Statistical Analysis Plan

A prospective, randomized, multicenter study evaluating saypha® VOLUME Lidocaine* for the correction of nasolabial folds

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Abbreviations and definitions

AE	adverse event
ADE	adverse device effects
ATC	anatomical therapeutic chemical
C1	Manufacturing site C1 Beautyplant
CIP	clinical investigation plan
DMP	data management plan
EDC	electronic data capture
eCRF	electronic case report form
GAIS	global aesthetic improvement scale
HA	hyaluronic acid
HQ	Manufacturing site Headquarter
IMD	investigational medical device
ITT	intent-to-treat
MedDRA	medical dictionary for regulatory affairs
NLF	nasolabial fold
NLF-SRS	nasolabial folds severity rating scale
NPRS	numeric pain rating scale
PP	per-protocol
SADE	serious adverse device effects
SAE	serious adverse events
SAP	statistical analysis plan
SAS	Statistical Analysis System
TEAE	treatment emergent adverse event

1 Overview

This Statistical analysis plan (SAP) is issued to provide a comprehensive and detailed description of strategy, rationale, and statistical technique that will be used to assess the safety and effectiveness of saypha® VOLUME Lidocaine in the correction of moderate-to-severe nasolabial folds (NLFs).

The credibility of the investigation findings will be ensured by pre-specifying the statistical approaches to the analysis of the data prior to results available in this open clinical investigation.

This SAP is based on the clinical investigation plan (CIP) number CPH-101-201477 Version 5.0, dated June 09, 2020.

1.1 Background / rationale

Skin aging is a natural and progressive process, driven by intrinsic and extrinsic factors. In addition to the skin, it also involves the skin support systems including the bone, cartilage, and subcutaneous compartments. Within the skin, aging results in reduced collagen production, fragmentation of elastin network, and decreased turnover of skin cells. The loss of extracellular matrix and its major component, hyaluronic acid (HA), which forms a viscoelastic surrounding for collagen and elastin fibres, results in reduced skin elasticity and turgor. Due to reduced elasticity, the repeated muscle action produces prominent wrinkles and creases in the mimetic areas of facial skin, while concomitant involution of facial fat deposits and bone atrophy contribute to skin laxity and facial volume loss and redistribution, resulting in aged face.

Appearance of nasolabial folds is one of the typical clinical manifestations of facial aging, which also include flaccidity of the skin and subcutaneous tissue, wrinkle expression in the upper third of the face, tear through, drop of the angle of the mouth, loss of definition in the mandibular border, cervico-facial platysmal bands, and changes in skin pigmentation.

Perception of age and health is critical in the judgement of attractiveness. Young faces are generally perceived to be more attractive than old faces, and estimated age is negatively correlated with perceived attractiveness. Attractiveness influences both the self-perception and behaviour toward others, and is related to traits such as self-confidence and social acceptance. It is not surprising, therefore, that aesthetic interventions can improve the psychological well-being and quality of life in people who elect to undergo such procedures due to aging. Common positive changes include increased satisfaction with self-appearance, reduced depression or anxiety, improved emotional well-being and increased self-confidence.

Dermal fillers are widely used for facial rejuvenation and correction of deep wrinkles, including nasolabial folds. These treatments provide desirable aesthetic outcomes with minimal invasiveness and without the downtime associated with surgery. HA dermal fillers are most popular because of their ease of administration, predictable effectiveness, good safety profile, and quick patient recovery. In order to improve the comfort of filler injections, a local anaesthetic (lidocaine hydrochloride) has been included in their formulation to reduce procedural pain and to bypass the need for additional anaesthesia.

1.2 Objectives

1.2.1 Primary performance endpoints

The primary endpoints evaluated for performance of the investigational device are the proportion of subjects with the NLF-SRS grade reduced by ≥1 point versus baseline at Week 24, within each manufacturing site, C1 and HQ, separately and for the whole analysis population.

1.2.2 Secondary performance endpoints

Secondary endpoints evaluated for performance of the investigational device are:

- The average change versus baseline in the NLF-SRS grade at Week 4, Week 24, Week 36, Week 52 and, optional at Week 65, Week 78 and Week 104 as evaluated by the investigator.
- The proportion of subjects with the NLF-SRS grade reduced by ≥1 point versus baseline at Week 4, Week 36, Week 52 and optional at Week 65, Week 78 and Week 104

All secondary performance endpoints will be evaluated within each manufacturing site, C1 and HQ, separately and for the whole analysis population

1.2.3 Exploratory performance endpoints

As exploratory endpoints the primary and secondary performance endpoints will be evaluated within the subgroups defined by the injection technique and device within each manufacturing site and for the whole analysis population:

- The proportion of subjects with the NLF-SRS grade reduced by ≥1 point versus baseline at Week 4, Week 24, Week 36, Week 52 and optional at Week 65, Week 78 and Week 104 by by injection technique (retrograde, bolus) and device (needle, cannula).
- The average change versus baseline in the NLF-SRS grade at Week 4, Week 24, Week 36, Week 52 and, optional at Week 65, Week 78 and Week 104 as evaluated by the investigator by injection technique (retrograde, bolus) and device (needle, cannula).

The following exploratory endpoints will be assessed for the whole analysis population only:

- The proportion of subjects with the NLF-SRS grade reduced by ≥2 point versus baseline at Week 4, Week 24, Week 36 and Week 52 and optional at Week 65, Week 78 and Week 104.
- The proportion of subjects with aesthetic improvement at Week 4, Week 24, Week 36, Week 52 and optional at Week 65, Week 78 and Week 104, as evaluated by the investigator using the Global Aesthetic Improvement Scale (GAIS)
- The proportion of subjects with aesthetic improvement at Week 4, Week 24, Week 36, Week 52 and optional at Week 65, Week 78 and Week 104, as evaluated by the subject using the Global Aesthetic Improvement Scale (GAIS)
- Subjects' satisfaction with aesthetic outcome of the treatment at Week 4, Week 24, Week 36, Week 52 and optional at Week 65, Week 78 and Week 104 using the Face-Q Satisfaction with outcome Scale as evaluated by the subject
- The pain intensity during and after the treatment, as evaluated by the subject using an 11-point Numeric Pain Rating Scale (NPRS) immediately after the last injection and 15 min. thereafter, respectively
- The proportion of subjects with the NLF-SRS grade reduced by ≥1 point versus baseline at Week 4, Week 36, Week 52 and optional at Week 65, Week 78 and Week 104 as evaluated by the independent reviewer of photographs.

- The proportion of subjects having an aesthetic effect at Weeks 24, Week 36, Week 52 and optional at Week 65, Week 78 and Week 104 based on the investigator's life assessment.

1.2.4 Safety endpoints

Endpoints to evaluate the safety and long term safety of the device are:

- Occurrence and frequency of adverse events within each manufacturing site, C1 and HQ, separately and for the whole analysis population
- Occurrence and frequency of adverse events within each subgroup defined by the injection device, needle and cannula, respectively.

Concomitant medications documented throughout the study and device deficiencies will be reported.

1.3 Modifications from the statistical section in the protocol

Not applicable.

2 Investigational plan

2.1 Design description and randomisation

The present investigation is designed as a prospective, non-comparative, randomized, multicenter study. As justified in the CIP, this type of design is considered appropriate in view of the purpose and objectives of the study.

The investigation will consist of 11 visits (the three last visits are optional): the baseline (Day 0) visit, which will entail informed consent, screening assessments, the treatment, and early post-treatment assessments, telephone communication approximately 24 hours post-administration for monitoring of adverse events and follow-up visits at Week 2, 4, 24, 36, 52, 65 (optional), 78 (optional) and 104 (optional) after the treatment. Procedures to be performed at each visit are specified in section 2.3 Study plan.

In case it is observed by the investigators that at a given visit no aesthetic effect is any more visible in approximately 75 % of the subjects, the study can be terminated at an earlier time point, but not before week 52.

Once a subject has consented to enter this study the study participants receive a unique 5-digit number at Day 0, with the first two digits identifying the site and the last three digits identifying the subject, e.g. 01-001. Eligible subjects are assigned to random numbers (starting with 501) in ascending order within each site beginning with the lowest number available. It is mandatory to stick to this procedure throughout the study. Each treated subject will receive test product produced by one of the two manufacturing sites only. The manufacturing sites (C1, HQ) will be assigned to the codes A or B by CROMA.

2.2 Sample size justification

Up to approx. 100 + 10 subjects with moderate to severe nasolabial folds will be randomized with a 1:1 allocation to the manufacturing sites C1 and HQ, in order to obtain the 24-week performance and safety data from approximately 50 of them in each manufacturing site. This sample size is considered appropriate for the clinical investigation and sufficient to provide robust estimations on performance and safety parameters in the study population. A sample

size of 50 allows a meaningful range estimation, the confidence interval, for the true proportion of success (reduction in NLF-SRS grades of ≥1) at week 24. With a sample size of 50, a confidence level of (1- α) with α=0.05 and an estimated proportion of 0.9 a two-sided 95% confidence interval for the true proportion using the large sample normal approximation is given through [0.817;0.983]. Thus, in compliance with the study design, the true proportion is expected in the range of the confidence interval with an error probability of 5%.

2.3 Study plan

Assessment	VISIT 1*	VISIT 2∞	VISIT 3	VISIT 4∞Ω	VISIT 5	VISIT 6	VISIT 7	VISIT 8	VISIT 9§	VISIT 10§	VISIT 11§
	Day 0 Baseline	**Day 0** TC 24 h after treatment	**Week 2** (±2 days)	**Week 2** TC 24 h after treatment	**Week 4** (±4 days)	**Week 24** (±7 days)	**Week 36** (±7 days)	**Week 52** (±7 days)	**Week 65** (±7 days)	**Week 78** (±7 days)	**Week 104** (±7 days)
Informed consent	x**										
Demographic data[a]	x**										
Medical/ aesthetic history	x**										
Prior medication[b]	x**										
NLF-SRS grading of nasolabial folds[c]	x**				x	x	x	x	x§	x§	x§
Urine pregnancy test[d]	x**		x**		x	x	x	x	x§	x§	x§
Eligibility assessment	x**										
Treatment	X		x#								
Photography	x**		x**		x	x	x	x	x§	x§	x§
Pain assessment[e]	x		xΩ								
GAIS assessment[f]					x	x	x	x	x§	x§	x§
GAIS assessment by the subject					x	x	x	x	x§	x§	x§
Subject satisfaction[g]					x	x	x	x	x§	x§	x§

Assessment	VISIT 1*	VISIT 2**	VISIT 3	VISIT 4**Ω	VISIT 5	VISIT 6	VISIT 7	VISIT 8	VISIT 9§	VISIT 10§	VISIT 11§
	Day 0 Baseline	**Day 0** TC 24 h after treatment	**Week 2** (±2 days)	**Week 2** TC 24 h after treatment	**Week 4** (±4 days)	**Week 24** (±7 days)	**Week 36** (±7 days)	**Week 52** (±7 days)	**Week 65** (±7 days)	**Week 78** (±7 days)	**Week 104** (±7 days)
Assessment of aesthetic effect by the investigator						x	x	x§§	x§	x§	x§
Adverse events[h]	x***	x**	x	xΩ	x	x	x	x	x§	x§	x§
Concomitant medication[h]	x***		x		x	x	x	x	x§	x§	x§

* Includes screening and treatment.

** Prior to application of the investigational device

*** From beginning of the treatment onwards

§ Optional the evaluation of the duration of the clinical investigation is planned for 104 Weeks at a maximum. In case it is observed by the investigator that no aesthetic effect is any more visible in approximately 75 % of the subjects, the study can be terminated at an earlier time point, but not before week 52.

§§ If a subject no longer has an aesthetic effect as of Week 52, this may prematurely lead to the termination of the clinical examination of the respective subject.

Touch-up treatment is optional (at investigator's discretion, if full correction was not achieved after initial treatment).

** Telephone communication approximately 24 hours post-administration in order to monitor adverse events. In case of AEs an unscheduled visit should take place.

Ω To be performed only if Touch-up treatment occurred

[a] Includes date of birth, sex, and race

[b] All medication taken by the subject within the previous 10 days

[c] Performed by the investigator using the Nasolabial Folds Severity Rating Scale (NLF-SRS); the severity of the left and the right fold will be separately graded

[d] In females of child-bearing potential only, including women who are postmenopausal for less than 12 months

[e] Evaluated by the subject immediately after injection and approximately 15 min. thereafter using an 11-point Numeric Pain Rating Scale

[f] Evaluated by the investigator using the Global Aesthetic Improvement Scale (GAIS)

[g] Evaluated by the subject using the FACE-Q Satisfaction with Outcome

[h] To be collected throughout the investigation, from beginning of the treatment until the last visit, in order to identify potential adverse events post-administration an safety evaluation after 15 minutes needs to take place.

3 Statistical and analytical procedures

3.1 Definitions

The following definitions apply:

- Baseline – last observation collected prior to first administering of IMD.
- Change from baseline – post-treatment assessment minus baseline assessment.
- Prior medication – all medication taken within 10 days (whether continuing or not) prior to Day 0.
- Concomitant medication – all medication taken from Day 0 (including medication taken immediately pre-injection and post-injection) until the Week 104 visit.
- Duration of adverse event (AE) – stop date minus onset date + 1.
- Treatment emergent AE (TEAE) – AE starting at the time point of first IMD dosing or thereafter.
- Local TEAEs – TEAE occurring at the treatment area or just around the treatment area (≤ 2 cm from treatment area).
- Adverse device effect (ADE) – AE related to IMD and/or study procedures as well as any AE related to a device deficiency.

3.2 Analysis variables

3.2.1 Performance variables

3.2.1.1 NLF-SRS grading of nasolabial folds

The severity of NLFs will be evaluated live by the investigator and on photographs by an independent reviewer using the NLF-SRS[1].

The scale is described in Table 1.

Table 1 Nasolabial folds severity rating scale (NLF-SRS)

CROMA NLF-SRS grade	Description
0	None/minimal: No visible/minimal nasolabial folds
1	Mild: Shallow but visible nasolabial fold with a slight indentation
2	Moderate: Moderately deep nasolabial fold
3	Severe: Very deep nasolabial fold with prominent facial feature
4	Extreme: Extremely deep and long nasolabial fold with skin redundancy

The left and right nasolabial fold are separately graded.

3.2.1.2 GAIS

Aesthetic improvement will be evaluated by both the investigator and the subject, for each treatment location (right NLF, left NLF) separately, using the GAIS[2], a widely-used instrument presented in Table 2.

Table 2 Global Aesthetic Improvement Scale (GAIS)

[redacted]

3.2.1.3 Subject's satisfaction assessment

Subject's satisfaction with the treatment will be assessed using the FACE-Q questionnaire "Satisfaction with Outcome" scale[3] in Table 3:

Table 3 FACE-Q questionnaire

[redacted]

The results of the six items (a – f) will be summed up. If data is missing for less than three of the six items, the mean of the completed items will be inserted for the missing items. This raw scale summed score (from 1 to 24) will be converted into a satisfaction with outcome score (from 0 to 100) according the FACE-Q satisfaction via outcome conversion table[3].

3.2.1.4 Pain assessment

The subjects will be asked to quantify the pain associated with IMD administration by means of a semi-quantitative 11 point Numeric Pain Rating Scale (NPRS)[4], where 0 corresponds to no pain, and 10 to the worst pain imaginable. Pain intensity will be assessed immediately after completion of initial treatment and approximately 15 min thereafter.

3.2.1.5 Assessment of aesthetic effect

The investigator will assess whether the aesthetic effect is still present in the subject. A live-assessment of the treated areas will be performed and the treated areas will be compared to the subject's photographs obtained at the Baseline Visit. The presence of the aesthetic effect will be recorded as either "Yes" or "No".

3.2.2 Safety variables

3.2.2.1 Medical history and demographic data

Medical history will be collected, covering relevant past medical history with particular reference to facial aesthetic or surgical procedures. Information on year of birth, gender and race will be collected as well.

3.2.2.2 Adverse events

All AEs will be assessed in terms of seriousness (yes/no), severity (mild/moderate/severe), relationship to the IMD or clinical investigation procedures (definite/probable/possible/unlikely/ not related), and outcome (resolved/ongoing/resolved with sequel ae/fatal/unknown). For details see CIP, section 14.4 "AE/SAE assessment".

3.2.2.3 Prior and concomitant medications

Prior medication is defined as all medication taken within 10 days (whether continuing or not) prior to Day 0.

Concomitant medication is defined as all medication taken from Day 0 (including medication taken immediately pre-injection and post-injection) until the Week 104 visit.

At each visit subjects are asked about any new medication taken or changes in current medication, as well as, about any aesthetic procedure applied in the area treated with the investigational device.

3.2.2.4 Pregnancy test

In females of childbearing potential, including women who are postmenopausal for less than 12 months, a urine pregnancy test will be performed using a dipstick test. The result will be recorded in the subject's medical record and the eCRF. This test must be done at each visit except visits 2 and 4 which will be performed by telephone communication approximately 24h post-treatment.

3.2.3 Pharmacokinetic and pharmacodynamic variables

Not applicable.

3.3 Analysis sets

All safety analyses will be based on the Safety analysis set, defined as all subjects who received the IMD.

The Intent-to-Treat (ITT) population is defined as all subjects who received the IMD and have at least one post-treatment assessment. The ITT population will be the primary analysis population for analyses of performance of the investigational device and of aesthetic effects in interim and in final analysis.

The assignment of subjects to the safety analysis set and to the ITT population will be done prior to the interim analysis after Week 24.

A Per-Protocol (PP) population is defined to provide sensitivity analyses in the final analysis. The PP population comprises all subjects in the ITT population, who completed the Week 24 assessment without any major CIP deviations (i.e. CIP deviations that interfere with the performance evaluation or the aesthetic effect evaluation).

Subjects will be excluded from the PP population,

- who violated any inclusion/exclusion criteria during the course of the study;
- who's primary performance outcome measure, the ≥1-point improvement over Baseline on the NLF-SRS based on investigator's live assessment at Week 24 is missing, except it is a missing assessment for treatment related reason, e.g. discontinuation of assessments due to adverse events at least possibly related to IMD or due to lack of efficacy;
- who received any medication or procedure interfering with the performance or aesthetic effect evaluation at Week 24.

Prior to the final statistical analysis, other additional criteria may be added to the list to accommodate for unforeseen events that occurred during the conduct of the trial that result in noteworthy study protocol violations.

The assignment of subjects to the PP population will be finalized within a data review meeting for the final analysis.

3.4 Statistical methods

The final statistical analysis will be done after completion of the investigation by all subjects. The interim analysis will be done after all subjects have completed the Week 24 study procedures.

In general, collected data will be listed and descriptive statistics will be performed, with all repeating measurements being tabulated by visit.

For qualitative and discrete variables, the total number of observations, frequency and percentages of categories / scores will be calculated.

Quantitative and continuous variables will be described by declaring descriptive summary statistics (number of observations, the mean value, standard deviation, minimum, first quartile, median, third quartile, and maximum).

Two-sided 95% confidence intervals will be calculated assuming normal distribution, if not stated otherwise.

The primary and secondary performance analysis and the safety analysis will be done for each manufacturing site, C1 and HQ, separately and for the whole analysis population. The exploratory performance analysis will be done for the whole analysis population, ITT and PP respectively, only.

3.4.1 Demographics and baseline characteristics

Demographic and background data, initial amount of the filler applied, and occurrence of the Touch-up treatment with the amount of the filler applied will be summarized using descriptive statistical methods. Quantitative and continuous variables will be summarized by descriptive statistics and categorical data by frequency tables within each manufacturing site, C1 and HQ, separately and for the whole analysis population.

Prior medications, coded using the WHO Drug Global Dictionary and previous cosmetic procedures on the face as well as medical history including MedDRA coding will be listed per subject.

3.4.2 Discontinuations and dropouts

Subjects discontinuing the study will be listed with the reason for discontinuation and last study day.

3.4.3 Performance analyses

3.4.3.1 Hypotheses

This is a non-comparative clinical investigation and does not entail formal hypothesis testing. All analyses will be done using descriptive statistics.

3.4.3.2 Statistical analyses

The performance analyses will be done in the Intent-to-treat population. Additionally certain analyses will be presented for the per-protocol population also to provide sensitivity analyses in the final analysis.

Individual NLF-SRS grades per visit will be calculated as the mean of grades assigned to the left and the right NLF, respectively, for descriptive summaries.

The improvement over Baseline in the NLF-SRS grade assessed by the investigator will be computed for each subject by subtracting the NLF-SRS grade obtained at each post-baseline time point from ipsilateral NLF-SRS grade obtained at Baseline. The individual improvement per visit will be calculated as the mean of both improvements in the left and the right NLF, respectively, for descriptive summaries.

The response rate will be calculated as the proportion of subjects with NLF-SRS improvement (i.e, reduction in NLF severity grade) of a ≥1 point in both NLFs. The proportion of subjects with NLF-SRS improvement of ≥2 points in both NLFs will be determined accordingly.

Two-sided 95% confidence intervals for the percentages of responders at various time points will be given for the proportions of the NLF-SRS improvements of ≥1 or ≥2 points, respectively using the large sample normal approximation. Also, two-sided 95% confidence intervals for the mean of individual NLF-SRS improvement at various time points will be calculated assuming normal distribution.

Summaries will be provided for the whole analysis population, as well as within each manufacturing site, C1 and HQ, separately.

<u>Primary performance outcome measures</u>
For the primary performance outcome measure, the percentage of responders with a ≥1-point improvement over Baseline on the NLF-SRS based on investigator's live assessment at Week 24, the following will be given by manufacturing site and for the whole analysis population:

- percentage of responders with a ≥1-point improvement over Baseline on the 5-point NLF SRS, based on investigator's live assessment at Week 24 after initial treatment,

<u>Secondary performance outcome measures</u>
For secondary performance outcome measures the following will be given by manufacturing site and for the whole analysis population:

- percentage of responders with a ≥1-point improvement over Baseline on the 5-point NLF SRS, based on investigator's live assessment at Week 4, 36, 52 and optional at Week 65, 78 and 104 after initial treatment,

- descriptive summary statistics for average change versus baseline in the NLF-SRS grade, evaluated by the investigator at Week 4, 24, 36, 52 and optional at Week 65, 78 and 104 after initial treatment,

Exploratory performance outcome measures
For exploratory performance outcome measures the following will be given for the whole analysis population:

- percentage of responders with a ≥2-point improvement over Baseline on the 5-point NLF SRS, based on investigator's live assessment at Week 4, 24, 36, 52 and optional at Week 65, 78 and 104 after initial treatment,
- percentage of subjects with aesthetic improvement using the 5-point GAIS (subjects who have been rated as "very much improved" or "much improved" or "improved"), based on investigator's assessment at Week 4, 24, 36, 52 and optional at Week 65, 78 and 104 after initial treatment, for each treatment location (right NLF, left NLF) separately and overall,
- percentage of subjects with aesthetic improvement using the 5-point GAIS (subjects who have been rated as "very much improved" or "much improved" or "improved"), based on subject's assessment at Week 4, 24, 36, 52 and optional at Week 65, 78 and 104 after initial treatment, for each treatment location (right NLF, left NLF) separately and overall,
- percentage of responders with a ≥1-point improvement over Baseline on the 5-point NLF SRS, based on evaluation by an independent reviewer of photographs for Week 4, 24, 36, 52 and optional at Week 65, 78 and 104 after initial treatment,
- descriptive summary statistics for extent of subject satisfaction with outcome of the treatment, as assessed by the Face-Q questionnaire "Satisfaction with Outcome" at Week 4, 24, 36, 52 and optional at Week 65, 78 and 104 after initial treatment,
- descriptive summary statistics for pain intensity, as evaluated by the subject using an 11-point Numeric Pain Rating Scale (NPRS) immediately after the last injection and 15 min thereafter, at Day 0 and optional at Week 2.
- percentage of subjects having an aesthetic effect, based on the investigator's life assessment at Week 4, 24, 36, 52 and optional at Week 65, 78 and 104.

Subgroups by injection device and by injection technique for performance outcome measures
For analyses by the injection device (needle, cannula) and by injection technique (retrograde, bolus) the following will be given for the whole analysis population:

- percentage of responders with a ≥1-point improvement over Baseline on the 5-point NLF SRS, based on investigator's live assessment at Week 4, 24, 36, 52 and optional at Week 65, 78 and 104 after initial treatment,
- descriptive summary statistics for average change versus baseline in the NLF-SRS grade, evaluated by the investigator at Week 4, 24, 36, 52 and optional at Week 65, 78 and 104 after initial treatment

3.4.4 Safety analyses

The safety analyses will be done in the safety population.

Safety will be evaluated by tabulations of applied volume of the device and AEs.

3.4.4.1 Applied volume of the device

The applied volume of the study device will be summarized by the injection volume applied to achieve optimal aesthetic result with saypha® VOLUME at initial and (optimal) touch-up treatment, respectively. Descriptive statistics will be presented by visit, treatment area and center separately and overall.

3.4.4.2 Adverse events

Adverse events will be coded using the MedDRA dictionary Version 22.1 from September 2019 and listed by subject.

Summaries of AEs will be provided for seriousness, severity, causal relationship to the device and causal relationship to procedure. The summaries will be given for all AEs and regarding TEAEs by center, by manufacturing site and for the whole safety population and for local and non-local, separately.

The incidence of TEAEs will be summarized by preferred term and system organ class, and by seriousness, severity and by causal relationship to the device or procedure. The incidence will be given for all TEAEs, as the proportion of subjects with any TEAE in the safety population.

Incidences by local and non-local TEAE will be determined as the proportion of subjects having an TEAE accredited to a test field in the safety population of subjects exposed to the IMD.

At each level of summarization (system organ class or preferred term) subjects are only counted once, under the greatest reported seriousness, severity or closest relation

If appropriate, listings of ADEs, SAE, SADEs, device deficiencies and subjects who prematurely discontinued the investigation due to AEs will be given.

3.4.4.3 Concomitant medication

Concomitant medication and non-drug therapies will be listed.

For the whole analysis population incidences of concomitant medications by ATC Level 3 and Preferred Name (using the WHO Drug Global Dictionary release September 1, 2019) will be generated.

3.4.5 Pharmacokinetic and pharmacodynamic analyses

Not applicable.

3.5 Data handling conventions

All data management procedures will be detailed in separate, specifically identified files that collectively will be referenced as the Data Management Plan (DMP).

The study will utilize eCRFs, which will include validated 21CFR Part 11 compliant electronic data capture (EDC) software, to collect data. All requested information must be entered on the eCRFs in the areas provided in a timely manner. When changes or corrections are made in the eCRF, the EDC system will maintain a complete audit trail of the person making the changes, the date and time of the change, and the reason for the change.

Adverse event, medical history and procedure terms will be coded using the MedDRA dictionary (Version 22.1) according to the ICH MedDRA Term Selection: Points to Consider release 4.18. All MedDRA coded terms will be provided with all 5 levels, from System Organ Class to Lowest level term, including associated codes.

Prior and concomitant medication will be coded using the WHO Drug Global Dictionary release September 1, 2019. Route, indication and drug manufacturing country will be taken into account when determining the proper coding assignment. Product Name, Medical Product ID, Preferred Name, Drug Code and ATC Levels 1-4 with associated codes will be provided.

The data will be checked and the database structure validated. Once all queries are resolved satisfactorily, the database will be locked. The locked SAS Database will be used to generate the subject listings, tabulations, and analyses.

All data associated with the clinical database, including eCRF data, all external data such as medical coding, third party data will be protected from any changes and afterwards approved by 'Clinical Database Lock Form'.

3.5.1 Missing data

Missing data will not be estimated and/or imputed in any way.

A description of missing data will be provided in the clinical investigation report.

In case a subject prematurely discontinues the clinical investigation (except withdrawal of consent), following assessments should be done at minimum: AE assessment and concomitant medication. Attempts should be made to perform an early termination visit, which should consist of the assessments planned for the Week 104 visit (see section 2.3): AE assessment and concomitant medication, photo documentation, NLF-SRS, GAIS, Face-Q Satisfaction-with-outcome Scale, aesthetic effect by the investigator.

In case of premature discontinuation from the clinical investigation, safety assessments performed at the time point of withdrawal will be reported together with the end of trial visit.

Performance assessments at withdrawal will be assigned for analysis to the closest missing visit before withdrawal, if the subject's withdrawn is between the scheduled visits.

3.5.2 Window for time points

A strict adherence to the visit windows will be required.

Assessments performed out of the planned visit window will be assigned to visit as described in 3.5.1. If both preceding and following planned visits are missing for an performance assessment and the distances are equal, the assignment is performed to the preceding one.

Outcomes not assigned to a planned visit will not be included in the statistical evaluation and will be listed only.

3.5.3 Unscheduled visits

If applicable, the reason for unscheduled visit assessments will be given in data listings together with the outcome of the unscheduled assessment.

For the statistical analysis the unscheduled assessments will be assigned to a planned visit as scheduled in section 2.3, applying the procedure given in 3.5.1 and 3.5.2.

Individual assessments that were performed between visits, even if the visit was performed for the other assessments will be assigned for analysis to the closest missing visit. If both preceding and following performed visits are missing the assessment and the distances are equal, the assignment is performed to the preceding one.

In case a planned on-site visit cannot take place due to COVID-19 and the investigator performs an unscheduled visit as delayed on-site visit, including all missed assessments foreseen for the cancelled on-site visit, the results of the delayed on-site visit will be assigned for statistical analysis to the on-site visit that had to be cancelled.

In case an unscheduled safety phone call replaces an on-site visit the investigator will also record the subject's GAIS assessment and the subject's satisfaction questionnaire via phone and these results will be assigned for statistical analysis to the on-site visit that had to be cancelled .

3.5.4 Pooling of centers for statistical analyses

All statistical analyses for performance and safety variables will be presented over all test sites only.

3.5.5 Statistical technical issues

Not applicable.

3.5.6 Database related issues

Not applicable.

4 Interim analysis

An interim data analysis will be done upon completion of the Week 24 visit by all subjects to obtain information on safety and performance of the device as early as possible.

This interim analysis will be performed on the safety population and will comprise all safety tables planned on data in the state of subject's Week 24 visit.

Additionally all performance analyses up to Week 24 visit will be done on intent-to-treat population for the interim analysis.

The subject data listings delivered for the Interim analysis will only contain collected data up to the date of the last performance assessment assigned to week 24 (according to 3.5.3).

5 Software documentation

The statistical evaluation will be performed using SAS® version 9.3 or later, (Statistical Analysis System, SAS Inc., Cary, NC) software package.

6 References

1 Test-retest reliability of the Croma Nasolabial Folds Severity Rating Scale (NLF-SRS). CANFIELD Scientific, Inc. Final version dated 19-JAN-2017.

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A randomized, double-blind, multicenter comparison of the efficacy and tolerability of Restylane versus Zyplast for the correction of nasolabial folds. Dermatol Surg. 2003; 29: 588-95

3 Klassen AF, Cano SJ, Schwitzer JA, Scott AM, Pusic AL. FACE-Q scales for health-related quality of life, early life impact, satisfaction with outcomes, and decision to have treatment: development and validation. Plast Reconstr Surg. 2015; 135: 375-86.

4 Breivik H, Borchgrevink PC, Allen SM, Rosseland LA, Romundstad L, Hals EK, Kvarstein G, Stubhaug A. Assessment of pain. Br J Anaesth. 2008; 101: 17-24.