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Statistical Analysis Plan

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STATISTICAL ANALYSIS PLAN	
Study Title:	A prospective, open-label, multicentre, randomized study to evaluate the effectiveness, safety and long term safety of Saypha® FILLER Lidocaine for lip augmentation.
Sponsor Identification:	CROMA-PHARMA GmbH
Phase:	Interventional
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2 Signatures

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Prepared By [redacted]

Reviewed By [redacted]

Approved By
(Croma-Pharma GmbH) [redacted]

3 Document History

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Final 1.0	07 JUN 2021	Nil

4 Abbreviations

ADE	Adverse device effect
AE	Adverse event
C1	Manufacturing site 'Croma 1'
CIP	Clinical Investigation Plan
DRM	Data Review Meeting
eCRF	Electronic case report form
FAS	Full analysis set
GAIS	Global aesthetic improvement
HQ	Manufacturing site 'Headquater'
IMD	Investigational medical device
LFS	Lip Fullness Scale
MedDRA	Medical dictionary for regulatory activities
mL	Milliliter
NLS	Navitas life Sciences
NPRS	numerical pain rating scale
PPS	Per-protocol set
SADE	Serious adverse device effect
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
TEAE	Treatment Emergent Adverse Events

5 Documents

This statistical analysis plan is based on the Clinical Investigation Plan (CIP), version Final 2.0 dated 27 JUN 2019.

6 Introduction

This statistical analysis plan (SAP) provides explicit guidance and describes the planned statistical and data handling methods to be followed during the analyses and reporting. The intent of this document is to provide detailed information of the analysis of trial data related to safety and effectiveness and to describe any applicable statistical procedures explicitly. The relevant statements are quoted directly from the Clinical Investigation Plan, within the applicable sections in this document (SAP). This SAP should be read in conjunction with the Clinical Investigation Plan version Final 2.0 dated 27 JUN 2019 and electronic case report form (eCRF) (version Final 1.0 dated 10 SEP 2020).

7 Study Objectives

The following are the study objectives:

7.1.1 Main Objectives

1. To evaluate the effectiveness, safety and long-term safety of Saypha® FILLER Lidocaine for lip augmentation;
2. To assess the duration of the aesthetic effect of Saypha® FILLER Lidocaine for lip augmentation

7.1.2 Additional Objectives

1. To compare the effectiveness of Saypha® FILLER Lidocaine ('IMD-HQ' and 'IMD-C1') produced in the two different manufacturing sites ('HQ' and 'C1').
2. To compare the IMD injection techniques: 'retrograde technique' and 'bolus technique'
3. To compare the injection equipment used: '27G ½″ needle' versus cannula ('25G x 50mm cannula' or '22G x 70mm cannula')

8 Study Design

8.1 Overview

8.1.1 Study Design

This is a prospective, open-label, multicentre, randomized investigation to evaluate the effectiveness, safety and long-term safety of Saypha® FILLER Lidocaine for bilateral lip augmentation and to assess the duration of the aesthetic effect of the device. This type of design is considered appropriate in view of the purpose and objectives of the study.

Schedule of procedures and events:

Assessment	Screening/ Baseline	Telephone Visit	Touch up	Telephone Visit		Month 6	Month 12	Optional++ Month 18
	Day 0*	24h after IMD admin.)	Week 3 ± 2 days	24h after IMD admin.)	Week 6 ± 5 days	Week 26 ± 7 days	Week 52 ± 7 days	Week 76 ± 7 days
	Visit 1	**Visit 1a**	**Visit 2**	**Visit 2a**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
Informed consent	x**							
Eligibility assessment	x**							
Urine pregnancy test[b]	x**				x	x	x	x
Demographic data[a]	x**							
Medical history	x**							
Photography	x**				x	x	x	x
Initial treatment	x							
Touch-up treatment			(x)[+]					
LFS - independent photographic reviewer	x				x	x	x	x
LFS – investigator [c]	x**				x	x	x	x
GAIS - investigator					x	x	x	x
GAIS - subject					x	x	x	x
FACE-Q™ "Satisfaction with outcome" - Subject					x	x	x	x
FACE-Q™ "Satisfaction with lips" -Subject					x	x	x	x

Assessment	Screening/ Baseline	Telephone Visit	Touch up	Telephone Visit		Month 6	Month 12	Optional++ Month 18
	Day 0*	24h after IMD admin.)	Week 3 ± 2 days	24h after IMD admin.)	Week 6 ± 5 days	Week 26 ± 7 days	Week 52 ± 7 days	Week 76 ± 7 days
	Visit 1	**Visit 1a**	**Visit 2**	**Visit 2a**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
Assessment of aesthetic effect - investigator					x	x	x	x
Pain assessment [e] using the NPRS - subject	x		(x)+					
Prior and concomitant medication	x**	x	x	x	x	x	x	x
Adverse event [d]	x***	X$	x***	X$	x	x	x	x
Device deficiencies	x		(x)+					

* Includes screening and (initial) treatment
** Prior to application of the investigational device
*** In order to identify potential AEs post-administration of IMD, AEs should be assessed 15 minutes after each administration (initial and touch-up treatment)
\+ Touch-up treatment is optional (at investigator's discretion, if full correction was not achieved after initial treatment).
++ The duration of the clinical investigation is planned for 18 months at a maximum and depends on the assessment of the aesthetic effect. In case it is observed by the investigator that no aesthetic effect is any more visible the study can be terminated at Month 12 (Visit 5) for the respective subject
$ Safety follow-up via telephone: Any adverse events since injection? In case of an AE an unscheduled on-site visit should be performed
a Includes year of birth, sex, race, and smoking status
b In females of child-bearing potential only, including women who are postmenopausal for less than 12 months
c Evaluated by the investigator using LFS. The upper and lower lip will be graded separately
d To be collected throughout the investigation, beginning immediately after start of initial treatment until the last visit
e NPRS: Immediately and 15 minutes after initial and touch-up IMD treatment
Abbreviations: LFS: Lip Fullness Scale; GAIS: Global Aesthetic Improvement Scale, NPRS: Numerical Pain Rating Scale

8.1.2 Treatment Regimen

Saypha® FILLER Lidocaine is a sterile, biodegradable, viscoelastic, transparent, isotonic and homogenized injectable gel implant formulated in a physiologic buffer to a concentration of 23 mg/mL, with addition of 3 mg/mL (0.3%) lidocaine hydrochloride. Saypha® FILLER Lidocaine is administered by injection into the lips. The volume applied depends on the size of the area which requires correction and will be selected by the investigator. A maximum volume of 2 mL for both lips in total (i.e., for upper plus lower lip) including touch up might be needed per treatment but the treatment should not exceed 10 mL in total per treatment or 20 mL per year.

The manufacturing process of Saypha® FILLER Lidocaine established at Croma's manufacturing site 'Croma 1' ('C1') was recently implemented in addition in a new manufacturing facility (manufacturing site 'headquarter' ('HQ')). No changes were done to the finished product design or manufacturing technology or method of sterilization. The ingredients, the formulation, the packaging and the finished product specifications were not changed. The implementation of the second manufacturing site is not considered to impact the safety and effectiveness of the product.

This study will compare the IMD produced at the new manufacturing site 'HQ' with the IMD produced at 'C1' site. Therefore, each subject will randomly be assigned to one of the two IMDs ('IMD-HQ' or 'IMD-C1') at a 1:1 ratio.

Approximately 110 subjects will be included in this investigation to have 100 evaluable subjects. This sample size is considered sufficient to provide robust estimations on performance and safety parameters in the underlying overall study population as well as the IMD manufacturing site subgroups (subjects will be randomized 1:1 to IMD from either site 'C1' ('IMD-C1') or site 'HQ' ('IMD-HQ')).

8.2 Effectiveness endpoints

Effectiveness endpoint will be as follows:

8.2.1 Primary Performance Endpoint

1. The proportion of subjects ('responders') with the lip volume improved by ≥1 point versus baseline value at 6 weeks after initial treatment based on the investigator live assessment using the validated Lip Fullness Scale (LFS).

   'Responder' is defined having at least ≥ 1 grade improvement as evaluated with the 5 point-validated LFS at a given visit relative to Baseline score (prior to treatment). Individual LFS grades per visit will be calculated separately for the upper and the lower lip.

8.2.2 Secondary Performance Endpoint

1. The percentage of responders, based on the investigator live assessment at 6, 12 and optional 18 months after the initial treatment using the validated LFS.
2. The percentage of responders based on the independent photographic reviewer´s assessments before initial treatment and at Week 6, Month 6, 12 and optional Month 18 after initial treatment, based on photographs and using the validated LFS.
3. The percentage of subjects with an improvement relative to baseline photographs, (subjects who have been rated as "very much improved" or "much improved" or "improved"), based on the investigator assessment at Week 6, Month 6, 12 and optional Month 18 after initial treatment using the 5-point GAIS.
4. The percentage of subjects with an improvement relative to baseline photographs (subjects who have been rated as "very much improved" or "much improved" or "improved"), based on subject assessment at Week 6, Month 6, 12 and optional Month 18 after initial treatment, using the 5-point GAIS.
5. The extent of subject´s satisfaction with overall outcome of the treatment, at Week 6, Month 6, 12 and optional Month 18 after initial treatment, assessed by the subject using the Face-Q™ Questionnaire "Satisfaction with Outcome".
6. The extent of subject's satisfaction with augmentation of lips, at Week 6, Month 6, 12 and optional Month 18 after initial treatment, assessed by the subject using the Face-Q™ Questionnaire "Satisfaction with Lips".
7. Subject's perception of pain after initial and touch-up treatment with Saypha® FILLER Lidocaine using the 11-point Numeric Pain Rating Scale (NPRS), where 0 is no pain and 10 is the worst pain imaginable.
8. Percentage of subjects demonstrating an aesthetic effect at Week 6, Month 6, 12 and optional Month 18 based on the investigator's life assessment.
9. Injection volume (initial and touch-up) required for an optimal augmentation of the lips with Saypha® FILLER Lidocaine

8.3 Safety endpoints

The safety of the investigational device will be evaluated using the following endpoint:

- Occurrence and frequency of adverse events.

9 General Statistical Considerations

9.1 Descriptive Statistics

The following descriptive statistics will be calculated for continuous data and for ordered categorical data (ordinal data):

Summary statistics are displayed with the following digits:

Description	Characteristic	Number of decimal places
Count	n	0
Count corresponding to the number of subjects for a group	N	0
Mean	Mean	As in source + 1
Standard Deviation	SD	Mean+1
Minimum	Min	As in source
Median	Median	As in source + 1
Maximum	Max	As in source
Quartile 1	Q1	As in source+1
Quartile 3	Q3	As in source+1
Percentage relative to N #	%	1

Number of decimal places can be more than one, if necessary. All table percentages should be rounded to one decimal place if not stated otherwise.

All data will be presented in the subject data listings.

If either table or listing does not include any observation, then the following placeholder will be used: "NO SUBJECTS MET THE CONDITION FOR INCLUSION".

9.2 Analysis Population

Analysis Population	Definition
Safety Analysis Set (SAF)	The Safety Analysis Set (SAF) consists of all subjects who received at least one administration of the investigational medical device (IMD).
Full Analysis Set (FAS)	The Full Analysis Set (FAS) comprises all subjects who received at least one administration of the IMD and who had at least one post-treatment evaluation of the LFS.
Per-Protocol Set (PPS)	The Per-Protocol Set (PPS) includes all subjects of the FAS who have no major protocol deviations which affect the primary endpoint. Subjects with major protocol deviations which affect the primary endpoint will be excluded from the PPS.

For this purpose, protocol deviations that could interfere with the objectives of the study, use of prohibited concomitant medications/procedures or deviation of the inclusion/exclusion criteria etc. will be assessed as 'minor' or 'major' in collaboration with the sponsor in the Data Review Meeting (DRM). The criteria for this assessment will be defined before analysis in the SAP. Listings will be prepared to assess the eligibility of all subjects during the DRM.

All safety analyses will be based on the SAF. The primary data set for effectiveness analysis will be the FAS and PPS.

Subjects who have been administered wrong IMD which is different from randomized will be analyzed as randomized (Planned) for FAS and will be analyzed under IMD, which was administered at first, for SAF. These subjects will not be included in PPS.

9.3 Definitions

In the following table, the definitions and calculation of derived variables are summarized

Variable / Term	Definition / Way of calculation
Adverse Event (AE)	**Adverse Event (AE)** any untoward medical occurrence, unintended disease or injury or untoward clinical sign (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the IMD (for more detail refer to Clinical Investigation Plan section 14)
Adverse Device Effect (ADE)	**Adverse Device Effect (ADE)** is an AE related to the use of the IMD (for more detail refer to Clinical Investigation Plan section 14)
Serious Adverse Event (SAE)	**Serious Adverse Event (SAE)** is an AE that led to serious deterioration in the state of health including possible death (for more detail refer to Clinical Investigation Plan section 14)
Serious Adverse Device Effect (SADE)	**Serious Adverse Device Effect (SADE)** is an ADE that has resulted in any of the consequences characteristic of an SAE.
Unanticipated Serious Adverse Device Effect (USADE)	**Unanticipated Serious Adverse Device Effect (USADE)** is defined as a SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the Investigator´s Brochure (IB).
Device deficiency	**Device deficiency** is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or

Variable / Term	Definition / Way of calculation
	performance. This may include malfunctions, use errors, and inadequate labelling
Device deficiency that might have led to an SAE	**Device deficiency that might have led to an SAE** if a) suitable action had not been taken, or b) intervention had not been made, or c) if circumstances had been less fortunate, is classified as a special type of deficiency and is handled under the SAE reporting system
Baseline	The last valid value prior to IMD administration
Change from baseline at visit n	The difference between a value at time point n and the value at baseline.
Study duration [days]	The duration of the clinical investigation will be a maximum of eight weeks for each participating subject in Cohort I. Date of last visit or "last day on study or last contact" (whichever is latest) – date of informed consent + 1
Volume (mL)	Volume (mL) administered at the applicable visit
Total Volume (mL)	Sum of volume (mL) of administered IMD in all visits

9.4 Protocol Violation/Deviation

Protocol deviations that could interfere with the objectives of the study, use of prohibited concomitant medications/procedures or deviation of the inclusion/exclusion criteria etc. will be assessed as 'minor' or 'major' in collaboration with the sponsor in the Data Review Meeting (DRM). Subjects with major protocol deviations will be excluded from the PPS and listings will be provided.

Major PD: PDs with a direct influence on data for the primary endpoint and/or indirect influence on primary endpoint such as major GCP deviations.

For major deviations, a further distinction has to be made between:

- Subject *included* in PPS: subject can remain in PPS although having the major PD (e.g. ICF signature date was wrong, but had been corrected in an acceptable manner)
- Subject *excluded* from PPS: subject must be excluded from the PPS due to the major PD.

Minor PD: PDs without a relevant influence on data for the primary endpoint and no major GCP deviation. A minor PD will not exclude a subject from the per protocol set (PPS).

All safety analyses will be based on the SAF. The primary data set for effectiveness analysis will be the FAS and PPS. Certain sensitivity analyses may be also done in the PPS.

9.5 Data Handling

9.5.1 Imputation of Missing data

Effectiveness: For both FaceQ questionnaires the following rule applies: If missing data is less than 50% of the scale's items, insert the mean of the completed items

FACE-Q type	Scenario	Imputation method
FACE-Q-10 (Satisfaction with Lips)	Up to 4 items missing i.e <=4	Mean of non-missing score will be imputed for those missing <=4 items. *(Mean value will be rounded to nearest integer)*
	>4 items missing	No imputation will be done, and missing items will be set to missing.
FACE-Q-6 (Satisfaction with Outcome)	Up to 2 items missing i.e <=2	Mean of non-missing score will be imputed for those missing <=2 items. *(Mean value will be rounded to nearest integer)*
	>2 items missing	No imputation will be done, and missing items will be set to missing.

Safety: To handle missing or partial AE and concomitant medication date, the following rules will be applied.

For partial start dates:

1. If the year is unknown, then do not impute the date but assign a missing value.
2. If the month is unknown, then:
    a. If the year matches the year of the dose date, then impute the month and day of the dose date.
3. If the day is unknown, then:
    a. If the month and year match the month and year of the first dose date, then impute the day of the dose date.

For partial end dates:

1. If the year is unknown, then do not impute the date but assign a missing value.
2. If the month is unknown, then do not impute the date and mark as ongoing for AE and Concomitant medication.
3. If the day is unknown, then assign the last day of the month.

After implementing the rules above, to determine whether AEs (or medications) with missing start or stop dates are pretreatment or on/after treatment, the following strategy will be used:

1. If the start date and stop date are both missing, then the most conservative approach is taken, and medication is considered to be concomitant medication.

2. If the start date is missing but the stop date is not missing and is on or after the day of study dose administration, then the most conservative approach is taken, and the medication is considered to be concomitant medication.

3. If the start date is missing but the stop date is not missing and is before the day of first study dose and after the date of signed informed consent, then the AE is considered Medical History and medication is considered to be prior medication.

4. If the start date is not missing but the stop date is missing, then the most conservative approach is taken and medication is considered to be concomitant while the AE is defined by start date.

If the Adverse Event Relationship flag is missing, the relationship for adverse event will be imputed and will be considered as related. If the Adverse Event intensity flag is missing, the intensity will be imputed and the maximum intensity will be considered as severity.

9.5.2 Other Specifications

Summaries will be based on scheduled time points.
In general, subject data listings should include all dosed subjects with data. However, if a subject data listing includes only subjects who met a certain condition, i.e., subjects with serious adverse events, and there are no subjects who met that condition, then a page marker will appear indicating that "No subjects met the condition for inclusion."

9.6 Sample Size Calculation

Confidence Interval calculation has been performed for the primary performance endpoint "The proportion of subjects ('responders') with the lip volume improved by ≥1 point versus baseline value at 6 weeks after initial treatment based on the investigator live assessment using a validated Lip Fullness Scale (LFS)". A responder is defined having at least ≥ 1 grade improvement compared to baseline values on the 5 point-validate lip fullness scale".

Approximately 110 subjects with moderate to severe volume deficiency of lips will be enrolled in order to obtain performance and safety data.

This sample size is arbitrarily selected and is considered sufficient to provide robust estimations on performance and safety parameters in the overall study population and in the subgroups regarding IMD manufacturing site. With a sample size of 100, a two-sided 95% confidence interval for a single proportion using the large sample normal approximation will extend by 0.059 in the overall population and 0.083 in the two manufacturing site subgroups from the observed proportion for an expected proportion of 0.900 (i.e., responder rate of 90%; calculated with nQuery Advanced 8.2.1.0). In order to cover subjects' drop-out or

lost to follow-up the sample size will be increased by 10%. 110 subjects will be enrolled (with 55 subjects per manufacturing site). Thus, a robust estimation of the success rate at week 6 can be derived.

9.7 Interim Analysis

An interim analysis (IA) assessing the safety and effectiveness will be performed after all subjects have completed the follow-up visit at Month 6 (Visit 4).

The interim analysis will be performed for the following endpoints using the "overall population". Safety will be presented using SAF population and effectiveness will be estimated and presented for FAS population.

1. The proportion of subjects ('responders') with the lip volume improved by ≥1 point versus baseline value at 6 weeks after initial treatment based on the investigator live assessment using the validated Lip Fullness Scale (LFS).

2. The percentage of responders, based on the investigator live assessment at 6 months after the initial treatment using the validated LFS.

3. The percentage of subjects with an improvement relative to baseline photographs, (subjects who have been rated as "very much improved" or "much improved" or "improved"), based on the investigator assessment at Week 6, Month 6 after initial treatment using the 5-point GAIS.

4. The percentage of subjects with an improvement relative to baseline photographs (subjects who have been rated as "very much improved" or "much improved" or "improved"), based on subject assessment at Week 6, Month 6 after initial treatment, using the 5- point GAIS.

5. The extent of subject´s satisfaction with overall outcome of the treatment, at Week 6, Month 6 after initial treatment, assessed by the subject using the Face-Q™ Questionnaire "Satisfaction with Outcome".

6. The extent of subject's satisfaction with augmentation of lips, at Week 6, Month 6 after initial treatment, assessed by the subject using the Face-QTM Questionnaire "Satisfaction with Lips".

7. Subject's perception of pain after initial and touch-up treatment with Saypha® FILLER Lidocaine using the 11-point Numeric Pain Rating Scale (NPRS), where 0 is no pain and 10 is the worst pain imaginable.

8. Percentage of subjects demonstrating an aesthetic effect at Week 6, Month 6 based on the investigator's life assessment.

9. Injection volume (initial and touch-up) required for an optimal augmentation of the lips with Saypha® FILLER Lidocaine.
10. Occurrence and frequency of adverse events
11. Baseline characteristics and demographics
12. Prior and concomitant medications and non-drug therapies
13. Subject disposition

9.8 Final Analysis

Final analysis will be done after completion of the investigation by all subjects. All primary, secondary and safety endpoints will be tabulated by visit, if applicable, and summarized using descriptive statistics only. The final analysis will be done for the 'overall population' and for several defined subgroups.

9.9 Statistical Software

All statistical analyses will be performed with SAS®, Version 9.4 or later.

10 Statistical Analyses

In this section detailed described about how each modules will be analyzed for interim analysis or for final analysis or for both.

10.1 Subject Disposition

Summary tables will be provided for the following subject characteristics:

- Number of subjects, both screened and received at least one administration of IMD, included in the study.
- Number of subjects by visit.
- Number of subjects included in the SAF, FAS and PPS.
- Number of subjects withdrawn from the study and the reason for withdrawal

Subjects who prematurely discontinue the study or lost to follow-up after receiving at least one dose of the IMD will be defined as dropouts.

10.2 Demographic Data and Baseline Characteristics

The demographic data and baseline characteristics will be analyzed using descriptive statistics in summary or frequency tables.

- Gender
- Age
- Race
- Smoking habits
- Lip Fullness Scale (LFS) - Investigator
- LFS - Independent photographic reviewer

10.3 Medical History and aesthetic procedures

All general medical / surgical history conditions will be coded using MedDRA version 23.0. General medical/surgical history conditions will be summarized by system organ class, preferred term and by Overall population using SAF population. The version of the utilized dictionary will be presented as part of the provided tables and listings. Listing of medical history will be provided.

10.4 Prior and concomitant medication

Prior and concomitant medications will be assessed at screening and at each subsequent study visit. Medications will be coded using WHODG B3 MAR 1, 2020.

Medication will be classified as prior, if the end date is known and is prior to the first use of the study IMD. Medications that are ongoing or ended after the first use of the study medication will be classified as concomitant. If the end date of the medication is unknown, it will also be considered as concomitant. Handling of missing date explained in section (Imputation of missing data section 9.5).

Prior and concomitant medications will be separately summarized by ATC class (the highest available level), preferred name for the safety population. Listings will be presented for prior and concomitant medications.

10.5 Treatment Exposure

The following will be assessed for initial and for touch-up treatment:

- number of subjects who received treatment,
- volume,
- technique and
- equipment used.

Descriptive statistics will be performed in total (i.e., both IMD administrations – initial plus touch-up treatment) and per single administration (initial and touch-up treatment, each) for the total volume (both lips) and volume per lip.

Technique and equipment will be summarized by number and percentage using SAF population. Descriptive analysis will be performed for volume using SAF population.

Listings will be provided for initial and touch-up treatment

10.6 Effectiveness Endpoint

10.6.1 Primary Performance Endpoint

1. The proportion of subjects ('responders') with the lip volume improved by ≥1 point versus baseline value at 6 weeks after initial treatment based on the investigator live assessment using the validated Lip Fullness Scale (LFS).

'Responder' is defined having at least ≥ 1 grade improvement as evaluated with the 5-point validated LFS at a given visit relative to Baseline score (prior to treatment).. Individual LFS grades per visit will be calculated separately for the upper and the lower.

As two lips of each subject will be considered, there are two measurements per subject for LFS. Differences between the lips are expected, thus both measurements will be separately used for analyses.

Individual LFS grades per visit will be calculated separately to the upper and the lower lip, respectively. The absolute LFS change per lip versus baseline will be computed by subtracting the value obtained on Day 0 from that of the corresponding visit. Absolute LFS change from baseline will be summarized by the visit using descriptive statistics.

Subjects with the lip volume improved (≥1 point versus baseline) will be summarized by number and percentage using PPS and FAS population. Binomial proportion test at 5% level of significance will be performed to test the expected proportion of 0.900.

Listings will be provided for LFS.

10.6.2 Secondary Performance Endpoint

1. The percentage of responders, based on the investigator live assessment at 6, 12 and optional 18 months after the initial treatment using the validated LFS.

Percentage of responders, based on the investigator live assessment at 6, 12 and optional 18 months after the initial treatment using the validated LFS will be summarized by number and percentage using PPS and FAS population.

2. The percentage of responders based on the independent photographic reviewer´s assessments before initial treatment and at Week 6, Month 6, 12 and optional Month 18 after initial treatment, based on photographs and using the validated LFS.

Percentage of responders based on the independent photographic reviewer´s assessments before initial treatment and at Week 6, Month 6, 12 and optional Month 18 after initial treatment, based on photographs and using the validated LFS will be summarized by number and percentage using PPS and FAS population.

3. The percentage of subjects with an improvement relative to baseline photographs, (subjects who have been rated as "very much improved" or "much improved" or "improved"), based on the investigator assessment at Week 6, Month 6, 12 and optional Month 18 after initial treatment using the 5-point GAIS.

Percentage of subjects with an improvement relative to baseline photographs (subjects who have been rated as "very much improved" or "much improved" or "improved"), based on investigator assessment at Week 6, Month 6, 12 and optional Month 18 will be summarized by number and percentage using PPS and FAS population.

Listings will be provided for GAIS.

4. The percentage of subjects with an improvement relative to baseline photographs (subjects who have been rated as "very much improved" or "much improved" or "improved"), based on subject assessment at Week 6, Month 6, 12 and optional Month 18 after initial treatment, using the 5-point GAIS.

Percentage of subjects with an improvement relative to baseline photographs (subjects who have been rated as "very much improved" or "much improved" or "improved"), based on subject assessment at Week 6, Month 6, 12 and optional Month 18 will be summarized by number and percentage using PP and FAS population.

5. The extent of subject´s satisfaction with overall outcome of the treatment, at Week 6, Month 6, 12 and optional Month 18 after initial treatment, assessed by the subject using the Face-Q™ Questionnaire "Satisfaction with Outcome".

The extent of subject´s satisfaction with overall outcome of the treatment, at Week 6, Month 6, 12 and optional Month 18 after initial treatment, assessed by the subject using the Face-Q™ Questionnaire "Satisfaction with Outcome" for each question will be summarized by number and percentage using PPS and FAS population.

Face Q data will be analyzed according to the FaceQ USER'S GUIDE (VERSION 1.0 January 2015). The raw summed scale score is converted to a score from 0 to 100 by using the respective Conversion Tables available from the authors. Higher scores reflect a better outcome (i.e., 0 (worst) to 100 (best)).

Listings will be provided for Face-Q™ Questionnaire "Satisfaction with Outcome".

6. The extent of subject's satisfaction with augmentation of lips, at Week 6, Month 6, 12 and optional Month 18 after initial treatment, assessed by the subject using the Face-Q™ Questionnaire "Satisfaction with Lips".

The extent of subject's satisfaction with augmentation of lips, at Week 6, Month 6, 12 and optional Month 18 after initial treatment, assessed by the subject using the Face-Q™ Questionnaire "Satisfaction with Lips" for each question will be summarized by number and percentage using PPS and FAS population.

Listings will be provided for Face-Q™ Questionnaire "Satisfaction with Lips".

7. Subject's perception of pain after initial and touch-up treatment with Saypha® FILLER Lidocaine using the 11-point Numeric Pain Rating Scale (NPRS), where 0 is no pain and 10 is the worst pain imaginable.

Subject's perception of pain after initial and touch-up treatment with Saypha® FILLER Lidocaine using the 11-point Numeric Pain Rating Scale (NPRS) will be analyzed descriptively using PPS and FAS populations.

Paired t-test will be performed to check the mean difference between "immediately after" and "15 minutes later at each visit are significant at 5% level of significance.

Listings will be provided for Numeric Pain Rating Scale (NPRS).

8. Percentage of subjects demonstrating an aesthetic effect at Week 6, Month 6, 12 and optional Month 18 based on the investigator's life assessment.

Percentage of subjects demonstrating an aesthetic effect at Week 6, Month 6, 12 and optional Month 18 based on the investigator's life assessment will be summarized by number and percentage using PPS and FAS population.

9. Injection volume (initial and touch-up) required for an optimal augmentation of the lips with Saypha® FILLER Lidocaine

Summary of injection volume (initial and touch-up) required for an optimal augmentation of the lips by upper and lower lips will be analyzed descriptively using FAS and Safety analysis set for Overall population.

10.7 Safety Analysis

10.7.1 Adverse Events

Adverse Events will be coded using the Medical Dictionary of Regulatory Activities (MedDRA version 23.0), the coded terms will be used for summarizing the AE(s). Adverse events will be analyzed using SAF population.

Incidence of AEs for user´s and other persons (if reported), will be presented in a separate table and listing.

An AE will be considered as treatment-emergent if the time of onset is on or after the time of the first study IMD administration or any event that exist prior to first dose and if it increased in severity during the study period. Handling of missing data and date are explained in section 9.5 (Imputation of missing data).

An overall summary table, which summarizes, the number and percentages of subjects with adverse events, serious adverse events, adverse events leading to death, adverse events related to IMD, adverse event related to procedure, action taken with study device, action taken to treat AE, associated to a device deficiency, subject withdrawn due to adverse event and adverse events by intensity categories, serious adverse device effects, unanticipated serious adverse device effect, will be provided for overall population.

AEs assessed with the relationship “unrelated” or “unlikely” will be classified as “not related” and AEs assessed with “possible”, “probable” or “definite” will be classified as “related”.

AEs Tables such as TEAE, SAE tables will be summarized by system organ class and preferred term. SOC will be sorted in descending order of counts.

A subject experiencing the same AE multiple times will be counted only once for that preferred term. Similarly, if a subject experiences multiple AEs within the same system organ class that subject will be counted only once in that system organ class. Maximum intensity will be considered if a subject has multiple severity reported for same AE. In summaries by relationship, if a subject has the same AE on multiple occasions, the closest relationship to study drug, will be used for summary.

10.7.2 Device Deficiencies

The following will be assessed for the device deficiency:

- Nature of Device Deficiency:
- Is an individual affected by the Device Deficiency?
- Relatedness of Device Deficiency to an (S)AE
- Action Taken with the device

Device deficiency related items will be summarized by number and percentage using SAF population.
Listings will be provided for Device Deficiency.

10.7.3 Urine pregnancy test

Listing will be provided for the Urine pregnancy test.

10.7.4 Multicenter trial

This study will take place in up to three investigation sites, however, due to the limited number of subjects no site stratification is planned

10.8 Subgroup Analyses

Besides the 'overall population' (including all subjects enrolled in the investigation), which includes all enrolled subjects, the following subgroups will descriptively be analyzed:

- **IMD from manufacturing sites: 'HQ' and 'C1'**
  IMD from two different manufacturing sites ('C1' and 'HQ') will be used and subjects will be randomly assigned in a 1:1 ratio to 'IMD-C1' or 'IMD-HQ', respectively.
  Subgroup analysis will compare both IMDs ('IMD-HQ' or 'IMD-C1') and separately analyze the results for the 'IMD-C1' and 'IMD-HQ' subgroups.
  Summary of subgroup analysis will compare both IMDs ('IMD-HQ' or 'IMD-C1) will be analyzed descriptively using FAS populations
- **Injection technique: 'retrograde technique' and 'bolus technique'**
  Subgroup analysis will separately analyze the results for subjects treated with the two different injections techniques.
  Summary of different injections techniques will be analyzed descriptively using FAS populations
- **Injection equipment: '27G ½″ needle' versus cannula ('25G x 50mm cannula' or '22G x 70mm cannula')**
  Subgroup analysis will separately analyze the results for subjects treated by means of the different injection equipment.
  All subgroup analyses are planned to be performed for the primary performance endpoint and the main secondary performance endpoints.

All subgroup analyses are planned to be performed for the primary performance endpoint and the main secondary performance endpoints using FAS population only.
The following secondary performance endpoints are planned to be analyzed:

- The percentage of responders, based on the investigator live assessment at 6, 12 and optional 18 months after the initial treatment using the validated LFS.

- The percentage of responders based on the independent photographic reviewer´s assessments before initial treatment and at Week 6, Month 6, 12 and optional Month 18 after initial treatment, based on photographs and using the validated LFS.
- The percentage of subjects with an improvement relative to baseline photographs, (subjects who have been rated as "very much improved" or "much improved" or "improved"), based on the investigator assessment at Week 6, Month 6, 12 and optional Month 18 after initial treatment using the 5-point GAIS.
- The percentage of subjects with an improvement relative to baseline photographs (subjects who have been rated as "very much improved" or "much improved" or "improved"), based on subject assessment at Week 6, Month 6, 12 and optional Month 18 after initial treatment, using the 5-point GAIS.
- Subject's perception of pain after initial and touch-up treatment with Saypha® FILLER Lidocaine using the 11-point Numeric Pain Rating Scale (NPRS), where 0 is no pain and 10 is the worst pain imaginable.

10.9 Sensitivity Analyses

Sensitivity analysis will be performed on the primary endpoint to evaluate the site effect.

11 Deviation from the Study clinical investigation plan

The following are the changes from Clinical Investigation Plan to Statistical Analysis Plan.

S.no	Text From CIP	Clarification for SAP	Rationale
1	An interim analysis (IA) assessing the safety and effectiveness will be performed after all subjects have completed the follow-up visit at Month 6 (Visit 4).	• The percentage of responders based on the independent photographic reviewer´s assessments before initial treatment and at Week 6, Month 6, 12 and optional Month 18 after initial treatment, based on photographs and using the validated LFS. The above secondary effectiveness analysis will not be analyzed for the interim analysis. However, it will be analyzed in the final analysis	This secondary effectiveness endpoint will not be analyzed for the interim analysis to avoid a bias. All pictures of the subjects will be assessed in a single session by the Independent Photo Reviewer, including those from Month 12 and Month 18. The respective secondary effectiveness endpoint will be analyzed in the final analysis only.

12 Database Lock and Unblinding

A soft lock will be performed at the time of analysis. The SAP will be finalized prior to interim analysis. After the data cleaning process is finalized according to the data management plan (DMP) and the assignment of subjects to the analysis sets is agreed and signed by the sponsor, the study database will be locked. No Un-blinding is required since it's an open label study.

13 References

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3. Narins RS, Brandt F, Leyden J, Lorenc ZP, Rubin M, Smith S. A randomized, double-blind, multicenter comparison of the efficacy and tolerability of Restylane versus Zyplast for the correction of nasolabial folds. Dermatologic surgery: official publication for American Society for Dermatologic Surgery [et al]. 2003;29(6):588-95.