Statistical Analysis Plan
for
Final Analysis

Version 1.0

Study:	A prospective, open label, multicenter, post market study evaluating Princess® VOLUME Lidocaine for the correction of nasolabial folds
Study-ID:	CPH-401-201258
Sponsor / Contact:	CROMA-PHARMA GmbH Industriezeile 6 2100 Leobendorf Austria
Evaluation:	[redacted]
[redacted] code	3381
Version:	1.0 of 15Dec2016
Previous versions:	-

Revision history

Version	Author	Date	Reason for Revision
1.0	[redacted]	15Dec2016	Final Version 1.0

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List of Abbreviations

In the following abbreviations are listed as used within this statistical analysis plan or which might occur within the tables and listings:

AE	Adverse event
BMI	Body mass index
CI	Confidence interval
CRF	Case report form
ITT	Intent-to-treat
GAIS	Global aesthetic improvement scale
MedDRA	Medical dictionary for regulatory activities
modITT	modified ITT
N	Number of subjects
PP	Per-protocol
PT	Preferred term
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
TLG	Tables, listings, graphs
NPRS	Numeric pain rating scale
NLF-SRS	Nasolabial folds severity rating scale
WHO-DD	World health organization drug dictionary

1 General

This statistical analysis plan (SAP) was defined by the sponsor and the responsible statistician. It is based upon the study protocol (version 3.0 of 31Oct2016) and contains detailed description of the statistical methods described therein.

The SAP describes prospectively the analyses to be performed on study data. It was finalized prior to enrolment of first study subject.

Study design and objectives

This is a prospective, open label, multicenter, post-market investigation to evaluate the performance and safety of Princess® VOLUME Lidocaine for the correction of nasolabial folds.

Following informed consent and screening, eligible subjects with moderate to severe nasolabial folds will be treated with Princess® VOLUME Lidocaine, and will return for follow-up assessments 2, 4, 24 and 36 weeks after the treatment. A touch-up treatment may be done at Week 2, if deemed appropriate by the investigator.

Princess® VOLUME 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 0.3% lidocaine hydrochloride. It is administered by injection into the deep dermis or subcutis. The volume applied depends on the size of the area which requires correction and will be selected by the investigator, but will not exceed 10 mL in total per treatment.

The performance of the investigational device will be evaluated by the investigator by assessing severity of nasolabial folds using the nasolabial folds severity rating scale (NLF-SRS) (4, 24 and 36 weeks after the treatment and in comparison to Day 0), global aesthetic improvement scale (GAIS) (4, 24 and 36 weeks after the treatment). The subject will evaluate pain intensity associated with the treatment (at Day 0 and at Week 2 (if touch-up treatment occurred)), and satisfaction with the treatment at 4, 24 and 36 weeks after the treatment.

The safety will be evaluated based on occurrence of adverse events, which will be collected throughout the investigation.

Number of subjects

Sample size calculation was performed by the sponsor. Up to 60 subjects with moderate to severe nasolabial folds will be enrolled in order to obtain the 24-week performance and safety data from at least 40 of them. If less than 60 subjects will be recruited at the point when at least 40 subjects complete the Week 24 assessment, a decision to continue the recruitment up to 60 subjects in total will be made by the sponsor. This sample size is arbitrarily selected and is considered appropriate for the post-market follow-up clinical investigation and sufficient to provide robust estimations on performance and safety parameters in the study population. With a sample size of 40 to 60, a two-sided 95% confidence interval for a single proportion using the large sample normal approximation will extend 0.076 to 0.093 from the observed proportion for an expected proportion of 0.900. Thus, a robust estimation of the success rate at week 24 can be derived.

Study and treatment duration

The duration of the clinical investigation will be 9 months for each participating subject. A single application of Princess® VOLUME Lidocaine, with optional Touch-up treatment after two weeks, if the desired level of correction has not been achieved with the initial application, is planned.

The total expected duration of the clinical investigation is about 13 months with an expected recruitment period of 3 to 4 months.

2 Performance and Safety Endpoints

2.1 Primary Performance Endpoints

The primary performance endpoints for this study are:

- The average change versus baseline (Day 0) in the NLF-SRS grade of nasolabial folds at Week 24 as evaluated by the investigator.
- The proportion of subjects with the NLF-SRS grade reduced by ≥1 point versus baseline at Week 24.

2.2 Secondary Performance Endpoints

The following secondary performance endpoints will be analyzed:

- The average change versus baseline in the NLF-SRS grade at Week 4 and Week 36 as evaluated by the investigator.
- The proportion of subjects with the NLF-SRS grade reduced by ≥1 point versus baseline at Week 4 and Week 36.
- The proportion of subjects with aesthetic improvement at Week 4, Week 24 and Week 36, as evaluated by the investigator using the global aesthetic improvement scale (GAIS)
- Subjects' satisfaction with aesthetic outcome of the treatment at Week 4, Week 24 and Week 36, as evaluated by the subject.
- The average 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 Weeks 24 as evaluated by the independent reviewer of photographs.

2.3 Safety Endpoints

- Occurrence and frequency of adverse events (AEs).

2.4 Additional Endpoints

- The proportion of subjects with the NLF-SRS grade reduced by ≥2 points versus baseline at Week 4, 24 and Week 36.
- The proportion of subjects with the NLF-SRS grade reduced by ≥1 point versus baseline at Weeks 4 and 36 as evaluated by the independent reviewer of photographs.

3 Statistical Analysis Sets

3.1 Safety Analysis Set (SAF)

The safety analysis set (SAF) consists of all subjects who have been treated with the investigational device.

3.2 Intention-to-treat Population (ITT)

The intent-to-treat population (ITT) consists of all subjects who received the investigational device and had at least one post-treatment assessment (e.g., first pain assessment after injection).

3.3 Modified Intent-to-treat Population (modITT)

The modified intent-to-treat population (ITT) consists of all subjects who received the investigational device and had at least one post-treatment NLF-SRS assessment by the investigator.

3.4 Per-Protocol Set (PP)

All subjects who have received the investigational device and have completed the investigation without major clinical investigation plan deviations. Deviations from the protocol will be defined and classified during the data review meeting (see section 4.5). Subjects with major deviations from protocol will be excluded from the PP population.

3.5 Assignment of Analysis Sets to Analysis

The ITT will be considered the primary analysis set. All performance and additional endpoint analyses are based on the ITT. All primary endpoint analyses will be also performed for the modITT and PP. All secondary or additional endpoint analyses will be also performed for the PP. All safety analyses will be based on the SAF.

3.6 Visit Terminology

The following visit notation will be used for table, listing, and graph presentation:

Visit no.	Notation used on the case report form	Notation used for TLG
1	VISIT 1 (Day 0)	Baseline
2	VISIT 2 (Week 2 ± 2 days)	Week 2
3	VISIT 3 (Week 4 ± 4 days)	Week 4
4	VISIT 4 (Week 24 ± 7 days)	Week 24
5	VISIT 5 (Week 36 ± 7 days)	Week 36

4 Statistical Evaluation

Continuous variables will be presented using number of subjects with non-missing observations (N), mean, standard deviation (SD), median, minimum (min), maximum (max), 1st quartile and 3rd quartile. In general, min and max will be presented to the same level of precision as the raw data; means and medians, SD, and quartiles will be presented to one further decimal place. Categorical variables will be presented by frequency tables, using number and percentage. Percentages will be presented to one decimal place.

Baseline is defined as the measurements taken on Day 0 before treatment.

For each subject two facial folds (right and left) are rated per time point and grades (NLF-SRS and GAIS). As no great difference between those two folds is expected, the mean grade of both measurements will be calculated per time point.

4.1 Dispositions of Subjects and Analysis Sets

Disposition of subjects and analysis sets

The disposition of subjects and analysis sets, subjects per center, inclusion and exclusion criteria, and the status at study termination will be shown. In case subjects discontinue, the reason for discontinuation will be described.

The number of subjects available per visit will be presented.

4.2 Demographics and Other Covariates

Demographic data

Demographic data (age, gender, and race) will be tabulated. Age is derived from date of baseline – date of birth in days /365

Treatment application

Injection technique used, application of anesthetic cream (yes/no) will be tabulated using frequency tables by visit.

Basic statistics for number of devices used, injected total volume of right and left nasolabial fold will be given.

Pregnancy test

The results of the pregnancy test will be listed for females of childbearing potential only.

Previous and concomitant medication

Previous and concomitant medication will be coded according to World health organization drug dictionary (WHO-DD; June 2015).

Medications will be tabulated by anatomic group (ATC) level 4, and WHO-DD preferred term. The number of entries, as well as the number and percentage of affected subjects will be reported.

Previous and concomitant medications will be described separately.

- Previous medications are 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 medications taken immediately pre-injection and post-injection) until Week 36.

If the start or stop date is incomplete and the allocation to previous or concomitant is not clear the medication will be considered to be concomitant.

Medical history will be listed only.

4.3 Performance Analysis

This is a non-comparative study and does not entail formal hypothesis testing. All primary and secondary variables will be analyzed using descriptive methods.

The individual NLF-SRS grades and the individual GAIS grades per visit will be calculated as the mean of grades assigned to the left and the right nasolabial fold, respectively.

The absolute NLF-SRS change from baseline will be computed by subtracting the value obtained at baseline from the value of the respective visit.

All adverse events (AE), AEs with relationship to the investigational medical device or procedure, and SAEs will be summarized by preferred term and system organ class.

4.3.1 Analysis of Primary Performance Endpoints

The primary performance endpoints will be analyzed for the ITT, modITT and PP.

The change from baseline in the average grade of NLF-SRS as assessed by the investigator to Week 24 will be summarized with descriptive statistics for continuous variables. Additionally, the 95% confidence intervals of the mean will be given.

The proportion of subjects with the average grade of NLF-SRS as assessed by the investigator reduced by ≥1 point versus baseline will be summarized with frequency tables at Week 24.

4.3.2 Analysis of Secondary Performance Endpoints

All secondary performance endpoints will be analyzed for the ITT and PP

Basic statistics for the average grade of NLF-SRS will be tabulated by visit. The change from baseline in the average grade of NLF-SRS as assessed by the investigator to Week 4 and 36 will be summarized with descriptive statistics for continuous variables.

The proportion of subjects with the average grade of NLF-SRS as assessed by the investigator reduced by ≥1 point versus baseline will be summarized with frequency tables at Week 4 and 36.

The proportion of subjects with aesthetic improvement at Week 4, 24, and 36, as assessed by the investigator will be tabulated using frequency tables. Aesthetic improvement is defined as having a GAIS grade < 4 (yes/no).

GAIS categories:

- 1 - very much improved
- 2 - much improved
- 3 - improved
- 4 - no change
- 5 - worse

The proportion of subjects with the average grade of NLF-SRS as assessed by the independent reviewer of photographs reduced by ≥1 point versus baseline will be summarized with frequency tables at Week 24.

Subjects' satisfaction with aesthetic outcome of the treatment will be summarized with frequency tables at Week 4, 24 and 36 and displayed via individual profile plots.

Pain will be assessed twice after treatment by means of an 11-point numeric pain rating scale (NPRS).

Improvement in pain score will be categorized as follows:

- Yes: Pain score second assessment – pain score first assessment < 0
- No: Pain score second assessment – pain score first assessment > 0
- Equal: Pain score second assessment – pain score first assessment = 0

Resulting pain scores and improvement in pain score (yes/no/equal) will be tabulated with frequency tables by assessment (first and second) and visit in case of touch-up treatment. Further, basic statistics will be provided for the pain scores and the change between first and second pain score (= score at second assessment – score at first assessment).

4.4 Analysis of Additional Endpoints

All additional endpoints will be analyzed for the ITT and PP.

The proportion of subjects with the average grade of NLF-SRS as assessed by the investigator reduced by ≥2 points versus baseline will be summarized with frequency tables at Week 4, 24 and 36.

The proportion of subjects with the average grade of NLF-SRS as assessed by the independent reviewer of photographs reduced by ≥1 point versus baseline will be summarized with frequency tables at Week 4 and 36.

4.5 Safety Analysis

Adverse events (AEs)

AEs will be coded by using the Medical dictionary for regulatory activities (MedDRA) version 19.1.

AEs will be tabulated by system organ class (SOC) and preferred term (PT). The number of entries, as well as the number and rate of affected subjects will be reported.

Deaths, SAEs and AEs with a causal relationship to the investigational device or procedure (definite, probable, possible or missing relationship) and AEs by intensity (mild, moderate, severe) are presented separately. Listings of adverse events leading to treatment discontinuation and those identified as "severe" will be provided.

4.6 Missing Values

No missing value imputation methods will be applied.

4.7 Data Base Closure and Data Review

A data base closure will be performed prior to the analysis. All parameters will be checked, as specified in the data validation plan, and all queries will be resolved before data base closure and analysis. External data, such as "NLF-SRS grade as evaluated by the independent photographic reviewer" should be provided to [redacted] in an appropriate format (e.g., SAS database or excel file) two weeks prior to the data review meeting.

Data review meeting (DRM)

There will be a data review meeting prior to locking the database. Protocol deviations will be checked and subjects will be allocated to the analysis sets. At least the following items will be discussed:

- Any protocol deviation in general
- Use of prohibited medication
- Premature discontinuation during the study
- Missing primary performance variable at baseline and follow-up
- Visits performed out of visit window

These evaluations and assessments will be done together and in agreement with the sponsor, however [redacted] will provide the sponsor with the appropriate subject listings upfront to the DRM (as defined in appendix A). Data review can be done via a telephone conference or in writing. Afterwards DRM minutes will be prepared by [redacted] and signed by [redacted] and sponsor. DRM minutes must be finalized before data base closure.

4.8 Miscellaneous

For qualitative variables the frequencies (absolute and relative) are calculated. If no further remark is given in the description of the tables following format will be used for all tables with qualitative variables:

	Y-variable(s)					
	Category 1		Category 2		Total	
X-variable(s)	N	%	N	%	N	%
category 1						
category 2						
missing						
Total		100.0		100.0		100.0

For this standard format the description of the tables in Appendix A determines only the X- and Y-variables. If another format of table is described in the details to the tables, the real design will be determined by the technical possibilities within SAS and may not look identical to the provided example. However, all information as displayed will be included.

Quantitative parameters will be described by declaring the mean value, standard deviation, minimum, first quartile, median, third quartile, and maximum. In the description of the tables this will be denoted by „basic statistics".

The listings are always sorted by center and subject. If a different sorting order should be used for some listings this will be remarked separately. The variables for the special listings are explicitly given in the description of listings. All listings will be presented for the safety analysis set, if not stated differently, and indicator variables for further analysis sets, e.g., ITT, will be added.

The following title will be used for all generated tables and listings:

CROMA – VINO Page # of #

<Table/Listing/Graph NNN: Description of contents>

<Subtitle for description of contents - if applicable>

<Analysis set>

The numbering NNN of the tables/listings/graphs will be stated in the detailed description (Appendix A).

Following footnote will be used for all generated tables, listings, and graphs:

[redacted], <Actual date> Author: <Author of program> Program: <Name of program>

The statistical evaluation will be performed using SAS version 9.3 or higher.

6 Deviations from the Protocol

- Additional endpoint are included and will be analyzed:
  - The proportion of subjects with the NLF-SRS grade reduced by ≥2 points versus baseline at Week 4, 24 and Week 36.
  - The proportion of subjects with the NLF-SRS grade reduced by ≥1 point versus baseline at Weeks 4 and 36 as evaluated by the independent reviewer of photographs.
- An additional study population will be considered, the modified ITT for the primary endpoint.

7 Signatures

Statistician:
[redacted]
Date (ddmmmyyyy) Signature

Sponsor
[redacted]
Date (ddmmmyyyy) Signature

Sponsor
[redacted]
Date (ddmmmyyyy) Signature