigator at each follow-up visit

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1.2.3 Safety objectives

The safety objectives are:

- Incidence, intensity, duration and onset of adverse events (AEs) collected throughout the study

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1.3 Effectiveness assessments

For all assessments, 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.

1.3.1 Galderma Chin Retrusion Scale (GCRS)

GCRS is a validated Four-Point scale assessing the Chin Retrusion from no retrusion (0) to severe retrusion (3) as described below.

The Blinded Evaluator will rate the subject's Chin Retrusion using the GCRS at screening, baseline, 3, 6, 9 and 12 months in Treatment Group; and at screening, baseline 3 and 6 months after randomization, as well as 3, 6, 9 and 12 months after last treatment in Control Group.

The Treating Investigator will do the GCRS evaluation at all visits in each group.

Table 1. The Galderma Chin Retrusion Scale.

GCRS	
0	No Retrusion: The most anterior portion of the chin is at or near a vertical line drawn from the vermillion border of the lower lip.
1	Mild Retrusion: The most anterior portion of the chin is clearly recessed, but less than midway, between vertical lines drawn from the vermillion border of the lower lip and the oral commissure.
2	Moderate Retrusion: The most anterior portion of the chin is recessed approximately midway between vertical lines drawn from the vermillion border of the lower lip and the oral commissure.
3	Severe Retrusion: The most anterior portion of the chin is clearly posterior to the midway point between vertical lines drawn from the vermillion border of the lower lip and the oral commissure.

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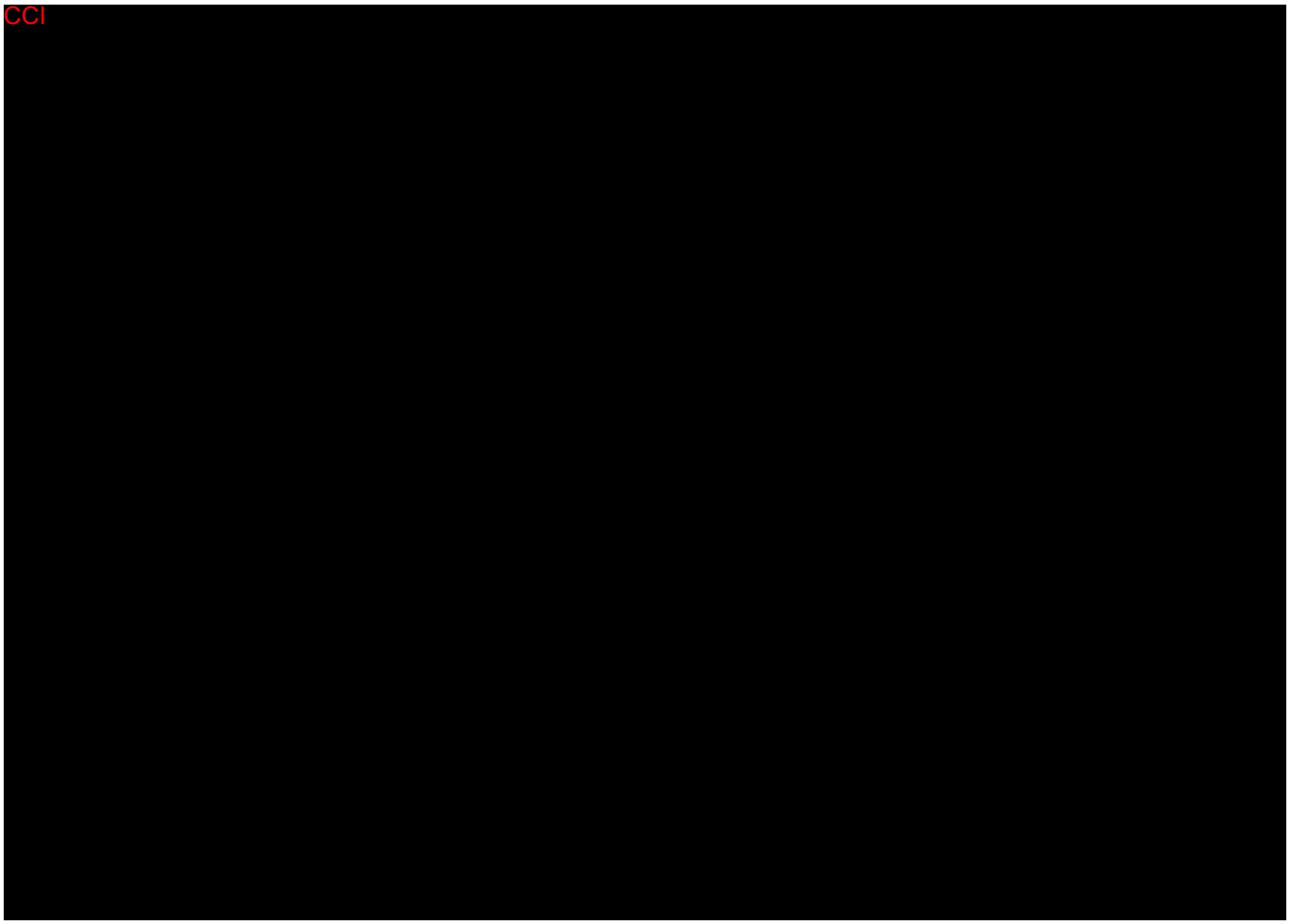

1.4 Effectiveness endpoints

1.4.1 Primary effectiveness endpoint

Percentage of responders based on the GCRS as measured by the Blinded Evaluator at 6 months (after last treatment in Treatment Group and after randomization in Control Group).

A responder is defined as a subject who achieves a score of at least 1 point improvement from baseline to 6 months on the GCRS.

1.4.2 Secondary effectiveness endpoints

Secondary effectiveness endpoints include:

(i) Percentage of responders as measured by the Blinded Evaluator at 3, 9 and 12 months after last treatment in Treatment group and at 3 months after randomization as well as 3, 6, 9 and 12 months after last treatment in Control group

A responder is defined as a subject who achieves a score of at least 1 point improvement from baseline on the GCRS.

(ii) Percentage of responders as assessed by the Treating Investigator at each follow-up visit

The follow-up assessments will be done 3 months, 6 months, 9 months and 12 months after last treatment for the Treatment Group, and at 3 months and 6 months after randomization as well as 3 months, 6 months, 9 months and 12 months after last treatment for Control Group.

A responder is defined as a subject who achieves a score of at least 1 point improvement from baseline on the GCRS.

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1.5 Safety assessments

The methods for collecting safety data are described in Section 8 of the Clinical Study Protocol (CSP) CCI [redacted] Adverse Events (AE), Serious Adverse Events (SAE). Laboratory assessments will be performed at screening and at 6 months after last treatment or at early termination if termination occurs before 6 months visit after last treatment for all subjects. In Control Group, it will also be taken at 6 months visit before treatment. ECG will also be assessed, but at screening only.

A two-point scale ("Yes" or "No" response) will be used for the causality assessments. 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

Safety endpoints include:

(v) Incidence, intensity, duration, and onset of related Adverse Events (AEs) collected throughout 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 9.4 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.

Any change made to the finalized statistical analysis plan (SAP) will be documented in the Clinical Study Report (CSR).

2.2 Analysis Populations

The following populations will be defined:

- Safety — Includes all subjects who were treated with Restylane Defyne or randomized to no-treatment group. Subjects are analyzed based on the as treated principle
- Full Analysis Set (FAS) — Includes all subjects who were treated with Restylane Defyne or randomized to no-treatment group. Subjects are analyzed according to the randomization 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.

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, subject might be excluded from the PP population, which shall be documented prior to database lock.

For this study, the protocol deviations that will exclude 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 6 after last treatment performed earlier than 1 week before or later than 2 weeks after the scheduled visit for the treatment group
	*	Follow-up at Month 6 after randomization performed earlier than 1 week before or later than 2 weeks after the scheduled visit for the control group
EFFECTIVENESS		
		Primary effectiveness endpoint
	*	Pre-treatment GCRS by blinded evaluator not done
	*	GCRS by blinded evaluator missing at Month 6 after last treatment for treatment group
	*	GCRS by blinded evaluator not done at Month 6 after randomization for control group
		Treatment
	*	Wrong treatment given at baseline
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

Number of missing values will be summarized and reported as appropriate. The baseline observation carried forward (BOCF) method will be used as the primary method to handle missing data on the primary effectiveness variable at the Month 6 visit in the FAS analysis set. This strategy is a conservative approach as it treats subjects with missing data as non-responders. Impact of missing data on the primary analysis for Month 6 endpoint will be evaluated by performing sensitivity analysis based on the PP population. In addition, missing data for the primary analysis will also be handled using the hot deck method.

All other endpoints will be analyzed on available data, i.e. no imputations will be done.

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2.4.3 Primary effectiveness analysis

The responder rate will be calculated for each group at Month 6 (after last treatment in Treatment Group and after randomization in Control group) based on the blinded evaluator's assessment. The responder rate in the Treatment Group will then be compared with the responder rate in the Control Group using a Fisher's exact test at a significance level of 5%. In addition, for each group the two-sided 95% confidence interval 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.

In order to assess robustness of the conclusions of the primary endpoint analysis, a logistic regression will be utilized, including baseline GCRS and treatment group as factors. The overall treatment effect will be used for assessing the robustness of the result of the primary analysis when corrected for baseline GCRS.

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

- *Percentage of responders as measured by the Blinded Evaluator at 3, 9 and 12 months after last treatment in Treatment group and at 3 months after randomization as well as 3, 6, 9 and 12 months after last treatment for control group*

The percentage of responders will be calculated at each time point and analyzed descriptively. At 3 months after last treatment for Treatment group and after randomization for Control group Fishers' Exact test will be used to compare the responder rates.

- *Percentage of responders as assessed by the Treating Investigator at each follow-up visit*

The percentage of responders will be calculated at each time point. At Week 4, Month 3 and Month 6 after last treatment for Treatment group and after randomization for Control group Fishers' Exact test will be used to compare the responder rates.

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2.5 Safety Analysis

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

2.5.1 Extent of exposure

Data of extent of exposure and treatment procedure will be summarized in total and by group, for initial treatment and touch-up separately. Injection volume will be summarized by group for initial treatment and touch-up separately. Other relevant injection parameters, such as injection depth, injection method will be presented in a similar way

2.5.2 Adverse events

All AEs will be coded according to MedDRA. All AE summaries below will be presented by treatment.

An overall summary of AEs will be presented. The summary will include the total number of events, frequency counts and percentages of subjects with

- Any AEs and SAEs reported
- Any AEs and SAEs related to product and/or injection procedure
- Unrelated AEs and SAEs
- No AEs reported

Summaries of related AEs after each treatment occasion (including the total number of events, number and percentage of subjects) will be displayed by system organ class (SOC), preferred term

(PT) and intensity. The duration and number of days to onset of related AEs will be summarized by SOC and PT using mean, SD, minimum, maximum, and median statistics.

Time to onset of an AE will be derived as the start date minus the date 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.

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. Missing stop date 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.

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2.6 Interim Analysis

An interim analysis will be performed once all subjects in Treatment Group complete the 12 Months visit after last treatment (or discontinued before) and all subjects in Control Group complete the 6 months visit after last treatment (or discontinued before).

2.7 Determination of Sample Size

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2.8 Changes in the Analysis Planned in the Protocol

No.

3 Planned Tables and Figures

Table of tables

Table of figures

Table A 1. Subject disposition (all subjects)

Number of subjects		Restylane Defyne	Control	Total
Screened		-	-	xx
Screening failures		-	-	xx (%)
Reasons for screening failure	*Reason 1*	xx (%)	xx (%)	xx (%)
	Reason 2	xx (%)	xx (%)	xx (%)
	.	xx (%)	xx (%)	xx (%)
Randomized		xx	xx	xx
Completed primary endpoint		xx (%)	xx (%)	xx (%)
Completed		xx (%)	xx (%)	xx (%)
Withdrawn		xx (%)	xx (%)	xx (%)
Reason for withdrawal	Withdrawn consent	xx (%)	xx (%)	xx (%)
	Lost to follow-up	xx (%)	xx (%)	xx (%)
	Medical reason	xx (%)	xx (%)	xx (%)
	Other	xx (%)	xx (%)	xx (%)

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

Table A 2. Analysis populations (all randomized subjects)

Site	Subject number	Safety		FAS		PP	
		n	%	n	%	n	%
PPD		xx	xx.x	xx	xx.x	xx	xx.x
		xx	xx.x	xx	xx.x	xx	xx.x
		xx	xx.x	xx	xx.x	xx	xx.x
		xx	xx.x	xx	xx.x	xx	xx.x
		xx	xx.x	xx	xx.x	xx	xx.x
Total (N)	-	xx	100.0	xx	100.0	xx	100.0

% = 100*n/N

Table A 3. Subject accountability (all subjects in Restylane Defyne group)

Number of subjects	Observed	Missed	Withdrawals	Continuing on study
Baseline/initial treatment	xx	xx	xx	xx
4W follow up/optional touch-up	xx	xx	xx	xx
4W follow up after last treatment	xx	xx	xx	xx
3M after last treatment	xx	xx	xx	xx
6M after last treatment	xx	xx	xx	xx
9M after last treatment	xx	xx	xx	xx
12M after last treatment	xx	xx	xx	xx

Table A 4. Subject accountability (all subjects in Control group)

Number of subjects	Observed	Missed	Withdrawals	Continuing on study
Baseline	xx	xx	xx	xx
4W follow up after randomization	xx	xx	xx	xx
3M after randomization	xx	xx	xx	xx
6M after randomization /treatment	xx	xx	xx	xx
4W follow up/optional touch-up	xx	xx	xx	xx
4W follow up after last treatment	xx	xx	xx	xx
3M after last treatment	xx	xx	xx	xx
6M after last treatment	xx	xx	xx	xx
9M after last treatment	xx	xx	xx	xx
12M after last treatment	xx	xx	xx	xx

Table A 5. Withdrawn subjects

Site	Subject number	Group	Date of treatment		Last visit performed	Date of last visit performed	Date of withdrawal	Reason for withdrawal
			Treatment	Optional touch up				

Table A 6. Protocol deviations affecting PP population

Protocol deviation (category)	Number of subjects/subject number	Number of deviations

Table A 7. Protocol deviations not affecting PP population

Protocol deviation (category)	Number of subjects/subject number	Number of deviations

Table A 8. Demographic and baseline characteristics (FAS)

Variable		Parameter	Restylane Defyne N = XX	Control N = XX	Total N = XX
Age (years)		N	xx	xx	xx
		Mean	xx.x	xx.x	xx.x
		SD	xx.x	xx.x	xx.x
		Median	xx.x	xx.x	xx.x
		Minimum	xx.x	xx.x	xx.x
		Maximum	xx.x	xx.x	xx.x
Gender	Female	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Male	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ethnic Origin	Han Chinese	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Other*	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Baseline GCRS**	1 Mild retrusion	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	2 Moderate retrusion	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

% = 100*n/N
* Other: xxx
** As evaluated by the Blinded Evaluator

Table A 9. Subjects reporting medical history/concurrent disease and number of conditions by the MedDRA System Organ Class (FAS)

	Restylane Defyne N=xx						Control N=xx					
Primary SOC	All			Ongoing at study start			All			Ongoing at study start		
	Subjects		Conditions	Subjects		Conditions	Subjects		Conditions	Subjects		Conditions
	n	%	n	n	%	n	n	%	n	n	%	n
	xx	xx.x	xx	xx	xx.x	xx	xx	xx.x	xx	xx	xx.x	xx
	xx	xx.x	xx	xx	xx.x	xx	xx	xx.x	xx	xx	xx.x	xx
Total*	xx	xx.x	xx	xx	xx.x	xx	xx	xx.x	xx	xx	xx.x	xx

%= 100*n/N

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

Table A 10. Prior use of facial fillers or implants (FAS)

Facial filler/implant	Restylane Defyne N=xx		Control N=xx	
	Subjects		Subjects	
	n	%	n	%
Hyaluronic Acid (HA)	xx	xx.x	xx	xx.x
Permanent implant	xx	xx.x	xx	xx.x
Semi-permanent implant	xx	xx.x	xx	xx.x
.	xx	xx.x	xx	xx.x
.	xx	xx.x	xx	xx.x
.	xx	xx.x	xx	xx.x
Total	xx	xx.x	xx	xx.x

%=100*n/N

Table A 11. Prior use of other facial dermatological procedures (FAS)

Facial dermatological procedure	Restylane Defyne N=xx		Control N=xx	
	Subjects		Subjects	
	n	%	n	%
Butolinum toxin injection	xx	xx.x	xx	xx.x
Resurfacing	xx	xx.x	xx	xx.x
Mesotherapy	xx	xx.x	xx	xx.x
.	xx	xx.x	xx	xx.x
.	xx	xx.x	xx	xx.x
.	xx	xx.x	xx	xx.x
Total	xx	xx.x	xx	xx.x

%=100*n/N

Table A 12. Subjects reporting concomitant medication (FAS)

Concomitant medication	Any concomitant medication?							
	Restylane Defyne N=xx				Control N=xx			
	No		Yes		No		Yes	
	n	%	n	%	n	%	n	%
Ongoing at study start								
Initiated during study								
Total								

%=100*n/N

Table A 13. Subjects reporting concomitant medication and number of medications by reason (FAS)

Reason for concomitant medication	Restylane Defyne N=xx			Control N=xx		
	Subjects		Medications	Subjects		Medications
	n	%	No. of medications	n	%	No. of medications
Medical History	xx	xx.x	xx	xx	xx.x	xx
Adverse Event	xx	xx.x	xx	xx	xx.x	xx
Other	xx	xx.x	xx	xx	xx.x	xx

%=100*n/N

Table A 14. Subjects reporting concomitant medication and number of medications by ATC code (FAS)

ATC code	ATC text	Restylane Defyne N=xx			Control N=xx		
		Subjects		Medications	Subjects		Medications
		n	%	No. of medications	n	%	No. of medications
		xx	xx.x	xx	xx	xx.x	xx
		xx	xx.x	xx	xx	xx.x	xx

%=100*n/N

Table A 15. Concomitant medication taken due to an AE by ATC code (FAS)

Concomitant medication			Adverse event	
ATC text (ATC code)	No. of subjects	No. of medications	MedDRA Preferred term	Related
ATC 1	xx	xx	PT 1	Yes/No
ATC 1	xx	xx	PT 2	Yes/No
ATC 1	xx	xx	PT 3	Yes/No
ATC 1	xx	xx	PT 4	Yes/No
ATC 2	xx	xx	PT 1	Yes/No
ATC 3	xx	xx	PT 1	Yes/No
.	xx	xx	.	Yes/No
Total	xx	xx	-	-

Table A 16. Subjects reporting concomitant procedure/treatment by reason (FAS)

	Restylane Defyne N=xx			Control N=xx		
Reason for concomitant procedure/treatment	No. of subjects		No. of procedures/treatments	No. of subjects		No. of procedures/treatment
	n	%		n	%	
Medical history	xx	xx.x	xx	xx	xx.x	xx
Adverse event	xx	xx.x	xx	xx	xx.x	xx
Other	xx	xx.x	xx	xx	xx.x	xx
Total	xx	xx.x	xx	xx	xx.x	xx

%=100*n/N

Table A 17. GCRS responder rate by treatment at Month 6, Blinded Evaluator (FAS)

Time point	Treatment group	# of subjects in FAS	# of responders	Proportion of responders	95% confidence interval	P-value
6 month after last treatment	Restylane Defyne	xx	xx	x.xx	x.xx, x.xx	
6 month after randomization	Control	xx	xx	x.xx	x.xx, x.xx	
	Difference	-		x.xx	x.xx, x.xx	x.xx

Note: Subjects with a missing GCRS have their values imputed using BOCF at Month 6
Note: Responder is defined as a subject with an improvement of at least one grade on the GCRS from baseline
Note: Responder rate is calculated as the number of Responders divided by the number of subjects in the FAS population for the specific treatment group.
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 binomial distribution

Table A 18. GCRS responder rate by treatment at Month 6, Blinded Evaluator (PP)

As Table A 17.

Note: No imputation is used for the PP analysis. Only subjects with complete data are included.
Note: Responder is defined as a subject with an improvement of at least one grade on the GCRS from baseline
Note: Responder rate is calculated as the number of Responders divided by the number of subjects in the FAS population for the specific treatment group.
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 binomial distribution

Table A 19. Sensitivity analysis for the GCRS responder rate by treatment at Month 6, Blinded Evaluator (FAS)

As Table A 17.

Note: Subjects with a missing GCRS have their values imputed using the hot deck method at Month 6
Note: Responder is defined as a subject with an improvement of at least one grade on the GCRS from baseline
Note: Responder rate is calculated as the number of Responders divided by the number of subjects in the FAS population for the specific treatment group.
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 binomial distribution

Table A 20. Logistic regression, Blinded Evaluator (FAS)

Parameter	Coefficient	SE	Wald Chi-Square	Degrees of freedom	P-value
Baseline GCRS	x.xx	x.xx	x.xx	x	x.xx
Treatment Group	x.xx	x.xx	x.xx	x	x.xx

Table A 21. GCRS responder rate by treatment at Month 3, Blinded Evaluator (FAS)

As Table A 17.

Note: Subjects with a missing GCRS are not imputed
Note: Responder is defined as a subject with an improvement of at least one grade on the GCRS from baseline
Note: Responder rate is calculated as the number of Responders divided by the number of subjects in the FAS population for the specific treatment group.
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 binomial distribution

Table A 22. GCRS responder rate by treatment at Week 4, Month 3 and Month 6, Treating Investigator (FAS)

Time point	Treatment group	# of subjects in FAS with non-missing values	# of responders	Proportion of responders	95% confidence interval	P-value
4 Week	Restylane Defyne	xx	xx	x.xx	x.xx, x.xx	
	Control	xx	xx	x.xx	x.xx, x.xx	
	Difference	-		x.xx	x.xx, x.xx	x.xx
3 Month	Restylane Defyne	xx	xx	x.xx	x.xx, x.xx	
	Control	xx	xx	x.xx	x.xx, x.xx	
	Difference	-		x.xx	x.xx, x.xx	x.xx
6 Month	Restylane Defyne	xx	xx	x.xx	x.xx, x.xx	
	Control	xx	xx	x.xx	x.xx, x.xx	
	Difference	-		x.xx	x.xx, x.xx	x.xx

Note: Subjects with a missing GCRS are not imputed
Note: Responder is defined as a subject with an improvement of at least one grade on the GCRS from baseline
Note: Responder rate is calculated as the number of Responders divided by the number of subjects in the FAS population for the specific treatment group.
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 binomial distribution

Table A 23. GCRS responder rate over time at Month 3 and Month 6, Blinded Evaluator (FAS)

Time point	Treatment group	# of subjects in FAS with non-missing values	# of responders	Proportion of responders	95% confidence interval
3 Months after last treatment	Restylane Defyne	xx	xx	x.xx	x.xx, x.xx
3 Months after randomization	Control	xx	xx	x.xx	x.xx, x.xx
	Difference	-		x.xx	x.xx, x.xx
6 Months after last treatment	Restylane Defyne	xx	xx	x.xx	x.xx, x.xx
6 Months after randomization/treatment	Control	xx	xx	x.xx	x.xx, x.xx
	Difference	-		x.xx	x.xx, x.xx

Note: Missing GCRS are imputed at Month 6
Note: Responder is defined as a subject with an improvement of at least one grade on the GCRS from baseline
Note: Responder rate = # of Responders/# of subjects in FAS with non-missing values
Note: Subjects in Control group receive optional treatment at Month 6 after randomization

Table A 24. GCRS responder rate over time, Blinded Evaluator (FAS)

Time point	Treatment group	# of subjects in FAS with non-missing values	# of responders	Proportion of responders	95% confidence interval
9 Months after last treatment	Restylane Defyne	xx	xx	x.xx	x.xx, x.xx
12 Months after last treatment	Restylane Defyne	xx	xx	x.xx	x.xx, x.xx
3 Months after last treatment	Control	xx	xx	x.xx	x.xx, x.xx
6 Months after last treatment	Control	xx	xx	x.xx	x.xx, x.xx
9 Months after last treatment	Control	xx	xx	x.xx	x.xx, x.xx
12 Months after last treatment	Control	xx	xx	x.xx	x.xx, x.xx

Note: Missing GCRS are not imputed
Note: Responder is defined as a subject with an improvement of at least one grade on the GCRS from baseline
Note: Responder rate = # of Responders/# of subjects in FAS with non-missing values
Note: Subjects in Control group receive optional treatment at Month 6 after randomization

Table A 25. GCRS responder rate over time, Treating Investigator (FAS)

As Table A 24.
Note: Missing GCRS are not imputed
Note: Responder is defined as a subject with an improvement of at least one grade on the GCRS from baseline
Note: Responder rate = # of Responders/# of subjects in FAS with non-missing values
Note: Subjects in Control group receive optional treatment at Month 6 after randomization

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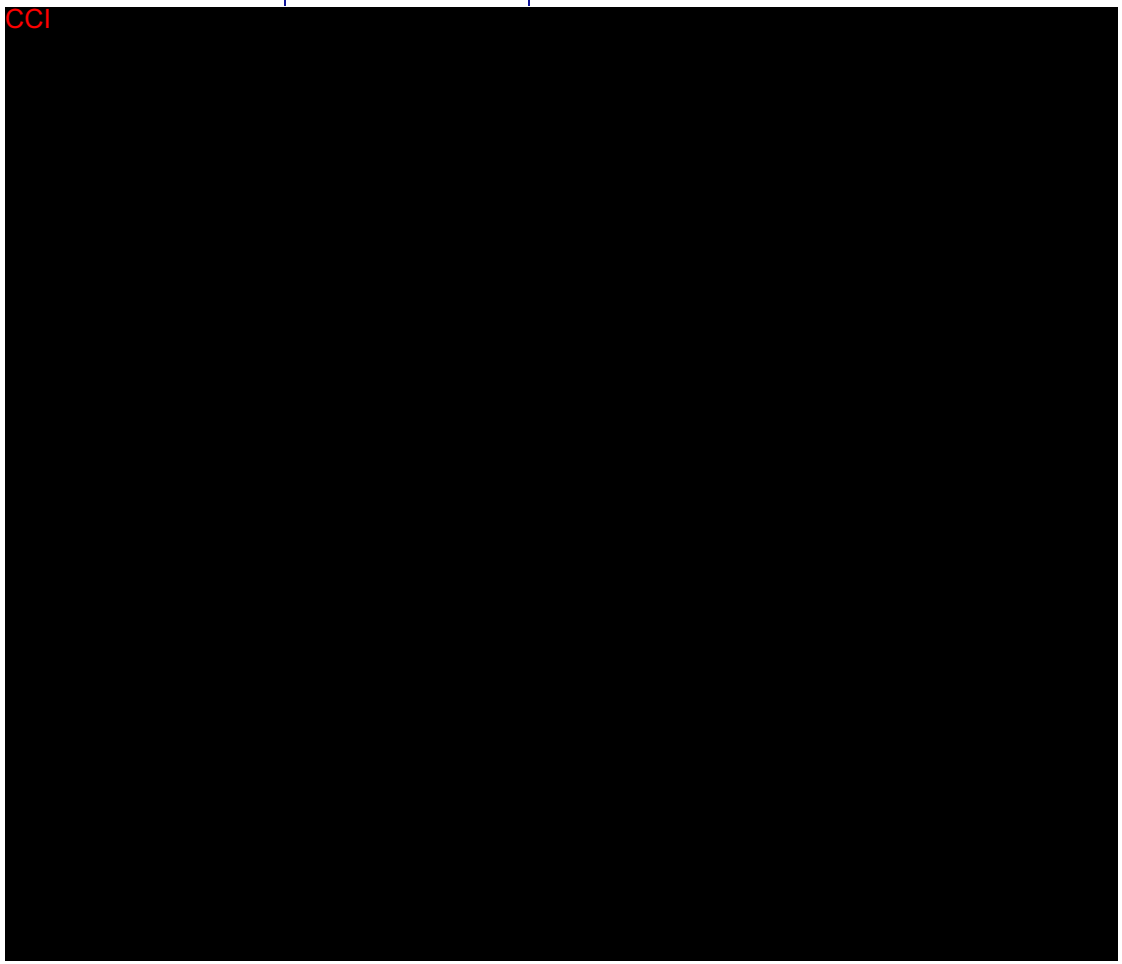

Table A 30. GCRS responses over time for subjects randomized to Restylane Defyne, Blinded Evaluator (FAS)

	GCRS								
	0 No Retrusion		1 Mild Retrusion		2 Moderate Retrusion		3 Severe Retrusion		Total N
Time point	n	%	n	%	n	%	n	%	
Baseline/initial treatment	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx
3M after last treatment	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx
6M after last treatment	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx
9M after last treatment	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx
12M after last treatment	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx

% = (n/N)*100

Table A 31. GCRS responses over time for subjects randomized to Control Group, Blinded Evaluator (FAS)

	GCRS								
	0 No Retrusion		1 Mild Retrusion		2 Moderate Retrusion		3 Severe Retrusion		Total N
Time point	n	%	n	%	n	%	n	%	
Baseline/randomization	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx
3M after randomization	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx
6M after randomization/treatment	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx
3M after last treatment	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx
6M after last treatment	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx
9M after last treatment	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx
12M after last treatment	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx

% = (n/N)*100

Table A 32. GCRS responses over time for subjects randomized to Restylane Defyne, Treating Investigator (FAS)

Same as table A 30

% = (n/N)*100

Table A 33. GCRS responses over time for subjects randomized to Control Group, Treating Investigator (FAS)

Same as table A 31

% = (n/N)*100

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Table A 39. Exposure to study treatment (Safety)

Assessment	Parameter	Restylane Defyne N=xx	Control (optional treatment) N=xx	Total N=xx
Volume of injection(mL) for treatment	N	xx	xx	xx
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
	Median	x.x	x.x	x.x
	Min, Max	x.x, x.x	x.x, x.x	x.x, x.x
Volume of injection(mL) for touch-up	N	xx	xx	xx
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
	Median	x.x	x.x	x.x
	Min, Max	x.x, x.x	x.x, x.x	x.x, x.x
Total volume of injection (mL) for treatment+touch-up	N	xx	xx	xx
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
	Median	x.x	x.x	x.x
	Min, Max	x.x, x.x	x.x, x.x	x.x, x.x
Depth of injection for treatment Mid to deep dermis	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Subcutaneous	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Supraperiosteal	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Depth of injection for touch-up Mid to deep dermis	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Subcutaneous	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Supraperiosteal	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Method of injection for treatment	n (%)			
.	n (%)			
.	n (%)			
.	n (%)			
Method of injection for touch-up	n (%)			
.	n (%)			

% = 100*n/N

Table A 40. Treatment procedure (Safety)

Time point	Assessment		Parameter	Restylane N=xx	Control N=xx	Total N=xx
Treatment	Local anesthesia used?	Yes	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		No	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Whereof topical cream		n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Whereof local infiltration		n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Touch-up	Local anesthesia used?	Yes	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		No	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Whereof topical cream		n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Whereof local infiltration		n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Treatment	Post-treatment care	None	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Massage	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Ice pack	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		No	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Touch-up	Post-treatment care	None	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Massage	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Ice pack	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Other	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

% = 100*n/N

Table A 41. A brief summary of all AEs (Safety)

	No treatment at baseline N=xx			Treatment with Restylane Defyne N=xx		
	Subjects		Events	Subjects		Events
	n	%	#	n	%	#
Any AEs reported, total	xx	xx.x	xx	xx	xx.x	xx
Of which were serious	xx	xx.x	xx	xx	xx.x	xx
AEs related to product and/or injection procedure	xx	xx.x	xx	xx	xx.x	xx
Of which were serious	xx	xx.x	xx	xx	xx.x	xx
AEs unrelated to product and/or injection procedure	xx	xx.x	xx	xx	xx.x	xx
Of which were serious	xx	xx.x	xx	xx	xx.x	xx
Subjects with no AE reported	xx	xx.x	-	xx	xx.x	-

Note: Treatment with Restylane Defyne columns include data from subjects in the Restylane Defyne group after their initial treatment at baseline, as well as data from subjects in the Control group after their initial treatment at Month 6 after randomization
% = 100*n/N

Table A 42. All AEs by MedDRA System Organ Class, Preferred Term and intensity (Safety)

		No treatment at baseline N=xx		Treatment with Restylane Defyne N=xx	
Primary System Organ Class Preferred Term	Intensity	Events	Subjects	Events #	Subjects n (%)
Any AE	Total	xx	xx (xx.x)	xx	xx (xx.x)
	Mild	xx	xx (xx.x)	xx	xx (xx.x)
	Moderate	xx	xx (xx.x)	xx	xx (xx.x)
	Severe	xx	xx (xx.x)	xx	xx (xx.x)
SOC1	Total	xx	xx (xx.x)	xx	xx (xx.x)
	Mild	xx	xx (xx.x)	xx	xx (xx.x)
	Moderate	xx	xx (xx.x)	xx	xx (xx.x)
	Severe	xx	xx (xx.x)	xx	xx (xx.x)
PT11	Total	xx	xx (xx.x)	xx	xx (xx.x)
	Mild	xx	xx (xx.x)	xx	xx (xx.x)
	Moderate	xx	xx (xx.x)	xx	xx (xx.x)
	Severe	xx	xx (xx.x)	xx	xx (xx.x)

Table A 43. Related AEs by MedDRA System Organ Class, Preferred Term and intensity (Safety)

		Treatment with Restylane Defyne N=xx	
Primary System Organ Class Preferred Term	Intensity	Events #	Subjects n (%)
Any related AE	Total	xx	xx (xx.x)
	Mild	xx	xx (xx.x)
	Moderate	xx	xx (xx.x)
	Severe	xx	xx (xx.x)
SOC1	Total	xx	xx (xx.x)
	Mild	xx	xx (xx.x)
	Moderate	xx	xx (xx.x)
	Severe	xx	xx (xx.x)
PT11	Total	xx	xx (xx.x)
	Mild	xx	xx (xx.x)
	Moderate	xx	xx (xx.x)
	Severe	xx	xx (xx.x)

Note: Treatment with Restylane Defyne columns include data from subjects in the Restylane Defyne group after their initial treatment at baseline, as well as data from subjects in the Control group after their initial treatment at Month 6 after randomization
Note: At each level of summarization subjects are counted once
% = 100*n/N

Table A 44. Duration (days) of related AEs by MedDRA System Organ Class and Preferred Term (safety)

	Treatment with Restylane Defyne N=xx						
	Ongoing	n	mean	SD	min	Median	Max
Any related AE							
SOC1							
PT11							
PT12							

Note: Treatment with Restylane Defyne columns include data from subjects in the Restylane Defyne group after their initial treatment at baseline, as well as data from subjects in the Control group after their initial treatment at Month 6 after randomization

Table A 45. Time to onset (days) of related AEs, by MedDRA System Organ Class and Preferred Term (Safety)

As Table A 44.

Note: Treatment with Restylane Defyne columns include data from subjects in the Restylane Defyne group after their initial treatment at baseline, as well as data from subjects in the Control group after their initial treatment at Month 6 after randomization

Table A 46. Unrelated AEs by MedDRA System Organ Class, Preferred Term and intensity (Safety)

As Table A 43.

Note: Treatment with Restylane Defyne columns include data from subjects in the Restylane Defyne group after their initial treatment at baseline, as well as data from subjects in the Control group after their initial treatment at Month 6 after randomization

Table A 47. Action taken due to related AEs by MedDRA System Organ Class and Preferred Term (Safety)

System Organ Class *Preferred Term*	Action taken			
	Treatment with Restylane-Defyne N=xx			
	None	Medication treatment	Non-pharmacological treatment or other procedures/tests	Subject withdrawn
SOC				
PT1				
PT2				
…				
All				

Note: Treatment with Restylane Defyne columns include data from subjects in the Restylane Defyne group after their initial treatment at baseline, as well as data from subjects in the Control group after their initial treatment at Month 6 after randomization

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SIGNATURES PAGE

Date	Signed by
2018-08-22 11:44	PPD
Justification	Approved by Owner

2018-08-22 11:47	PPD
Justification	Approved by Technical Expert

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Justification	Approved by Project Manager