A urine pregnancy test (dipstick test) was performed prior to applications of investigational product at the planned visits (Visit 1 to Visit 3).

3.3 Ethical considerations

Taking into account the risks and benefits as outlined in the CIP, the performance of the investigation was considered ethically sound since the expected benefits of the IMD appeared greater at present than the risks for the volunteers.

3.4 Data quality assurance

This clinical investigation was monitored by the Sponsor's representative. The extent of monitoring and source data verification was specified in the Monitoring Plan.

Prior to initiation of the clinical investigation at any of the investigation sites, the monitor had visited the site in the course of Site Initiation Visit and had discussed the CIP, the Electronic Case Report Form (eCRF) and other investigation-related documents and forms with the investigator and their staff, and verified that all prerequisites for the initiation were met. No subject should have been enrolled into the investigation before the initiation visit.

During the investigation, further monitoring visits were performed according to ISO 14155:2011, the applicable standard operating procedures, and local regulations. At each visit the monitor had checked the progress of enrolment, and reviewed source data for adherence to the CIP, reviewed eCRFs against source data for completeness, accuracy and consistency, and was also checked if the IMD had been stored, dispensed and accounted for according to respective specifications. The monitor had informed the investigator or their authorized designee on any error/discrepancies in the eCRF and the source data, and ensured that appropriate data corrections or clarifications were made in appropriate manner, according to GCP. In case of any other observed default, the monitor would have been informed the investigator, and the Sponsor when appropriate, would have discussed and agreed with the investigator suitable corrective actions, and would have followed-up their implementation and resolution.

Upon completion of the investigation, the monitor will ensure that all investigator's records are accurate and complete, all documents needed for the Sponsor's files are retrieved, the remaining investigation supplies, including the IMD, will be disposed of or returned, and that all previously identified issues have been resolved.

The investigator and their institution should have permitted the monitoring of the investigation, and should have provided the monitor a direct access to those portions of the subject's primary medical records, which directly concern this clinical investigation. Furthermore, key study personnel should have been available to assist the monitor during the monitoring visits.

A GCP audit (by an internal quality assurance unit) was not performed during the course of the study.

An inspection was carried out by "Bundesamt fuer Sicherheit im Gesundheitswesen/Austrian Federal Office for Safety in Health Care" (BASG) from 15JUL2019 until 17JUL2019 at MaRa-Medical Aesthetic Research Academy, Dr. Thomas Rappl (site 03). Details of the inspection outcome will be provided as soon as the inspection report is available.

3.5 Subject population

3.5.1 Selection of subjects

The subjects were selected according to defined inclusion and exclusion criteria.

A gender specific subdivision into groups was not necessary in this clinical investigation.

3.5.2 Inclusion criteria

All of the following criteria had to be met for inclusion of a subject into this clinical investigation:

1. Male or female, 18 years of age or older.
2. Subjects deemed by the treating physician to have LCL and/or PR of sufficient baseline severity to merit treatment with Princess® RICH to be corrected.
3. A negative urine pregnancy test at Visit 1 and commitment to use an adequate method of birth control for the duration of the clinical investigation (for women of childbearing potential only).
4. Healthy skin in the facial area and free of diseases that could have interfered in cutaneous aging evaluation.
5. Willingness to abstain from any aesthetic or surgical procedures in the treatment area for the duration of the clinical investigation.
6. Written signed and dated informed consent.

3.5.3 Exclusion criteria

Subjects were to be excluded from the clinical investigation, when one or more of the following conditions were met:

1. Subjects who tended to develop hypertrophic scars, had pigment disorders or had susceptibility to keloid formation.
2. Subjects with a history of autoimmune disease or who were receiving therapy for modification of immune response, e.g. biologics, systemic corticosteroids, cytostatic drugs.
3. Subjects who were known to be hypersensitive to hyaluronic acid or glycerol.
4. Subjects who had previously received permanent fillers in the areas to be treated.
5. Subjects who were pregnant or breast feeding.
6. Subjects who were anticoagulated or with history of bleeding disorder.
7. Subjects receiving daily treatment with platelet aggregation inhibitors (e.g. acetylsalicylic acid) unless previously cleared by their primary care physician.
8. Subjects who had cutaneous, inflammatory and/or infectious processes (e.g., acne, herpes) present at V0, recurrent herpes simplex or (pre) cancerous lesions in the areas to be treated.
9. Subjects with known Diabetes mellitus or uncontrolled systemic diseases in the assessment of the investigator.
10. Subjects who had or were planning to undergo laser therapy, chemical peeling, dermabrasion or botulin toxin treatment in the area to be treated within less than three months prior to and during the course of the study.
11. Current participation in another clinical investigation.
12. Subjects whose participation in clinical trials was prohibited by the Austrian Medical Devices Act (e.g., persons with a legal custodian appointed due to mental disability, prisoners, soldiers and other members of the armed forces, civil servants).

3.5.4 Restrictions during the clinical investigation

Contraception

The safety of Princess® RICH for use during pregnancy has not been established, so women of childbearing potential should have used contraception or avoid unprotected sexual intercourse throughout the clinical investigation. Any pregnancy occurring in study subjects during the investigation should have been reported as an AE and followed-up as described in Section 14.6 of CIP V3.0.

Other restrictions

The following restrictions were applied to all subjects:

- Make-up should not be applied for 12 hours after injection;
- Subjects should have kept their facial skin care and makeup regimen constant over the study duration and must not apply any of those in the measured area on the day of corneometer and cutometer measurements. This includes the first day, so subjects must have been informed in advance;
- Prolonged exposure to sunlight or ultraviolet radiation had to be avoided for one week after the injection; subjects should abstain from frequent solarium visits;
- To avoid a risk of implant mobility, the treatment site should not have been massaged or exposed to pressure for few days following the injection;
- Use of saunas or Turkish baths were prohibited for one week after the injection.

3.5.5 Sample size

It was planned to recruit approximately 100 subjects in order to obtain Week 8 performance and safety data from at least 93 of them.

3.6 Treatment and treatment allocation schedule

3.6.1 Assignment of treatments and enrollment

Enrollment was performed competitively between the centers

Upon signature of informed consent (screening period) each subject received a 5-digit screening number, which was composed of:

Digits 1 and 2: trial center (01, 02, 03)

Digits 3, 4, and 5: individual screening number within the center (consecutively in the order of screening within the center: 001, 002, etc.)

The center number and the individual screening number were separated by a hyphen.

It was at the discretion of the treating physicians which area was selected for IMD treatment (LCL left and right, and/or PR).

3.6.2 Manner of treatment and selection of doses

Methods of use

The IMD was administered to eligible subjects at Visit 1(Day 0), Visit 2 (Week 3) and Visit 3 (Week 6)

Preparation for administration

The treated skin was thoroughly cleaned and disinfected prior to injection of the device and appropriate aseptic technique was employed throughout the procedure. Sensitive skin might have been pre-treated with a local anesthetic patch or cream. If anesthetic was used, the type of anesthetic and exact time of application would have been recorded in the electronic Case Report Form (eCRF).

Prior to use of the device, the luer-lock adapter was held securely and the tip cap was removed by twisting and pulling carefully, to prevent formation of bubbles. The syringe was held and the enclosed needle was firmly attached. The needle was secured tightly by twisting clockwise. The syringe was held correctly if the backstop opens at the back, toward the hand in which it was held. These steps were illustrated in the IFU.

Injection technique

Princess® RICH was indicated to inject into the superficial dermal tissue. The treating physician had selected the technique for IMD application. The device might be injected using the multipuncture technique which is used in superficial wrinkle treatment. This technique consists in administering multiple injections alongside the wrinkle.

Completion of administration

After treatment, the subject was requested to stay in the trial site for ten minutes after completion of treatment, to detect for possible blanching caused by arterial occlusions. After this time the investigator checked the subject for any adverse event and confirmed that there were no adverse events before leaving the trial site.

Application of ice packs for 5-10 min. post injection was optional and might reduce redness and swelling.

Applied volume of the device

The amount of the device injected depended on the condition treated and was selected by the investigator. The actual volume injected was read off the syringe by the investigator and recorded in the eCRF, incl. area of application, date, and exact start time and end time of injection.

Precautions

- This device should have been administered only by a doctor who is familiar with superficial dermal injections
- The device should not be used in areas presenting cutaneous, inflammatory and/or infectious processes (e.g. acne, herpes).
- Sensitive skin might be pre-treated using a local anaesthetic patch or cream.
- An automated injection system should not have been used to inject this product.
- Subjects should have been advised not to apply any make-up for 12 hours after the injection and to avoid prolonged exposure to sunlight and UV or using saunas or Turkish baths for one week after the injection.
- To avoid a possible risk of product mobility, the patient should have been advised not to massage the treatment site for a few days after the injection.
- There are incompatibilities between sodium hyaluronate and quaternary ammonium compounds such as benzalkonium chloride solutions. Therefore the device should never be placed in contact with these substances or with medical-surgical instruments that have been in contact with these substances.
- The device should have been used only with the needle and syringe provided by the manufacturer.
- The needle should not have been manipulated or bent, if the needle is blocked, pressure on the plunger rod should not be increased, instead injection should have been stopped and the needle replaced.
- After use of the syringe, needle and remaining contents should have been disposed appropriately and the device should have never been re-used.
- There are no available clinical data (efficacy, tolerance) about injecting the device into an area which has already been treated with any other filling product.

Rescue medication

In case of overcorrection or occurrence of nodules or vascular compromise, a commercially available hyaluronidase injection (e.g., Hylase® or equivalent) could be used at investigator's discretion.

3.7 Prior and concomitant therapy

Prior medication was defined as all medication taken within 10 days (whether continuing or not) prior to the IMD administration on Visit 1.

Concomitant medication was defined as all medication taken from Day 0 (including medication taken immediately pre-injection and post-injection) until Week 16.

At each visit the subject was 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.

All prior and concomitant medication and treatments were recorded in the subject's medical record and the eCRF.

3.8 Follow-up

Three follow-up visits (Visit 4, 5 and 6) were scheduled at 8, 12 and 16 weeks after the initial treatment. The follow-up period was extended to evaluate long-term safety/performance. The prolongation/extension of investigation included 3 optional further visits (Weeks 24, 36, and 52).

3.9 Statistical analysis

The statistical evaluation was performed at bioskin using the software program SAS version 9.3 (Statistical Analysis System, SAS Inc., Cary, NC).

3.9.1 Hypotheses

This was a non-comparative study and does not entail any hypothesis testing.

3.9.2 Rationale for the sample size

Approximately 100 subjects were planned to be enrolled in order to obtain Week 8 performance and safety data from at least 93 of them.

With a sample size of 93, a two-sided 95% confidence interval for a single proportion using the large sample normal approximation would extend 0.10 from the observed proportion for an expected proportion of 0.60. Thus, a robust estimation of the response rate at Week 8 could be derived.

3.9.3 Analysis sets and type of analysis

All performance analyses were done in the Intent-to-Treat population, defined as all subjects who received the investigational device and had at least one post-treatment assessment. All safety analyses were based on the safety analysis set, defined as all subjects who received the investigational device.

A Per-Protocol (PP) population (valid cases set = VCS) for performance analysis was defined as all subjects in the Intent-to-Treat population, who completed the trial without any protocol deviation that interferes with the performance evaluation for the primary endpoint.

Subjects were to be excluded from the PP population (VCS),

- who violated any inclusion/exclusion criteria during the course of the study;
- who had taken any medication or procedure interfering with the performance evaluation;

who's primary performance endpoint, the at least "improved" versus baseline in the fine lines of the LCL on both sides and/or the PR as assessed with the GAIS (see Section 3.2.2, based on the investigator assessment at Week 8 is missing.

Prior to statistical analysis other additional criteria might have been 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 was finalized within the data review meeting (DRM).

The ITT population was the primary analysis population for performance analyses. Performance analyses in the PP population were supportive.

Two-sided 95% confidence intervals for the percentages of responders were given.

The primary performance outcome measure was the percentage of responders defined as at least "improved" versus baseline in the fine lines of the LCL on both sides and/or the PR, as assessed with the GAIS and based on the investigator's assessment at Week 8.

The secondary performance outcome measures

- Change from baseline in skin hydration at Weeks 3, 6, 8, 12 16, and optional at Weeks 24, 36 and 52,
- Change from baseline in skin tone (R0) at Weeks 3, 6, 8, 12 16, and optional at Weeks 24, 36 and 52,
- Change from baseline in skin elasticity (R2) at Weeks 3, 6, 8, 12 16, and optional at Weeks 24, 36 and 52

were analyzed by visit using descriptive statistics including 95% confidence intervals for the mean.

For the secondary performance outcome measures

- Percentage of responders defined as at least "improved" versus baseline in the fine lines of the LCL on both sides and/or the PR, as assessed with the GAIS and based on the investigator's assessment at Weeks 12 and 16 after initial treatment,
- Subject satisfaction with treatment at Weeks 8, 12, 16, and optional at Weeks 24, 36 and 52
- Aesthetic effect assessed by investigator optional at Weeks 24, 36 and 52

frequency tables were given.

Note that according to the design of the study the clinical investigation might have been terminated at an earlier time point.

Note that according to the design of the study the clinical investigation can be extended to 52 weeks at a maximum based on the outcome of the assessment on aesthetic effect. This interim reports contains data until Week 16.

3.9.4.4 Safety analyses

The safety analyses were done in the safety analysis set. Safety was evaluated by tabulations of extent of exposure to investigational device, use of additional anaesthetic and adverse events (AEs).

3.9.4.4.1 Extent of exposure to investigational device

The extent of exposure to investigational product was presented by applied injection volumes of Princess® RICH per right and left LCL, per PR, total per visit, as well as overall and descriptive statistics were presented.

Additionally a frequency table that shows the counts for use of additional anaesthetic was given.

3.9.4 Statistical methods

The statistical analysis was done after completion of the investigation by all subjects.

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

If not described otherwise descriptive statistics for continuous variables are included the number of observations, minimum, maximum, mean, standard deviation, median, and interquartile range. For discrete variables, summary statistics were included the total number of observations, frequency and percentages. All percentages were calculated based on the number of non-missing observations.

Two-sided 95% confidence intervals for proportions and for mean values using large sample normal approximation were calculated.

3.9.4.1 Demographics and baseline characteristics

Demographic and background data were summarized using descriptive statistical methods. Continuous data were summarized by descriptive statistics and categorical data by frequency tables.

Previous and concomitant medications were coded using the WHO Drug Global Dictionary in its latest available version at the time point of coding was listed.

3.9.4.2 Discontinuations and dropouts

Subjects discontinuing the study were to be listed in the clinical study report with reason for discontinuation and last study day given.

3.9.4.3 Performance analyses

3.9.4.3.1 Hypotheses

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

3.9.4.3.2 Statistical analyses

All safety analyses were based on the safety analysis set, defined as all subjects who received the investigational device. The performance analyses were done in the Intent-to-treat population. Additionally the performance analyses were presented for the per-protocol population also.

For descriptive summaries individual skin hydration, skin tone (R0) and skin elasticity (R2) values were calculated as the mean of the 6 repeated measurements (3 left and 3 right) and as the mean of 6 repeated measurements for PR (PR left and PR right).

The percentage of responders was calculated as the proportion of subjects with at least “improved” versus baseline in the fine lines of the LCL on both sides and/or the PR as assessed with the GAIS by investigator assessment at Weeks 8, 12 and 16 after initial treatment. Note that an “improved” for one of the treatment areas (either LCL or PR) is sufficient for subjects with LCL and PR treated.

3.9.4.4.2 Adverse events

Adverse events were coded using the medical dictionary for regulatory affairs (MedDRA) dictionary (starting with version 21.1 and interim analysis with current valid version, 22.0 from March 2019) and listed by subject.

Summaries of AEs were provided for seriousness, severity, duration, causal relationship to the device and causal relationship to procedure. These summaries were given for local (i.e. at most 2 cm from test area or on test area) and non-local (i.e. more than 2 cm from test area or no location related to test area) AEs, separately.

For local AEs the treatment area of the IMD application was documented in the electronic case report form (eCRF), while non-local AEs were accredited to an individual IMD dose, if the start of the AE is at the time point of application of the IMD or thereafter.

The incidence of AEs was summarized by preferred term (PT) and system organ class (SOC), and by seriousness, severity, duration, and by causal relationship to the device or procedure.

The incidence was given for all AEs, as the proportion of subjects with any AE in the safety analysis set. At each level of summarization (SOC or PT) subjects were only counted once, under the greatest reported severity, duration or closest relation.

If appropriate, listings of adverse devices effects (ADEs), serious adverse events (SAEs), serious adverse devices effects (SADEs) and subjects who prematurely discontinued the investigation due to AEs were to be given.

3.9.4.4.3 Laboratory analyses

Outcomes of the urine pregnancy tests were listed.

4. Results

The first subject was screened, gave informed consent, and received initial treatment on October 25, 2018 at the site Yuvell Fine Aesthetics. The last subject was enrolled at the site Dermatology and Venerology Clinic on 13FEB2019. For the clinical investigational period until Week 16, this was the last subject who completed the Week 16 Visit on 12JUN2019.

4.1 Deviations from the CIP

Major deviations from the CIP

In total 28 major deviations from the CIP were reported in 18 subjects (see Appendix B, Listing 2.1).

Most of these major protocol deviations (PDs) belonged to the PD category 5.7 'Wrong study treatment/administration/dose': 14 PDs in 8 subjects; in these 8 subjects the IMD treatment was not administered per protocol.

Subject ID No.	Major PD description, category 5.7 'Wrong study treatment/administration/dose'
01-004	Visit 3: injection not done for perioral rhytids due to subject decision.
01-016	Visit 2: injection not done for left lateral canthal lines due to previous AE.
	Visit 2: injection not done for right lateral canthal lines due to previous AE.
	Visit 2: injection not done for perioral rhytids due previous AE.
	Visit 3: injection not done for perioral rhytids due to subject decision.
02-007	Visit 3: injection not done for perioral rhytids due subject decision.
03-001	Visit 3: A cannula and not the needle included in the IMD kit was used at injection.
03-002	Visit 3: A cannula and not the needle included in the IMD kit was used at injection.
03-011	Visit 3: No administration of canthal lines done - not wanted.
	Visit 3: A cannula and not the needle included in the IMD kit was used at injection.
	Visit 2: A cannula and not the needle included in the IMD kit was used at injection.
03-014	Visit 2: Cannula was used for device administration (cannula type technique = linear threading) of lower lip and multipuncture of upper lip.
	Visit 2: Cannula (cannula type technique = linear threading) was used for device administration of perioral rhytids.
03-033	Visit 3: Cannula was used for device administration.

The next frequently noted PD category was 5.5 'Visit completion': 11 PDs in 8 subjects. These subjects had either a missed visit or the visit (including phone contact) was out of window. 1 of the subjects (Subject ID No. 01-022) dropped out after Visit 1 (see also Section 4.2).

Subject ID No.	Major PD description, category was 5.5 'Visit completion'
01-002	Visit 2: Visit missed. Visit 2: Patient missed the visit.
01-003	Visit 4: was not done 52 to 60 days after Visit 1; difference 78 days. Visit 2: Patient missed the visit.
01-005	Visit 4: was not done 52 to 60 days after Visit 1; difference 78 days.
01-015	Visit 3: Visit missed. Visit 3: Patient missed the visit.
01-018	Visit 3: Visit missed.
01-022	Subject dropped out after Visit 1.
01-024	Visit 4: was not done 52 to 60 days after Visit 1; difference 75 days.
01-025	Visit 4: was not done 52 to 60 days after Visit 1; difference 74 days.

3 PDs reported in 3 subjects belonged to the PD category 5.6 'Assessment or time point completion' (1 of these subjects* had also a major PD of category 5.7, see above).

Subject ID No.	PD description category 5.6 'Assessment or time point completion'
01-008	Visit 1: right lateral canthus photography done after IMD administration.
03-014*	Visit 4: Photos were done 5 days after IMD. Photos done 26JAN2019 and visit was done 21JAN2019.
03-023	Visit 4: Photos were done 5 days after IMD. Photos done 26JAN2019 and visit was done on 21JAN2019.

18 of the major PDs led to exclusion from the PP population (see also Section 4.2) as these may have had an impact on effect and may thus have interfered with the evaluation for GAIS at Week 8'. This applies for 17 subjects, 1 subject was the dropout.

Minor deviations from the CIP which did not affect the outcome of the investigation as they had no impact on effect and thus did not interfere with GAIS evaluation at Week 8 are listed in Appendix B, Listing 2.1.

4.2 Disposition of subjects and data sets analyzed

A summary of subject enrollment and evaluability can be found in Appendix A, Table 1.1 A summary of subject completion/discontinuation can be found in Appendix A, Table 1.2.

It was planned to recruit approximately 100 subjects in order to obtain Week 8 performance and safety data from at least 93 of them. A total of 102 subjects were screened. All 102 subjects (101 female and 1 male) were ≥ 18 years, with sufficient severity of LCL and/or perioral rhytids as assessed by the treating physicians and were enrolled across 3 centers in this clinical investigation.

The enrolment per site was follows:

- Site 1 Dermatology and venerology clinic: 25 subjects
- Site 2 Yuvell fine aesthetics: 34 subjects
- Site 3 Mara Graz: 43 subjects

102 subjects were included in the safety analysis set.

101 subjects were included in the intent-to-treat (ITT) population; 1 subject (site 1) was excluded (primary exclusionary reason: other [patient suffers from familial catastrophes)].

84 subjects were included in the per-protocol population (PP).

18 subjects (site 1: 11 subjects, site 2: 1 subject, and site 3: 6 subjects) were excluded from the PP population. The primary exclusionary reason was 'subject with protocol deviation interfering with the evaluation for GAIS at Week 8' for 17 subjects. For 1 subject 'other' was given as primary reason; subject dropped out after Visit 1 (see below and Section 4.1).

There were 2 dropouts (both at site 1):

- Subject ID No. 01-022 dropped out after Visit 1
- Subject ID No. 01-003 dropped out after Visit 4.

The subjects were discontinued for the following reasons:

'Withdrawal by subject' (personal reasons) an 'Other' (subject suffered from family catastrophes), respectively.

In addition, partial exclusions from statistical analysis of the PP population (VCS) were performed due to study deviations as agreed in the Data review meeting (see TMF, Data review meeting minutes Version 1.0, dated 16Jul2019). These study deviations considered invalid visits at site 03 and were reported in altogether 11 subjects (Visit 5/Week 12: N = 9, Visit 2/Week 3: N = 1; in another subject* Visit 5 was considered invalid, but this subject was already completely excluded from the VCS due to major PD (see Section 4.1). The invalid visits are documented in the "Definition of Analysis Sets" document (TMF).

Subject ID No.	Study deviation description
03-007	**Visit 5:** Invalid for statistical analysis of VCS due to study deviation. Visit 6: Cutometer and corneometer measurement invalid for statistical analysis of VCS due to deviation from required climatic conditions.
03-010	**Visit 5:** Invalid for statistical analysis of VCS due to study deviation
03-014*	Visit 2: Cannula was used for device administration Visit 4: Photos were done 5 days after IMD. Photos done 26JAN2019 and visit were done 21JAN2019. **Visit 5:** Invalid for statistical analysis of VCS due to study deviation Visit 4, Visit 5: Cutometer and corneometer measurement invalid for statistical analysis of VCS due to deviation from required climatic conditions.
03-015	**Visit 5:** Invalid for statistical analysis of VCS due to study deviation
03-018	**Visit 5:** Invalid for statistical analysis of VCS due to study deviation
03-019	**Visit 5:** Invalid for statistical analysis of VCS due to study deviation. Visit 4: Cutometer and corneometer measurement invalid for statistical analysis of VCS due to deviation from required climatic conditions.
03-021	**Visit 5:** Invalid for statistical analysis of VCS due to study deviation
03-024	**Visit 5:** Invalid for statistical analysis of VCS due to study deviation
03-026	**Visit 5:** Invalid for statistical analysis of VCS due to study deviation
03-027	**Visit 5:** Invalid for statistical analysis of VCS due to study deviation
03-031	**Visit 2:** Invalid for statistical analysis of VCS due to study deviation Visit 4: Cutometer and corneometer measurement invalid for statistical analysis of VCS due to deviation from required climatic conditions.

*Subject with major protocol deviations

4.3 Dropouts and missing data

The 2 dropouts prematurely discontinued the clinical investigation for reasons not related to IMD (AE). These subjects were not replaced. The data of Subject ID No. 01-003 were included in all analyses of the safety analysis set, ITT and PP populations. The data of Subject ID No. 01-022 was not included in the analyses of the ITT and PP populations as the subject already discontinued the investigation after Visit 1.

4.4 Disposal of IMD

At the end of the clinical investigation, all remaining supplies of investigational devices will be returned to the Sponsor. Empty or used syringes will not be returned to the Sponsor, as these were destroyed at the investigation site, in line with their routine procedure for medical waste disposal after drug accountability has been performed. Used needles were disposed immediately after the use as per routine procedure for medical waste disposal at the site.

Additional anaesthetic and rescue medication

As can be seen in Table 5, a comparable share of subject took additional anaesthetic medication on Day 0 and at Week 6 (44.1% and 48.8%, respectively), less subjects (22.4%) at Week 3.

Only 1 subject (Subject ID No. 03-020) took the rescue medication hyaluronidase once at Week 3 (see above AE: 'Injection site oedema' at LCL right and left).

Table 5: Additional anaesthetic and rescue medication

(N_{SES} = 102)	Additional anaesthetics used	Rescue medication hyaluronidase
Day 0		
N	102	102
No	57 (55.9%)	102 (100%)
Yes	45 (44.1%)	0 (0.0%)
Week 3		
N	85	85
No	66 (77.6%)	84 (98.8%)
Yes	19 (22.4%)	1 (1.2%)
Week 6		
N	84	84
No	43 (51.2%)	84 (100%)
Yes	41 (48.8%)	0 (0.0%)
Overall		
N	102	102
No	38 (37.3%)	101 (99.0%)
Yes	64 (62.7%)	1 (1.0%)

Source: Appendix A, Table 3.2

4.6 CIP compliance

A listing for device administration is provided in Appendix B, Listing 13.

4.5 Demographic and other baseline characteristics

A summary of subject demographic characteristics can be found in Table 4 and in Appendix A, Table 1.4. The individual demographic data can be found in Appendix B, Listing 4.

All subjects (101 female and 1 male) were between 28 to 77 years and were white.

All 102 subjects had sufficient severity of either their LCL or PR or both as assessed by treating investigator.

Table 4: Summary of subject demographic and baseline characteristics

	Safety analysis set	Intent-to-treat population	Per-protocol population
Number of subjects	N=102	N=101	N=84
Age[1] [years]			
N	102	101	84
Mean ± SD	51.9 ± 9.0	51.9 ± 9.0	52.0 ± 9.5
Median	51.0	51.0	51.0
Min, max	28, 77	28, 77	28, 77
Sex			
N	102	101	84
Female	101 (99%)	100 (99%)	83 (99%)
Male	1 (1%)	1 (1%)	1 (1%)
Race			
N	102	101	84
White	102 (100%)	101 (100%)	84 (100%)

[1] Age derived as year of first subject starting the investigation (2018) minus year of subject's birth

Source: Appendix A, Table 1.4

Medical history

Medical history findings were reported in 22 subjects: in 11 subjects thyroid disorders (including thyroid dysfunction or ectomy, hypotherosis, benign neoplasm of thyroid gland), in 3 subjects, each hypertension and menopausal symptoms, in 2 subjects hysterectomy, in 1 subject, each ovariectomy, breast cancer, and rheumatoid arthritis.

Previous and concomitant therapies

A listing of prior and concomitant therapy can be found in Appendix B, Listing 11.

13 subjects used a therapy for any medical history.

8 subjects took medication or underwent a therapy (surgery) for treatment of adverse events (see also Section 4.8, Safety results, adverse events):

- 3 subjects: medication for common cold, 1 of these subject also for sinusitis (Parkemed N=2, ACC N=1, Grippostad C Forte granulatea N=1, Ciproxim N=1)
- 1 subject: Amoxi-Clavulan for sinusitis
- 1 subject: medications for 3 AEs: Descloratadine for birch allergy, gastrozol for acid reflux, and meniscus surgery left knee
- 1 subject (Subject ID No. 03-020): Hyaluronidase for 'Injection site oedema' at LCL right and left (see also Table 5)
- 1 subject: Prednisolon for neuropathia vestibularis right arm
- 1 subject: Mexalen and Novalgin for planned shoulder OP right arm

4.7 Performance results

A summary of the performance results is presented in Appendix A, Tables 2.1-2.10. The individual subject's performance results can be found in Appendix B, Listings 15-18.

4.7.1 Primary performance results

The performance/effectiveness of Princess® RICH to correct fine lines on the face, including LCL and/or PR, was primarily assessed by the investigator's assessment of improvement in wrinkle severity using the Global Aesthetic Improvement Scale (GAIS).

The primary performance endpoint in this clinical investigation was:

Percentage of responders at Week 8 after initial treatment point.

Responder was defined as at least "improved" versus baseline in the fine lines of the LCL on both sides and/or the PR as assessed with the GAIS, based on the investigator's assessment.

The majority of subjects of the ITT population were found to be responders for IMD treatment of fine lines either of LCL, PR or both areas at Week 8 (see Table 6):

- LCL: 90.6%
- PR: 89.4%
- at least 1 test area (LCL or PR): 90.1%

The results for the PP population were similar (85.0%, 87.3%, and 88.1%, respectively) and supported the results of the primary ITT analysis (Table 6).

Table 6: Responders regarding GAIS at Week 8 after initial treatment (ITT and PP)

Responders regarding GAIS at Week 8	LCL	PR	At least one test area (LCL or PR)[1]
ITT (N_{ITT} = 101)			
N	32	94	101
No improvement	3 (9.4%)	10 (10.6%)	10 (9.9%)
Improvement	29 (90.6%)	84 (89.4%)	91 (90.1%)
Limits of 95% CI for percentage of responders	(80.5%, 100%)	(83.1%, 95.6%)	(84.3%, 95.9%)
PP (N_{PP} = 84)			
N	20	79	84
No improvement	3 (15.0%)	10 (12.7%)	10 (11.9%)
Improvement	17 (85.0%)	69 (87.3%)	74 (88.1%)
Limits of 95% CI for percentage of responders	(69.4%, 100%)	(80.0%, 94.7%)	(81.2%, 95.0%)

[1] Subjects responding on both test areas counted once

GAIS = Global Aesthetic Improvement Scale

Source: Appendix A, Table 2.3 and 2.4

The investigator rated 'improved' to 'very much improved' in the vast majority of the subjects for right and left LCL (both 90.6%), and PR (89.4%) at Week 8 (see Table 7); 'much improved' was rated most frequently (see Table 7). 'No change' compared with baseline was reported for the remaining subjects (LCL: both 9.4%; PR: 10.6%). No 'worsening' was observed for any treatment area in any of the subjects.

Similar results were obtained for the PP population (see Table 7).

Table 7: GAIS by Investigator at Week 8 after Initial Treatment (ITT and PP)

GAIS by investigator[1] at Week 8	Right LCL	Left LCL	PR
ITT (N_{ITT} = 101)			
N	32	32	94
Very much improved	7 (21.9%)	7 (21.9%)	24 (25.5%)
Much improved	16 (50.0%)	16 (50.0%)	31 (33.0%)
Improved	6 (18.8%)	6 (18.8%)	29 (30.9%)
No change	3 (9.4%)	3 (9.4%)	10 (10.6%)
Worse	0 (0.0%)	0 (0.0%)	0 (0.0%)
PP (N_{PP} = 84)			
N	20	20	79
Very much improved	6 (30.0%)	6 (30.0%)	21 (26.6%)
Much improved	9 (45.0%)	9 (45.0%)	24 (30.4%)
Improved	2 (10.0%)	2 (10.0%)	24 (30.4%)
No change	3 (15.0%)	3 (15.0%)	10 (12.7%)
Worse	0 (0.0%)	0 (0.0%)	0 (0.0%)

[1] Very much improved = Optimal aesthetic result for the implant in this subject,
Much improved = Marked improvement in appearance from the initial condition, but not completely optimal for this subject. A touch-up would slightly improve the result,
Improved = Obvious improvement in appearance from the initial condition, but a touch-up or retreatment is indicated,
No change = The appearance is essentially the same as the original condition,
Worse = The appearance is worse than the original condition.

GAIS = Global Aesthetic Improvement Scale

Source: Appendix A, Table 2.1 and Table 2.2

4.7.2 Secondary performance/efficacy results

4.7.2.1 Global aesthetic improvement score (GAIS)

Percentage of responders at weeks 12 and 16 after initial treatment

At Week 12 (see Table 8), the proportion of responders was almost the same for LCL when compared to Week 8 (see Table 8) (90.0% and 90.6%, respectively) while for PR and at least 1 test area, the proportion of responders had decreased (PR: from 89.4% to 76.9%; LCL and/or PR 90.1% to 78.6%).

Similar results were seen for the PP population with no decrease in LCL from Week 8 to Week 12 (85.0% and 88.2%, respectively), but for PR (87.3% to 80.9%) and at least 1 test area (88.1% to 82.2%) (see Appendix A, Table 2.4).

After further 4 weeks at Week 16, the proportion of responders had decreased for LCL, PR and at least 1 test area to 61.3%, 54.8% and 57.0%, respectively (PP: 65.0%, 55.7% and 57.1%, respectively).

Table 8: Responders Regarding GAIS (ITT)

Responders regarding GAIS (N_{ITT} = 101)	LCL	PR	At least one test area (LCL or PR)[1]
Week 3			
N	31	92	99
No improvement	3 (9.7%)	17 (18.5%)	17 (17.2%)
Improvement	28 (90.3%)	75 (81.5%)	82 (82.8%)
Limits of 95% CI for percentage of responders	(79.9%, 100%)	(73.6%, 89.5%)	(75.4%, 90.3%)
Week 6			
N	31	93	99
No improvement	3 (9.7%)	13 (14.0%)	13 (13.1%)
Improvement	28 (90.3%)	80 (86.0%)	86 (86.9%)
Limits of 95% CI for percentage of responders	(79.9%, 100%)	(79.0%, 93.1%)	(80.2%, 93.5%)
Week 8			
N	32	94	101
No improvement	3 (9.4%)	10 (10.6%)	10 (9.9%)
Improvement	29 (90.6%)	84 (89.4%)	91 (90.1%)
Limits of 95% CI for percentage of responders	(80.5%, 100%)	(83.1%, 95.6%)	(84.3%, 95.9%)
Week 12			
N	30	91	98
No improvement	3 (10.0%)	21 (23.1%)	21 (21.4%)
Improvement	27 (90.0%)	70 (76.9%)	77 (78.6%)
Limits of 95% CI for percentage of responders	(79.3%, 100%)	(68.3%, 85.6%)	(70.4%, 86.7%)
Week 16			
N	31	93	100
No improvement	12 (38.7%)	42 (45.2%)	43 (43.0%)
Improvement	19 (61.3%)	51 (54.8%)	57 (57.0%)
Limits of 95% CI for percentage of responders	(44.1%, 78.4%)	(44.7%, 65.0%)	(47.3%, 66.7%)

[1] Subjects responding on both test areas counted once

GAIS = Global Aesthetic Improvement Scale

Source: Appendix A, Table 2.3

At Week 12, (see Table 9) the investigator still rated improved' to 'very much improved' in the vast majority of the subjects for right and left LCL (Week 8: both 90.6%, Week 12: both 90.0%); with 'moderately improved assessed mostly as for Week 8, but somewhat less subjects with 'very much improved' (see Table). For PR, fewer subjects were rated with an improvement compared to Week 8 (Week 8: 89.3%, Week 12: 76.9%).

At 16 weeks, the investigator rated 'improved' to 'very much improved' for both right and left LCL in 61.2% of the subjects, and for PR in 54.9% of the subjects. In the other subjects 'no change' was rated for the respective areas.

No worsening was observed for any area in any subject neither at Week 12 nor at Week16.

Similar ratings were reported for the PP population.

Table 9: GAIS by investigator (ITT)

Global aesthetic improvement score (GAIS) by investigator[1] (N_{ITT} = 101)	Right LCL	Left LCL	PR
Week 3			
N	31	31	92
Very much improved	1 (3.2%)	1 (3.2%)	3 (3.3%)
Much improved	14 (45.2%)	13 (41.9%)	29 (31.5%)
Improved	13 (41.9%)	14 (45.2%)	43 (46.7%)
No change	3 (9.7%)	3 (9.7%)	17 (18.5%)
Worse	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 6			
N	31	31	93
Very much improved	5 (16.1%)	4 (12.9%)	12 (12.9%)
Much improved	16 (51.6%)	17 (54.8%)	32 (34.4%)
Improved	7 (22.6%)	7 (22.6%)	36 (38.7%)
No change	3 (9.7%)	3 (9.7%)	13 (14.0%)
Worse	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 8			
N	32	32	94
Very much improved	7 (21.9%)	7 (21.9%)	24 (25.5%)
Much improved	16 (50.0%)	16 (50.0%)	31 (33.0%)
Improved	6 (18.8%)	6 (18.8%)	29 (30.9%)
No change	3 (9.4%)	3 (9.4%)	10 (10.6%)
Worse	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 12			
N	30	30	91
Very much improved	3 (10.0%)	3 (10.0%)	17 (18.7%)
Much improved	16 (53.3%)	16 (53.3%)	34 (37.4%)
Improved	8 (26.7%)	8 (26.7%)	19 (20.9%)
No change	3 (10.0%)	3 (10.0%)	21 (23.1%)
Worse	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 16			
N	31	31	93
Very much improved	5 (16.1%)	5 (16.1%)	14 (15.1%)
Much improved	5 (16.1%)	5 (16.1%)	24 (25.8%)
Improved	9 (29.0%)	9 (29.0%)	13 (14.0%)
No change	12 (38.7%)	12 (38.7%)	42 (45.2%)
Worse	0 (0.0%)	0 (0.0%)	0 (0.0%)

[1] Very much improved = Optimal aesthetic result for the implant in this patient,
Much improved = Marked improvement in appearance from the initial condition, but not completely optimal for this patient.
A touch-up would slightly improve the result,
Improved = Obvious improvement in appearance from the initial condition, but a touch-up or retreatment is indicated,
No change = The appearance is essentially the same as the original condition,
Worse = The appearance is worse than the original condition, GAIS = Global Aesthetic Improvement Scale.
Source: Appendix A, Table 2.1

4.7.2.2 Measures of skin hydration, skin tone and skin elasticity

Change from baseline at Weeks 3, 6, 8, 12, and 16 in skin hydration assessed with the corneometer device.

As can be seen in Table 10 (ITT), only minor changes in mean change from baseline in skin hydration were observed over the investigational period until Week 16. The greatest increase was noted for both LCL and PR at Week 12 (1.7 and 3.0 i.u., respectively); the greatest decrease for LCL at Week 3 (-4.0 i.u.) and PR at Week 6 (-1.2 i.u.).

Similar results were reported for the PP (see Appendix A, Table 2.8).

Table 10: Corneometer Measurements [I.U.] (ITT)

	Skin hydration [I.U.]	
Corneometer measurements[1] (N_{ITT} = 101)	**LCL**	**PR**
Baseline (Day 0)		
N	35	92
Mean ± SD	57.4 ± 15.7	55.6 ± 13.7
95% Confidence interval for mean	52.0 , 62.8	52.8 , 58.5
Median	54.0	54.3
Q1 , Q3	47.1 , 69.4	46.7 , 64.0
Min, max	21, 88	23, 91
Mean Changes from Baseline (Day 0)		
Week 3		
N	28	89
Mean Change from Baseline (Day 0) ± SD	-4.0 ± 11.9	-0.6 ± 11.9
95% Confidence interval for mean	-8.6 , 0.6	-3.1 , 1.9
Median Change from Baseline (Day 0)	-4.3	0.0
Q1 , Q3	-12.3 , 5.5	-6.9 , 6.5
Min, max	-27, 20	-27, 31
Week 6		
N	31	91
Mean Change from Baseline (Day 0)± SD	-2.0 ± 13.6	-1.2 ± 13.2
95% Confidence interval for mean	-7.0 , 2.9	-3.9 , 1.6
Median Change from Baseline (Day 0)	-1.4	-1.8
Q1 , Q3	-12.3 , 4.6	-8.0 , 6.7
Min, max	-22, 38	-28, 52
Week 8		
N	30	91
Mean Change from Baseline (Day 0)± SD	0.3 ± 12.0	0.4 ± 14.9
95% Confidence interval for mean	-4.2 , 4.7	-2.7 , 3.5
Median Change from Baseline (Day 0)	0.2	-1.2
Q1 , Q3	-2.2 , 5.5	-10.7 , 10.5
Min, max	-28, 37	-27, 43
Week 12		
N	29	89
Mean Change from Baseline (Day 0)± SD	1.7 ± 14.3	3.0 ± 13.4
95% Confidence interval for mean	-3.7 , 7.2	0.2 , 5.8
Median	-0.3	1.3
Q1 , Q3	-7.4 , 9.0	-3.8 , 10.2
Min, max	-26, 38	-32, 42
Week 16		
N	31	91
Mean Change from Baseline (Day 0) ± SD	1.6 ± 12.7	2.2 ± 13.3
95% Confidence interval for mean	-3.0 , 6.3	-0.6 , 5.0
Median Change from Baseline (Day 0)	0.8	0.8
Q1 , Q3	-9.0 , 11.3	-7.4 , 11.4
Min, max	-17, 40	-23, 36

[1] Individual subject values were calculated as the mean of the repeated measurements per test area

Source: Appendix A, Table 2.7

Changes from baseline at Weeks 3, 6, 8, 12, and 16 in skin tone assessed with the cutometer device.

Lower mean values compared to baseline were reported for the parameter R0—reflecting an increase in skin tone/firmness over the investigational period until Week 16. The greatest decrease in R0 was noted for LCL at Week 8 (mean change = -0.087 mm) and for PR at Week 16 (mean change = -0.058 mm) (see Table 11).

Similar results were reported for the PP (see Appendix A, Table 2.10).

Table 11: Cutometer Measurements, Skin Tone [mm] (ITT)

Cutometer measurements[1] (N_{ITT} = 101)	LCL, Skin tone R0 [mm]	PR, Skin tone R0 [mm]
Day 0		
N	34	93
Mean ± SD	0.240 ± 0.082	0.246 ± 0.086
95% Confidence interval for mean	0.211 , 0.269	0.228 , 0.263
Median	0.238	0.266
Q1 , Q3	0.177 , 0.300	0.180 , 0.308
Min, max	0.087, 0.392	0.040, 0.409
Mean Changes from Baseline (Day 0)		
Week 3		
N	28	91
Mean Change from Baseline (Day 0) ± SD	-0.029 ± 0.077	-0.026 ± 0.050
95% Confidence interval for mean	-0.059 , 0.001	-0.037 , -0.016
Median Change from Baseline (Day 0)	-0.024	-0.022
Q1 , Q3	-0.048 , 0.020	-0.053 , 0.006
Min, max	-0.277, 0.078	-0.206, 0.061
Week 6		
N	30	91
Mean Change from Baseline (Day 0) ± SD	-0.078 ± 0.069	-0.037 ± 0.060
95% Confidence interval for mean	-0.103 , -0.052	-0.050 , -0.025
Median Change from Baseline (Day 0)	-0.071	-0.038
Q1 , Q3	-0.131 , -0.032	-0.076 , 0.004
Min, max	-0.242, 0.043	-0.217, 0.107
Week 8		
N	30	93
Mean Change from Baseline (Day 0) ± SD	-0.087 ± 0.093	-0.051 ± 0.065
95% Confidence interval for mean	-0.122 , -0.052	-0.064 , -0.037
Median Change from Baseline (Day 0)	-0.083	-0.050
Q1 , Q3	-0.148 , -0.036	-0.092 , -0.013
Min, max	-0.295, 0.180	-0.245, 0.094
Week 12		
N	27	89
Mean Change from Baseline (Day 0) ± SD	-0.059 ± 0.097	-0.048 ± 0.072
95% Confidence interval for mean	-0.097 , -0.020	-0.064 , -0.033
Median Change from Baseline (Day 0)	-0.053	-0.047
Q1 , Q3	-0.147 , 0.028	-0.089 , -0.002
Min, max	-0.227, 0.140	-0.259, 0.144
Week 16		
N	30	92
Mean Change from Baseline (Day 0) ± SD	-0.029 ± 0.071	-0.058 ± 0.073
95% Confidence interval for mean	-0.056 , -0.003	-0.073 , -0.043
Median Change from Baseline (Day 0)	-0.020	-0.046
Q1 , Q3	-0.090 , 0.015	-0.099 , -0.008
Min, max	-0.172, 0.094	-0.259, 0.093

[1] Individual subject values were calculated as the mean of the repeated measurements per test area

Source: Appendix A, Table 2.9

Change from baseline at Weeks 3, 6, 8, 12, and 16 in skin elasticity as assessed with the cutometer device.

Higher mean values compared to baseline were reported for the parameter R2 over the investigational period until Week 16. This reflects an increase in skin elasticity as the closer the R2 ratio is to 1, the higher the skin elasticity. The greatest mean changes were noted for both LCL and PR at Week 12 (0.054 and 0.041, respectively) (see Table 12).

Similar results were reported for the PP (see Appendix A, Table 2.10).

Table 12: Cutometer Measurements, Skin Elasticity [ratio] (ITT)

Cutometer measurements[1] (N_{ITT} = 101)	LCL, Skin elasticity R2 [ratio]	PR, Skin elasticity R2 [ratio]
Day 0		
N	34	93
Mean ± SD	0.789 ± 0.090	0.867 ± 0.065
95% Confidence interval for mean	0.758 , 0.821	0.854 , 0.880
Median	0.813	0.882
Q1 , Q3	0.731 , 0.857	0.844 , 0.909
Min, max	0.538, 0.909	0.609, 0.955
Mean Changes from Baseline (Day 0)		
Week 3		
N	30	92
Mean Change from Baseline (Day 0)± SD	0.014 ± 0.055	0.022 ± 0.068
95% Confidence interval for mean	-0.007 , 0.034	0.008 , 0.036
Median Change from Baseline (Day 0)	0.010	0.015
Q1 , Q3	-0.028 , 0.047	-0.025 , 0.059
Min, max	-0.078, 0.149	-0.139, 0.265
Week 6		
N	30	91
Mean Change from Baseline (Day 0)± SD	0.040 ± 0.066	0.021 ± 0.069
95% Confidence interval for mean	0.016 , 0.065	0.007 , 0.036
Median Change from Baseline (Day 0)	0.032	0.016
Q1 , Q3	-0.005 , 0.068	-0.023 , 0.059
Min, max	-0.083, 0.218	-0.138, 0.272
Week 8		
N	30	93
Mean Change from Baseline (Day 0)± SD	0.033 ± 0.058	0.022 ± 0.061
95% Confidence interval for mean	0.011 , 0.054	0.009 , 0.034
Median Change from Baseline (Day 0)	0.034	0.014
Q1 , Q3	-0.008 , 0.063	-0.014 , 0.046
Min, max	-0.064, 0.196	-0.094, 0.246
Week 12		
N	27	89
Mean Change from Baseline (Day 0)± SD	0.054 ± 0.066	0.041 ± 0.074
95% Confidence interval for mean	0.028 , 0.080	0.026 , 0.057
Median Change from Baseline (Day 0)	0.062	0.041
Q1 , Q3	-0.001 , 0.112	0.003 , 0.072
Min, max	-0.086, 0.158	-0.232, 0.287
Week 16		
N	30	92
Mean Change from Baseline (Day 0)± SD	0.047 ± 0.073	0.030 ± 0.088
95% Confidence interval for mean	0.019 , 0.074	0.012 , 0.048
Median Change from Baseline (Day 0)	0.034	0.027
Q1 , Q3	0.011 , 0.089	-0.010 , 0.069
Min, max	-0.090, 0.255	-0.400, 0.237

[1] Individual subject values were calculated as the mean of the repeated measurements per test area

Source: Appendix A, Table 2.9

4.7.2.3 Subject's treatment satisfaction questionnaire

Subject satisfaction with treatment at Weeks 8, 12, and 16 using one of the following categories: "Very unsatisfied", "Unsatisfied", "Neither unsatisfied nor satisfied", "Satisfied", or "Very satisfied"

At Week 8, the majority of the subjects (82%) was 'satisfied' or 'very satisfied' with the IMD treatment (see Table 13). 'Neither satisfied nor unsatisfied' was rated by 15.8% and only 2 subjects (2%) were unsatisfied.

Four weeks later at Week 12, 69.4% of the subjects continued to be 'satisfied' or 'very satisfied' with the IMD treatment. Neither satisfied nor unsatisfied' was rated by 21.4% and unsatisfied by 9.2% of the subjects.

After further 4 weeks at Week 16, more than half of the subjects (55%) were still 'satisfied' or 'very satisfied' with the IMD treatment. 'Neither satisfied nor unsatisfied' was rated by 29.0% and unsatisfied by 14% of the subjects. 'Very unsatisfied' was rated by 2 subjects (2%).

Similar results were reported for the PP (see Appendix A, Table 2.6).

Table 13: Subject's satisfaction with the treatment (ITT)

	Subject's satisfaction with the treatment (N_{ITT} = 101)
Week 8	
N	101
Very satisfied	44 (43.6%)
Satisfied	39 (38.6%)
Neither satisfied nor unsatisfied	16 (15.8%)
Unsatisfied	2 (2.0%)
Very unsatisfied	0 (0.0%)
Week 12	
N	98
Very satisfied	35 (35.7%)
Satisfied	33 (33.7%)
Neither satisfied nor unsatisfied	21 (21.4%)
Unsatisfied	9 (9.2%)
Very unsatisfied	0 (0.0%)
Week 16	
N	100
Very satisfied	34 (34.0%)
Satisfied	21 (21.0%)
Neither satisfied nor unsatisfied	29 (29.0%)
Unsatisfied	14 (14.0%)
Very unsatisfied	2 (2.0%)

Source: Appendix A, Table 2.5

4.8 Safety results

Injection volume

IMD treatment was performed in all 102 enrolled subjects on Day 0: in the majority of the subjects in the PR area (95 subjects, 93%), in less subjects in the left and right LCL area (35 subjects 34%, each).

At Weeks 3 and 6, further IMD treatments were performed in ≥ 82% of the enrolled subjects: in about three-fourths of the subjects in the PR area, in about a quarter of the subjects in the left and right LCL area.

The injection volume ranged between 0.2 to 3.0 ml for PR and between 0.1 to 1.0 ml per side for LCL at the respective visits (Day 0, Week 3 and Week 6).

The overall amount ranged between 0.3 to 8.0 ml for PR and between 0.2 to 1.7 ml (mean = 0.89 ml) for left LCL, and 0.2 to 1.6 ml (mean = 0.88 ml) for right LCL.

The total amount ranged between 0.5 and 9.0 ml (mean = 3.7 ml).

Table 14: Injection volume (Safety analysis set)

Injected volume [ml] (N_{SES} = 102)	Left LCL	Right LCL	PR	Total
Day 0				
N	35	35	95	102
Mean ± SD	0.34 ± 0.15	0.33 ± 0.14	1.22 ± 0.65	1.37 ± 0.56
Median	0.30	0.30	1.20	1.20
Min, max	0.2, 1.0	0.2, 1.0	0.2, 2.8	0.2, 3.0
Week 3				
N	28	28	78	85
Mean ± SD	0.34 ± 0.10	0.33 ± 0.11	1.29 ± 0.71	1.40 ± 0.66
Median	0.30	0.30	1.00	1.00
Min, max	0.2, 0.5	0.1, 0.5	0.2, 3.0	0.2, 3.0
Week 6				
N	26	26	75	84
Mean ± SD	0.38 ± 0.16	0.38 ± 0.16	1.31 ± 0.63	1.41 ± 0.62
Median	0.30	0.30	1.00	1.00
Min, max	0.2, 1.0	0.2, 1.0	0.4, 3.0	0.4, 3.0
Overall				
N	35	35	95	102
Mean ± SD	0.89 ± 0.32	0.88 ± 0.31	3.32 ± 1.95	3.70 ± 1.80
Median	0.90	0.90	3.20	3.20
Min, max	0.2, 1.7	0.2, 1.6	0.3, 8.0	0.5, 9.0

Source: Appendix A, Table 3.1

Adverse events (AEs)

A summary of AE characteristics can be found in Table 15 and in Appendix A, Table 3.3. A listing of AEs by subject can be found in Appendix B, Listing 20.

In total, 42 treatment-emergent adverse events (TEAEs) were reported in 26 subjects (25%).

2 of the TEAEs were serious (SAEs):

- Neuropathia vestibularis right
  Intensity: severe
  Causal relationship to investigational device and to procedure: unlikely
- Meniscus partial rupture left knee
  Intensity: moderate
  Causal relationship to investigational device and to procedure: not related

40 of the TEAEs were non-serious TEAEs, of which 31 TEAEs reported in 20 subjects were with location related to test fields, i.e., at treatment area or just around treatment area.

11 TEAEs (including both SAEs) reported in 8 subjects were with location not related to test fields.

The causal relationship to IMD was considered to be not or unlikely related for 35 of the 42 TEAEs, probable for 1 TEAE, and definite for 6 TEAEs.

The causal relationship to procedure was found to be not or unlikely related for 12 TEAEs, possible for 2 TEAEs, probable for 1 TEAE, and definite for 27 TEAEs.

The intensity of most of the TEAEs was assessed as mild (74%). 24% of the TEAEs were assessed moderate (including 1 SAE, see above), and 1 TEAE was assessed severe (SAE, see above).

The most frequently reported system organ class (SOC) according to MedDRA class (see Table 16) was 'general disorders and administration site conditions' noted in 19 subjects (19%) with 'injection site haematoma' reported as most frequent preferred term (PT) (in 18 subjects, 18%). 'Injection site oedema' was reported in 2 subjects and 'injection site swelling' in 1 subject.

The next frequently reported SOC was 'infections and infestations' noted in 7 subjects (7%) with 'nasopharyngitis' reported as most frequent PT (in 3 subjects, 3%). 'Sinusitis' was reported in 2 subjects, and 'gastroenteritis', 'oral herpes' and 'vestibular neuronitis' in 1 subject each.

Other SOCs 'immune system disorders', 'injury, poisoning and procedural complications' and 'surgical and medical procedures' were reported once with the PTs 'seasonal allergy', meniscus injury' and 'shoulder operation'.

The duration of the TEAEs was in most cases > 7 days (SOC 'general disorders and administration site conditions': 14 TEAEs; SOC 'infections and infestations': 3 TEAEs), followed by > 3 days and ≤ 7 days (SOC 'general disorders and administration site conditions': 5 TEAEs; SOC 'infections and infestations': 2 TEAEs). Particularly, the TEAEs with location related to test fields especially 'injection site haematoma' (14 TEAEs) showed these longer durations (see Appendix A, Table 3.7).

None of the TEAEs led to subject's withdrawal. 8 subjects took a medication for treatment of AE. 1 of these subjects took rescue medication hyaluronidase once at Week 3 for treatment of injection site oedema.

The outcome of the TEAEs was 'resolved' in most cases. 'Ongoing' was noted for 2 TEAEs (PTs: gastrooesophageal reflux disease and seasonal allergy) and 'resolved with sequelae' for 1 TEAE (PT: shoulder operation).

Table 15: Summary of AE characteristics (SES)

Adverse event characteristics (N_{SES} = 102)	All adverse events (=TEAE[1])	TEAE[1] with location related[2] to test fields	TEAE[1] with location not related[2] to test fields
Number of subjects reporting any adverse event[3]	26 (25%)	20 (20%)	8 (8%)
Number of adverse events reported	42	31	11
Serious AEs			
No	40 (95%)	31 (100%)	9 (82%)
Yes	2 (5%)	0 (0%)	2 (18%)
Intensity			
Mild	31 (74%)	23 (74%)	8 (73%)
Moderate	10 (24%)	8 (26%)	2 (18%)
Severe	1 (2%)	0 (0%)	1 (9%)
Causal relationship to investigational device			
Definite	6 (14%)	6 (19%)	0 (0%)
Probable	1 (2%)	1 (3%)	0 (0%)
Possible	0 (0%)	0 (0%)	0 (0%)
Unlikely	4 (10%)	3 (10%)	1 (9%)
Not related	31 (74%)	21 (68%)	10 (91%)
Causal relationship to procedure			
Definite	27 (64%)	27 (87%)	0 (0%)
Probable	1 (2%)	1 (3%)	0 (0%)
Possible	2 (5%)	2 (6%)	0 (0%)
Unlikely	2 (5%)	1 (3%)	1 (9%)
Not related	10 (24%)	0 (0%)	10 (91%)
Duration[4]			
≤ 1 day	2 (5%)	0 (0%)	2 (18%)
> 1 day and ≤ 3 days	2 (5%)	0 (0%)	2 (18%)
> 3 days and ≤ 7 days	11 (26%)	8 (26%)	3 (27%)
> 7 days	25 (60%)	23 (74%)	2 (18%)
missing	2 (5%)	0 (0%)	2 (18%)

[1] AE with a start at the time point of first device administration or later
[2] Related to test fields = at treatment area or just around treatment area,
Not related to test fields = distant from treatment area or not local
[3] Counts reflect numbers of subjects reporting one or more adverse events
[4] Duration of adverse event was derived as stop date minus onset date + 1

Source: Appendix A, Table 3.3

Table 16: Subjects with adverse events by MedDRA class (SES)

Subjects with adverse events by MedDRA class (N_{SES} = 102)	All adverse events (=TEAE[1])	TEAE[1] with location related to test fields[2]	TEAE[1] with location not related to test fields[2]
System organ class / Preferred term[3]			
Gastrointestinal disorders	1 (1%)	0 (0%)	1 (1%)
Gastrooesophageal reflux disease	1 (1%)	0 (0%)	1 (1%)
General disorders and administration site conditions	19 (19%)	19 (19%)	0 (0%)
Injection site haematoma	18 (18%)	18 (18%)	0 (0%)
Injection site oedema	2 (2%)	2 (2%)	0 (0%)
Injection site swelling	1 (1%)	1 (1%)	0 (0%)
Immune system disorders	1 (1%)	0 (0%)	1 (1%)
Seasonal allergy	1 (1%)	0 (0%)	1 (1%)
Infections and infestations	7 (7%)	1 (1%)	6 (6%)
Gastroenteritis	1 (1%)	0 (0%)	1 (1%)
Nasopharyngitis	3 (3%)	0 (0%)	3 (3%)
Oral herpes	1 (1%)	1 (1%)	0 (0%)
Sinusitis	2 (2%)	0 (0%)	2 (2%)
Vestibular neuronitis	1 (1%)	0 (0%)	1 (1%)
Injury, poisoning and procedural complications	1 (1%)	0 (0%)	1 (1%)
Meniscus injury	1 (1%)	0 (0%)	1 (1%)
Surgical and medical procedures	1 (1%)	0 (0%)	1 (1%)
Shoulder operation	1 (1%)	0 (0%)	1 (1%)

[1] AE with a start at the time point of first device administration or later
[2] Related to test fields = at treatment area or just around treatment area,
Not related to test fields = distant from treatment area or not local
[3] Counts reflect numbers of subjects reporting one or more adverse events that map to the current MedDRA Classification, starting with Version 21.1 (interim analysis: Version 22.0)
At each level of summarization (system organ class or preferred term) subjects are only counted once.

Source: Appendix A, Table 3.4

Device deficiencies

No device deficiencies were recorded during the clinical investigation.

5 Discussion and conclusions

The performance results of Princess® RICH clearly showed high effectiveness in the correction of fine lines on the face either on lateral canthal lines (LCL) or perioral rhytids (PR) alone or for both areas (LCL and PR) combined as assessed by investigators. The investigator ratings using the global aesthetic improvement score (GAIS) showed high responder rates at the primary assessment visit Week 8 (90.6% for LCL, 89.4% for PR, and 90.1% for at least one test area [LCL or PR]) and still substantial responder rates at Weeks 12 and 16.

These results were supported by the results seen in the subject ratings for satisfaction with IMD treatment. Subjects' treatment satisfaction was demonstrated at Week 8 with the majority of the subjects (82%) assessing either 'satisfied' or 'very satisfied'. Only 2 subjects (2%) were unsatisfied; the remaining subjects were 'neither satisfied nor unsatisfied' with IMD treatment. Four weeks later at Week 12, most of the subjects (69.4%) continued to be 'satisfied' or 'very satisfied' and at Week 16 more than half of the subjects (55%) were still 'satisfied' or 'very satisfied' with the IMD treatment. 'Not satisfied' was rated by 9.2% of the subjects at Week 12 and by 14% of the subject at Week 16. 'Very unsatisfied' was noted by 2 subjects only at Week 16.

The ability of Princess® RICH to improve skin tone and skin elasticity in the treatment areas was confirmed by cutometry. The cutometric measurements revealed mean lower R0 values (skin tone) and mean higher R2 ratios compared to baseline following IMD treatment, indicating an improvement in skin tone and skin elasticity in the treatment areas. Over the investigational period, the greatest decrease in R0 was noted for LCL at Week 8 and for PR at Week 12. The greatest increase in skin elasticity was noted for both LCL and PR at Week 12.

The assessment of skin hydration using corneometry demonstrated based on mean corneometric values of 57.4 for LCL and 55.6 for PR at baseline only minor changes over the investigational period until Week 16. The greatest increase was noted for both LCL and PR at Week 12 (1.7 and 3.0 i.u., respectively). These results reflect that the skin hydration maintained following treatment with Princess® RICH. An improvement of skin hydration could not be seen as the corneometric values throughout the investigation remained similar to baseline and below the values known for well hydrated skin (range between 60 und 85 i.u.; in the eye area generally higher as perioral).

In summary, the performance results of this clinical investigation demonstrate the benefit of the non-cross-linked, glycerol-added HA product Princess® RICH correcting fine lines in both treatment areas providing rejuvenation and an aesthetic effect lasting for a satisfactory duration.

The outcome of the primary performance analyses on the ITT population was supported by the analyses the PP population showing overall similar results.

The safety variables of this study demonstrated the safety and tolerability of Princess® RICH when either LCL or PR or both areas combined were treated and no new safety concerns were identified during this study. The safety results are consistent with the known safety profile of other HA fillers and show that the safety profile of Princess® RICH is typical for a natural HA (Baspeyras et al., 2013; Succi et al, 2012).

In total, 42 treatment-emergent adverse events (TEAEs) were reported in 26 subjects (25%). 2 of the TEAEs were SAEs (Neuropathia vestibularis right and meniscus partial rupture left knee), which were considered to be unlikely or not related to IMD or procedure. All other TEAEs were non-serious TEAEs, mostly located at treatment area or just around treatment area (31 TEAES in

20 subjects) and considered to be related to study procedure (mainly 'injection site haematoma' with 25 events, otherwise 4 events of 'injection site oedema' and 1 event of 'injection site swelling')'. The causal relationship to IMD was considered to be probable for 1 TEAE (injection site swelling), and definite for 6 TEAEs (5 events of 'injection site oedema', 1 event of 'injection site haematoma').

Local injection related side effects were expected in this clinical investigation (Lafaille and Benedetto, 2010; Gabriele F-H et al 2014): 30% in total, of that 25% 'injection site haematoma' which was low compared to other HA fillers. For a natural, non-cross-linked glycerol-added HA gel (Mesolis plus) 76% haematoma was seen (N = 20, Succi et al, 2012); for Restylane, a cross-linked product the incidence was: 93% of subjects showing injection site reactions and slightly over 50% of the subjects showing bruising (Joel Lee Cohen 2008).

In comparison to approximately 80% described in literature (Succi et al, 2012; Uth, Elberg and Zachariae, 2016), only 5 of subjects (5%) in this clinical investigation presented swelling or oedema.

None of the TEAEs led to subject's withdrawal and the outcome of the TEAEs was 'resolved' within a few days to one week in most cases, corresponding to other HA described in literature (Abduljabbar and Basendwh, 2016). 'Ongoing' was noted for 2 TEAEs (PTs: gastrooesophageal reflux disease and seasonal allergy) and 'resolved with sequelae' for 1 TEAE (PT: shoulder operation).

8 subjects took a medication for treatment of AE. 1 of these subjects took rescue medication hyaluronidase once at Week 3 for treatment of injection site oedema. None of the other subjects took a rescue medication. 44.1%, 22.4%, and 48.8% took an additional anaesthetic medication on Day 0, Week 3 and Week 6, respectively.

Furthermore, no device deficiencies were reported in this clinical investigation.

On the basis of the present results no specific risks or precautions are required to be mentioned over those already known and described. There were no safety concerns based on the results of this clinical investigation.

Overall, the IMD poses a well-tolerated, safe and effective alternative to current use of other comparable dermal fillers in the treatment of LCL and PR. Princess® RICH as a non-cross-linked glycerol-added HA product convinced with its performance lasting for a satisfactory duration and showed an improved safety profile better compared to cross-linked products such as Restylane®.

Overall, the IMD poses a well-tolerated, safe and effective alternative to current use of other comparable dermal fillers in the treatment of LCL and PR. Princess® RICH as a hyaluronic dermal injectable convinced with its performance on improving skin tone and elasticity and to act as a filler for small lines such as LCL and PR lasting for a satisfactory duration.

6 Abbreviated terms and definitions

AE	Adverse event
BASG	Bundesamt fuer Sicherheit im Gesundheitswesen
CIP	Clinical investigation plan
eCRF	Electronic Case Report Form
GAIS	Global Aesthetic Improvement Scale
GCP	Good clinical practice
HA	Hyaluronic acid
IB	Investigator's brochure
ICH	International conference on harmonization
IFU	Instructions for Use
IMD	Investigational medical device
ISO	International organization for standardization
ITT	Intention-to-treat
LCL	Lateral Canthal Lines
MedDRA	Medical Dictionary for Regulatory Activities
PP	Per-protocol
PR	Perioral rhytids
PT	Preferred term
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SES	Safety-evaluation-set
SOC	System Organ Class

7 Ethics

Before the start of the investigation, the CIP, informed consent document, and other appropriate documents were submitted to the responsible ethics committees for the approval.

The below listed ethics committees were contacted for the approval.

Leading Ethics Committee:

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Amt der Steiermaerkischen Landesregierung

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CIP V1.0, dated May 15, 2018 was submitted initially. Minor corrections were required, thus a CIP V2.0 dated 19 September 2018 was resubmitted. There was one substantial amendment to the CIP V2.0 due to the prolongation of the study period up to Week 52 from Week 16.

This clinical investigation was conducted according to the CIP version 3.0, dated 26 March 2019.

8 Investigators and administrative structure of clinical investigation

Table 17: Administrative structure of the investigation

Role	Title/Name	Address
Sponsor	**CROMA-PHARMA GmbH** *Clinical Project Managers:* - Marivic Narciso, M.S. (since June 2018) - Souyet Chang-Rodriguez, Ph.D. (November 2017-June 2018) *Team Lead:* - Sonja Hoeller, Ph.D. (November 2017-November 2018) *Director Clinical Development:* - Sonja Hoeller, Ph.D. (since November 2018) - Zrinka Ivezić Schoenfeld, Ph.D. (November 2017-November 2018)	Industriezeile 6 2100 Leobendorf, Austria
Coordinating investigator and Principal investigator Trial Center 01	Univ. Prof. Dr. Daisy Kopera	Medical University Graz Dermatology and Venerology Clinic Auenbruggerplatz 8 8036 Graz, Austria
Principal investigator Trial Center 02	Dr. Monika Sulovsky	YUVELL® Fine Aesthetics Weihburggasse 22/1 1010 Wien, Austria
Principal investigator Trial Center 03	Dr. Thomas Rappl	MaRa-Medical Aesthetic Research Academy Kaiser Franz Josef Kai 48 8010 Graz, Austria
CRO	**bioskin GmbH** *Head Clinical Trial Management:* - Kirstin Michaelis-Wittern, M.D. *Clinical Trial Manager:* - Fabian Ecke, Ph.D. *Medical monitor:* - Yi-Ling von Mackensen, M.D. *Biostatistician:* - Agnes Himmelmann, M.S. *Data Manager:* - Stefanie Felscher *Head Medical Writing* - Ragna Williams, M.S.	Burchardstrasse 17 20095 Hamburg, Germany
Safety Reporting	**FGK Pharmacovigilance GmbH** *Medical Safety Associate:* - Munhamo Chipandu	Heimeranstr. 35 80339 Munich, Germany
Clinical Photography	**Quantificare** *Clinical Trial Leader:* - Essia Sghaier	1180, route des Dolines Athena B 06560 Sophia Antipolis France
Skin Measurements	**Courage + Khazaka electronic GmbH** *Project Manager:* - Christiane Uhl	Mathias-Brueggen-Str. 91 50829 Koeln, Germany

9 Literature

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Signature page – Coordinating Investigator

We agree with the contents of this report and declare that to the best of our knowledge this clinical investigation was conducted in compliance with Good Clinical Practice [GCP], in accordance with the currently valid revision of the Declaration of Helsinki, ISO 14155-2011(E) and any applicable national laws and regulations. No deviations were identified which affect the quality and integrity of the clinical investigation or the interpretation of the results in this report.

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Signature page - Sponsor

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CLINICAL INVESTIGATION PLAN (CIP)

Title of the clinical investigation/CIP:	**A Prospective Open-label, Multicenter Study Evaluating Princess® RICH in Correction of Fine Lines**
Investigation ID code:	CPH-401-201364
Other IDs:	**RICH**
CIP version:	3.0
CIP version date:	**26 Mar 2019**
Sponsor:	Croma-Pharma GmbH Industriezeile 6, 2100 Leobendorf, Austria Phone: +43 2262 684 680; Fax: +43 2262 6846 8165 E-mail: office@croma.at; Web: www.croma.at
Investigation site(s):	Three sites are planned, located in European Union
Other institutions involved:	bioskin GmbH Burchardstrasse 17 20095 Hamburg, Germany phone: +49-40-606897-0 fax: +49-40-606897-30 email: info@bioskinCRO.com
CONFIDENTIAL	**This document is the property of Croma-Pharma GmbH and must be kept strictly confidential. Disclosure of the contents (in whole or part) to third parties is permissible only with written consent of Croma-Pharma GmbH.**

Sponsor: **Croma-Pharma GmbH**

The Sponsor will be responsible for overall implementation and oversight of the clinical investigation.

the cover page.

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Sponsor Approval and Signature Page

Study CPH-401-201364

This confirms that this trial was designed and planned in accordance with local legal requirements and also in accordance with the current version of the following:

- Declaration of Helsinki - current version
- ISO14155 - current version
- The International Conference on Harmonisation (ICH) harmonized tripartite guideline regarding Good Clinical Practice (GCP) (E6 Consolidated Guidance) 2016

Clinical investigation plan agreed to by the Sponsor

i.V. 26.03.2019

Dr. Sonja Höller
Corporate Director Clinical Development
Croma-Pharma GmbH

Date

Martin Prinz, MSc
Managing Director & CTO
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26.03.2019

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Approval and signature pages

Clinical investigation plan agreed to by the Coordinating investigator

31 MAR 2019

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Principal Investigator Approval and Signature Page

I agree:

- To assume responsibility for the proper conduct of the clinical investigation at the site specified below, and to conduct the investigation in compliance with this Clinical Investigation Plan (CIP), including any amendments thereof, any other study conduct procedures provided by the Sponsor or their authorized representatives, the principles of good clinical practice, and applicable regulatory requirements.
- Not to implement any deviations from, or changes to, the CIP (including CIP amendments) without agreement from the Sponsor, prior review and favourable opinion from the Ethics Committee, and approval from the Competent Authority, if applicable, except where necessary to eliminate an immediate hazard to the subject(s) or for administrative aspects of the clinical investigation (where permitted by all applicable regulatory requirements).
- That I am familiar with the appropriate use of the investigational medical device as described in this CIP and any other information provided by the Sponsor including, but not limited to, Instructions for use.
- To ensure that all persons providing assistance during the clinical investigation are adequately informed about the investigational medical device and of their study-related duties and functions.
- That I have been informed that certain regulatory authorities require the Sponsor to obtain and supply details about the investigator's ownership interest in the Sponsor or the study product, and more generally about his/her financial ties with the Sponsor. The Sponsor will use and disclose this information solely for the purpose of complying with regulatory requirements.

Investigator's name: DAISY KOPERA, M.D. Prof.

Investigation site: MEDICAL UNIV. GRAZ
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Investigator's signature: Daisy Kopera

Date: 31 MAR 2019

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- To assume responsibility for the proper conduct of the clinical investigation at the site specified below, and to conduct the investigation in compliance with this Clinical Investigation Plan (CIP), including any amendments thereof, any other study conduct procedures provided by the Sponsor or their authorized representatives, the principles of good clinical practice, and applicable regulatory requirements.
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- That I have been informed that certain regulatory authorities require the Sponsor to obtain and supply details about the investigator's ownership interest in the Sponsor or the study product, and more generally about his/her financial ties with the Sponsor. The Sponsor will use and disclose this information solely for the purpose of complying with regulatory requirements.

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Investigation site: MARA (medical aesthetic research academy)

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Investigator's signature: 27.3.2019

Date: 27.3.2019

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Principal Investigator Approval and Signature Page

I agree:

- To assume responsibility for the proper conduct of the clinical investigation at the site specified below, and to conduct the investigation in compliance with this Clinical Investigation Plan (CIP), including any amendments thereof, any other study conduct procedures provided by the Sponsor or their authorized representatives, the principles of good clinical practice, and applicable regulatory requirements.
- Not to implement any deviations from, or changes to, the CIP (including CIP amendments) without agreement from the Sponsor, prior review and favourable opinion from the Ethics Committee, and approval from the Competent Authority, if applicable, except where necessary to eliminate an immediate hazard to the subject(s) or for administrative aspects of the clinical investigation (where permitted by all applicable regulatory requirements).
- That I am familiar with the appropriate use of the investigational medical device as described in this CIP and any other information provided by the Sponsor including, but not limited to, Instructions for use.
- To ensure that all persons providing assistance during the clinical investigation are adequately informed about the investigational medical device and of their study-related duties and functions.
- That I have been informed that certain regulatory authorities require the Sponsor to obtain and supply details about the investigator's ownership interest in the Sponsor or the study product, and more generally about his/her financial ties with the Sponsor. The Sponsor will use and disclose this information solely for the purpose of complying with regulatory requirements.

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Synopsis

Sponsor	Croma-Pharma GmbH Industriezeile 6, 2100 Leobendorf, Austria
Investigational medical device	Princess® RICH
Synopsis Version	3.0
Investigation title	A prospective open-label, multicenter study evaluating Princess® RICH in correction of fine lines
Short title	RICH
Investigation code	CPH-401-201364
Phase of development	Investigation according to § 40 (2) MPG
Indication	Reduction of ..... perioral rhytids ..... and improvement of hydration, tone and elasticity of the skin
Investigation sites	Three sites are planned, located in the European Union
Planned duration	Sixteen months from FSFV to LSLV and assuming three months recruitment period; up to 52 weeks per subject.
Objectives	1. To assess the effectiveness of Princess® RICH to correct fine lines .... 2. To assess safety 3. To assess the ability of Princess® RICH to improve skin hydration, skin tone and skin elasticity in the treatment areas 4. To assess subject satisfaction with treatment 5. To assess the aesthetic effect of Princess® RICH
Methodology/ Study design	This is an open label, single treatment arm study. All subjects will be evaluated by the treating physician, at their initial clinic visit. Subjects deemed by treating physician to have sufficient severity to merit treatment of either their LCL or PR or both will be enrolled in the study. At the same time, measurements for skin hydration, tone and elasticity will be done. 1. Once selected, and prior to receiving any treatment, all subjects will be photographed using a frontal and two lateral (left and right) views to establish a baseline for LCL and/or PR. Measurements for skin hydration, tone and elasticity will be taken using the corneometer and cutometer devices to assess baseline status. 2. Subjects will then receive treatment of either their LCL or PR or both, based on the judgment of the treating physician, with Princess® RICH. This visit will be referred to as Study Visit 1.

	3. At week 3 (Visit 2) following injection, all subjects will return to the clinic and be photographed, evaluated for improvement of the severity of their LCL and/or PR using the Global Aesthetic Improvement Scale (GAIS) listed in Appendix 1, and measurements for skin hydration, tone and elasticity will be done using the corneometer and cutometer devices. At this visit assessment of concomitant medication and adverse events will be done. Subject will then receive the 2nd treatment, as per instructions for use. 4. At Week 6 (Visit 3) all subjects will return to the clinic and be photographed and evaluated for the improvement of the severity of their LCL and/or PR using the GAIS. Measurements for skin hydration, tone and elasticity will be taken prior to next injection. An assessment for concomitant medication and adverse events will be done. Subject will then receive the 3rd treatment, as per instructions for use. 5. At week 8 (Visit 4, primary endpoint assessment) all subjects will return to the clinic and be photographed, as above, as well as being evaluated by the treating physician to assess the following parameters: a. Assessment of improvement in the severity of their LCL and/or PR using GAIS b. Measurements for skin hydration, tone and elasticity, using the corneometer and cutometer devices. c. Each Subject will be asked to grade their satisfaction with the treatment using the Subject Treatment Satisfaction Questionnaire listed in Appendix 1. d. Assessment of concomitant medication and adverse events will be done. 6. At week 12 (Visit 5) all subjects will return to the clinic and be photographed, as above, as well as being evaluated by the treating physician to assess the following parameters: a. Assessment of improvement in the severity of their LCL and/or PR using GAIS b. Measurements for skin hydration, tone and elasticity using the corneometer and cutometer devices. c. Each Subject will be asked to grade their satisfaction with the treatment using the Subject Treatment Satisfaction Questionnaire. d. Concomitant medication and adverse events assessment will be performed. 7. At week 16 (Visit 6) all subjects will return to the clinic and be photographed, as above, as well as being evaluated by the treating physician to assess the following parameters: a. Assessment of the improvement in the severity of their LCL and PR using GAIS b. Measurements for skin hydration, tone and elasticity using the corneometer and cutometer devices.

	c. Each Subject will be asked to grade their satisfaction with the treatment using the Subject Treatment Satisfaction Questionnaire. d. Concomitant medication and adverse events assessment will be done. 8. At week 24 (Visit 7), 36 (Visit 8) and 52 (Visit 9) subjects who consented in the participation of a follow-up period of 52 weeks will return to the clinic. Subjects will be photographed, as above, and will be evaluated by the treating physician to assess the following parameters: a. Assessment of the improvement in the severity of their LCL and PR using GAIS b. Measurements for skin hydration, tone and elasticity using the corneometer and cutometer devices. c. Each Subject will be asked to grade their satisfaction with the treatment using the Subject Treatment Satisfaction Questionnaire. d. Assessment of the aesthetic effect of Princess® RICH as assessed by the investigator e. Concomitant medication and adverse events assessment will be done. 9. At the end of the study (independent of whether the subject participates in the 52-week follow-up period), all necessary study closeout procedures will be performed and the subjects will be discharged from the study. <u>Formal interim analysis:</u> An interim analysis (IA) will be performed after all subjects have completed the follow-up visit at Week 16. <u>End of Study:</u> The duration of the clinical investigation is planned for 52 weeks at a maximum. In case it is observed by the investigator that at a given visit no aesthetic effect is any more visible in approximately 75 % of the subjects participating the follow-up period of 52 weeks, the study can be terminated at an earlier time point.
Sample size	Approximately 100 subjects will be included, to obtain the week 8 performance and safety data for 93 subjects.
Eligibility criteria	<u>Inclusion criteria</u>: A subject must meet **ALL** of the following criteria to be eligible for the study: 1. Male or female, 18 years of age or older 2. Subjects deemed by the treating physician to have LCL and/or PR of sufficient baseline severity to merit treatment with Princess® RICH to be corrected 3. A negative urine pregnancy test at Visit 1 and commitment to use an adequate method of birth control for the duration of the clinical investigation (for women of childbearing potential only.)

	4. Healthy skin in the facial area and free of diseases that could interfere in cutaneous aging evaluation 5. Willingness to abstain from any aesthetic or surgical procedures in the treatment area for the duration of the clinical investigation 6. Written signed and dated informed consent Exclusion criteria: A subject who meets **ANY** of the following criteria is **NOT** eligible for the study: 1. Subjects who tend to develop hypertrophic scars, have pigment disorders or have susceptibility to keloid formation. 2. Subjects with a history of autoimmune disease or who are receiving therapy for modification of immune response, e.g. biologics, systemic corticosteroids, cytostatic drugs. 3. Subjects who are known to be hypersensitive to hyaluronic acid or glycerol. 4. Subjects who have previously received permanent fillers in the areas to be treated. 5. Subjects who are pregnant or breast feeding. 6. Subjects who are anticoagulated or with history of bleeding disorder. 7. Subjects receiving daily treatment with platelet aggregation inhibitors (e.g. acetylsalicytic acid) unless previously cleared by their primary care physician. 8. Subjects who have cutaneous, inflammatory and/or infectious processes (e.g.acne, herpes) present at V0, recurrent herpes simplex or (pre) cancerous lesions in the areas to be treated. 9. Subjects with known Diabetes mellitus or uncontrolled systemic diseases in the assessment of the investigator. 10. Subjects who have had or are planning to undergo laser therapy, chemical peeling, dermabrasion or botulin toxin treatment in the area to be treated within less than three months prior to and during the course of the study. 11. Current participation in another clinical investigation 12. Subjects whose participation in clinical trials is prohibited by the Austrian Medical Devices Act (e.g, persons with a legal custodian appointed due to mental disability, prisoners, soldiers and other members of the armed forces, civil servants)
Criteria for evaluation (endpoints)	Primary performance endpoint: Percentage of responders at week 8 after initial treatment point. [redacted] lines of the LCL and/or PR as assessed with the GAIS (Appendix 1), based on the investigator assessment. Secondary performance endpoints: Percentage of responders. Responder is defined as at least [redacted] assessed with the [redacted] at weeks 12, 16, 24, 36 and 52 after initial treatment.

	Change from baseline at weeks 3, 6, 8, 12, 16, 24, 36 and 52 in skin hydration assessed with the corneometer device. Changes from baseline at weeks 3, 6, 8, 12, 16, 24, 36 and 52 in tone assessed with the cutometer device. Change from baseline at weeks 3, 6, 8, 12 16, 24, 36 and 52 in and elasticity as assessed with the cutometer device. Subject satisfaction with treatment at weeks 8, 12, 16, 24, 36 and 52 (Appendix 1) Percentage of subjects demonstrating an aesthetic effect at weeks 24, 36 and 52 based on the investigator's life assessment. Safety endpoints: Occurrence and frequency of adverse events.
Statistical considerations	Planned statistical analyses are briefly summarized below. Data analyses will be described in detail in the Statistical Analysis Plan. *Sample Size* Approximately 100 subjects will be enrolled in order to obtain week 8 performance and safety data from at least 93 of them. With a sample size of 93, a two-sided 95% confidence interval for a single proportion using the large sample normal approximation will extend 0.10 from the observed proportion for an expected proportion of 0.60. Thus, a robust estimation of the response rate at week 8 can be derived. *Analysis Data Sets* All performance analyses will be done in the Intent-to-Treat population, defined as all subjects who received the investigational device and have at least one post-treatment assessment. All safety analyses will be based on the safety analysis set, defined as all subjects who received the investigational device. A Per-Protocol (PP) population for performance analysis is defined as all subjects in the Intent-to-Treat population, who completed the trial without any protocol deviation that interferes with the performance evaluation. Subjects will be excluded from the Per-Protocol population, who violated any inclusion/exclusion criteria during the course of the study; who have taken any medication or procedure interfering with the performance evaluation; versus baseline in the fine lines of the LCL on both sides and/or the PR as assessed with the GAIS (section **Fehler! Verweisquelle konnte nicht gefunden werden.**), based on the investigator assessment at Week 8 is missing *Methods of Analysis* Missing data will not be estimated and/or imputed in any way.

	In general, collected data will be listed and descriptive statistics will be performed, with all repeating measurements being tabulated by the visit. For continuous variables, descriptive statistics will include the number of observations, minimum, maximum, mean, standard deviation, median, and interquartile range. For discrete variables, summary statistics will include the total number of observations, frequency and percentages. All percentages will be calculated based on the number of non-missing observations. *Formal interim analysis* An interim analysis (IA) will be performed in the Intent-to-Treat population and PP-population after all subjects have completed the follow-up visit at Week 16. All analyses will be considered exploratory. Endpoints will be analysed in the following manner: *Performance endpoints* For the primary performance endpoint, percentage of responders at week 8 after initial treatment point will be reported, together with a 95% confidence interval. baseline in the fine lines of the LCL and/or PR as assessed with the GAIS (Appendix 1), based on the investigator assessment The change from baseline in skin hydration, tone, and elasticity will be analyzed by visit using basic statistics. Subject satisfaction with treatment will be analyzed using frequency tables by visit. *Safety endpoints* AEs will be coded by the Medical Dictionary for Regulatory Activities (MedDRA) and listed by subject. Incidence of AEs will be summarized by preferred term (PT) and system organ class (SOC), and by seriousness, intensity, relationship to the IMD or procedure, respectively, and outcome. Each subject will be counted only once within a SOC or a PT by using the event with the greatest severity or judged to have the closest causal relationship, respectively, within each category. Final analysis: Final analysis will be done after completion of the investigation by all subjects. All analyses will be considered exploratory. Endpoints will be analyzed as in the formal interim analysis. In the final analysis following performance endpoint will be included as well: The aesthetic effect will be analyzed using the percentage of subjects demonstrating an aesthetic effect at weeks 24, 36 and 52.

Schedule of Procedures and Events

Table 1. Schedule of procedures and eventsProcedure	VISIT 1 **Day 0** -	VISIT 2 **Week 3** (±4 days)	VISIT 3 **Week 6** (±4 days)	VISIT 4 **Primary Endpoint** **Week 8** (±4 days)	VISIT 5 **Week 12** (±4 days)	VISIT 6 **Week 16** (±4 days)	VISIT 7 (optional) **Week 24** (±7 days)	VISIT 8 (optional) **Week 36** (±7 days)	VISIT 9 (optional) **Week 52** (±7 days)
Informed consent	x*								
Informed consent addendum[x]						x			
Demographic data [a]	x*								
Medical/aesthetic history	x*								
Prior medication [b]	x*								
Urine pregnancy test [c]	x*	x*	x*	x	x	x	x	x	x
Eligibility check [d]	x*								
Photography [e]	x*	x*	x*	x	x	x	x	x	x
Investigator assessment (GAIS) [f]		x*	x*	x	x	x	x	x	x
Investigational device application	x	x	x						
Measurements with corneometer and cutometer [g]	x*	x*	x*	x	x	x	x	x	x
Subject satisfaction [h]				x	x	x	x	x	x
Assessment of aesthetic effect by the investigator							x	x	x
Adverse events	x**	x	x	x	x	x	x	x	x
Concomitant medication	x**	x	x	x	x	x	x	x	x

* Prior to application of the investigational device.
** From beginning of the treatment onwards.
a Includes year of birth, gender and race.
b All medication taken/received within the previous 10 days.
c In women of child-bearing potential only, including those who are postmenopausal for less than 12 months. Urine dipstick test to be used.
d ion, tone and elasticity.
e Photography should be taken before application of the investigational device
f
g Measurements for skin hydration, tone and elasticity using the corneometer and cutometer devices.
h
I The duration of the clinical investigation is planned for 52 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 participating the follow-up period of 52 weeks, the study can be terminated at an earlier time point.
x Only applicable for subjects willing to participate in the prolonged follow-up

List of Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
CA	Competent Authority
CE	Conformité Européene (European conformity)
CIP	Clinical Investigation Plan
EC	Ethics Committee
eCRF	Electronic Case Report Form
FSFV	First Subject First Visit
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
HA	Hyaluronic acid
IB	
IFU	Instructions for Use
IMD	Investigational Medical Device
LCL	Lateral Canthal Lines
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
mIU	Milli-international unit
MVDSS	Midface Volume Deficit Severity Scale
PMCF	Post-Market-Clinical-Follow-up
PR	Perioral rhytids
PT	Preferred term
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
USADE	Unanticipated Serious Adverse Device Effect

Table of Contents

1 Background

Facial aging is a natural and progressive process, driven by intrinsic and extrinsic factors. This gradual process of structural weakening of the face begins during the third decade of life and continues to worsen thereafter, changing the appearance of an i...
(DeFatta and Williams, 2009). Skin aging is characterized by reduced collagen production, fragmentation of elastin network, and decreased turnover of skin cells. The loss of extracellular matrix and its major component, hyaluronic acid, which forms a viscoelastic surrounding for collagen and elastin fibers, results in reduced skin elasticity and turgor (Sjerobabski-Masnec and Situm, 2010). Due to reduced elasticity, the repeated muscle action produces prominent wrinkles and creases in the mimetic areas of the face, while concomitant involution of facial fat deposits and bone atrophy contribute to skin laxity, facial volume loss and volume redistribution, resulting in aged face (DeFatta and Williams, 2009, Newman, 2009).It is nowadays recognized that volume deficit, rather than vertical descent or ptosis alone, is a critical component of facial aging (Tan and Kontis, 2015).

Typical clinical signs of facial aging include flaccidity of the skin and subcutaneous tissue, wrinkles expression in the upper third of the face, accentuation of tear troughs and nasolabial folds, drop of angles of the mouth, loss of definition in the mandibular border and changes in skin pigmentation (Goldman and Wollina, 2010).

At cellular level a reduced capacity of proliferation from the fibroblast has been observed and, as consequence, a decreased synthesis of collagen and elastin. This entails an alteration in the organization of the elastic fiber network, thus skin remains with reduced resilience and elasticity (Hwang et al., 2011).

Perception of age and health is critical in the judgment of attractiveness. Young faces are generally perceived to be more attractive than old faces, and estimated age is negatively correlated with perceived attractiveness (Porcheron et al., 2014, Samson et al., 2010). Attractiveness influences both the self-perception and behavior toward others, and is related to traits such as self-confidence and social acceptance. It is not surprising, therefore, that aesthetic interventions can improve well-being of people who elect to undergo such procedures. Common positive changes include increased satisfaction with self-appearance, reduced depression or anxiety, improved emotional well-being and increased self-confidence (Sadick, 2008).

Native HA is a linear polysaccharide composed of disaccharide units containing *N*-acetylglucosamine and glucuronic acid (Scott, 1995). It is one of the main constituents of the extracellular matrix and is therefore indispensable for the cellular framework (Fraser et al., 1997).

Since HA is present in the connective tissue of the skin, cartilage, bone and synovial fluid, injectable products containing HA are extensively used for soft tissue regeneration due to their unique chemical-physical properties, biocompatibility, biodegradability and versatility. HA has a superior safety profile and many complications of HA can be easily corrected with hyaluronidase (Cohen, 2008). With injection of native HA it is possible to promote skin rejuvenation and fibroblast activation (Iorizzo et al., 2008).Over the last years, HA injectable dermal fillers have become the most popular agents for soft tissue countering and volumizing.

In order to find a consensus regarding use, aims of treatment, indications and limitations of treatment with native HA, an expert conference took place. The conclusion from the expert

evaluation was that the treatment with native HA is a useful method for the extensive superficial treatment of the skin with the goal of improving elasticity, surface structure, moisture and turgor (Wiest and Kerscher, 2008).

Several clinical studies have been carried out in order to support the above mentioned characteristics and the peculiarities of HA fillers. Baspey d the efficacy of HA filler (Glytone) on skin elasticity and complexion radiance (Baspeyras et al., 2013). Moreover, a recent clinical study have demonstrated the rejuvenation of the periorbital region of the face, using a treatment with natural HA and glycerol, a product equivalent to Princess® RICH (Succi et al., 2012)

Princess® RICH is a viscoelastic solution used to replenish the loss of HA due to aging to improve hydration, tone and elasticity of the skin and to act as a filler for lateral canthal lines

2 Identification and Description of Investigational Medical Device (IMD)

The IMD tested in this clinical investigation is Princess® RICH [1.8% Sodium Hyaluronate with 2% Glycerol i.d.]. Please refer to the Princess® information on the investigational device.

2.1 Device description

Princess® RICH consists of 1.8% sodium hyaluronate with 2% glycerol i.d and is a sterile, biodegradable, viscoelastic, clear, transparent, isotonic and homogenized injectable gel implant. The device contains sodium hyaluronate, obtained by biofermentation from *Streptococcus equi* bacteria. The device is steam sterilized. No pharmaceuticals, human tissues, blood products or material from animal origin are integrated into the device.

The device differs from most similar products for intradermal injections by containing glycerol. Glycerol is added to the formulation for the following reasons: (1) It is used for the adjustment of the osmolality, instead of sodium chloride; (2) Glycerol is a scavenger of radicals and thus stabilizes hyaluronic acid molecules during steam sterilization. Due to this stabilization glycerol increases the viscosity of the device over formulations with the same concentration of hyaluronic acid and comparable molecular weight; (3) Glycerol increases the consistency of the product by increasing intermolecular interactions between the hyaluronic acid chains; (4) Glycerol is well-known cosmetic and humectant.

Princess® RICH device .
One syringe contains 1.0 mL of the device. The needles are ethylene oxide sterilized; they are medical devices according to their field of application, under class IIa (MDD93/42/EEC).

Princess® RICH is according to its field of application classified under class III medical device (MDD 93/42, Attachment IX, rule 8: Implantable devices and long-term surgically invasive devices (> 30 days)). The conformity assessment route complies with MDD 93/42 Annex II.3. (Quality System) and Annex II.4. (Design Examination for Class III Medical Devices).

Princess® RICH is CE-marked since 2009 under the name Princess® RICH. From 2009 and up to date more than 1,046,495 units of the product have been sold in more than 30 countries.

2.2 Manufacturer

Princess® RICH is manufactured by Croma-Pharma GmbH, Industriezeile 6, 2100 Leobendorf, Austria.

Enclosed needles are manufactured by TERUMO Europe N.V., Interleuvenlaan 40, 3001 Leuven, Belgium.

2.3 Intended Use and Mode of Administration

Princess® RICH is a viscoelastic solution used to replenish the loss of HA due to aging to improve hydration, tone and elasticity of the skin and to act as a filler for lateral canthal lines

The device is indicated to be injected into the superficial dermal tissue. The amount injected depends on the size of the area to be corrected and the desired level of replenish the loss of HA. It should be avoided to inject large volume in the periorbital area of the face. The amount inje - The injection technique, which is described in Section 6.2.2, is essential for success of the treatment. Therefore, Princess® RICH

3 Justification for the Design of the Clinical Investigation

3.1 Non-Clinical Data and Biocompatibility

Mechanism of action

HA represents a well characterized biodegradable molecule that is soluble in water and extremely hygroscopic. This ability to bind large amounts of water, its viscoelastic properties as well as its natural presence in the skin make it an attractive substance for dermal fillers for managing volume loss and to improve moisture, tone and elasticity in the skin.

Glycerol, also naturally present in human skin, represents a strong moisturizing agent that also plays an important role in skin elasticity and was added to the product to potentiate the effects of HA (Fluhr et al., 2008).

The combination of HA and glycerol is known to act rehydrating due to its water retaining capacity and therefore is expected to durably increase the hydration of the skin. Glycerol is a scavenger of radicals and thus stabilizes the hyaluronic acid during steam sterilization giving rise to an increased viscosity of the final product compared to non-crosslinked HA formulations without glycerol.

Biocompatibility and non-clinical safety

Nonclinical biocompatibility studies have investigated cytotoxicity, acute and subacute systemic toxicity, and local effects after implantation, sensitization, irritation and genotoxicity of Princess® RICH *in vitro and in vivo*. The studies confirmed that Princess® RICH was well tolerated. Princess® RICH was shown to be non-sensitizing, not cytotoxic, not systemically toxic, not mutagenic and non-irritant.

Clinical observations of test animals, overall body weight development, and histopathological examination demonstrated very good tolerability. There was no inflammation, no cell infiltration, no degeneration, fibrosis, vascularization or atypical reaction and biocompatibility. Princess® RICH was classified as a non-sensitizer. The genotoxicity testing for Princess® RICH showed no mutagenic activity thus did not induce gene mutations.

In conclusion, the overall results from animal experiments support the safety of the device when used as injectable dermal implant.

3.2 Clinical Data

Hyaluronic acid is a natural component of human skin and implanted native HA that usually lasts about three weeks to six months (Rzany et al., 2012, Andre, 2004). An open label study with native HA (Emervel Touch, now called Restylane Fynesse) demonstrated a significant decrease in wrinkle severity at three weeks lasting up to six months after treatment, hence the duration of contact with facial tissues can be expected to be up to six months (Rzany et al., 2012).

A prospective, open-label, noncomparative study was conducted in a single center in Brazil with a similar device, named Mesolis+. Twenty women with Fitzpatrick skin type I to IV aged 30 to 65 who had signs of aging in the periorbital region were eligible to be included. Up to 1.0 mL of HA plus glycerol was injected bilaterally throughout the periorbital region into the superficial dermis per session, using the micropuncture technique with 1 month intervals between sessions. Photographic documentation was done before treatment and two weeks after the second and

should be administered exclusively by physicians who have received specific training on its application and use in respective indications.

2.4 Traceability

Each package of Princess® RICH is identified and tracked by batch number. A set of two labels showing the batch number is situated at the bottom of each box. One of these labels should be attached to the subject An additional label, indicating that the device is exclusively for use in a clinical investigation will be placed on the outer commercial package of each investigational device, if required by national regulations.

third application, using a professional studio system (Canfield) with defined technical and lighting conditions. The photographs were analyzed (improvement in %) by three investigators and a blinded independent evaluator. Furthermore, patients were asked to report their satisfaction with the treatment on a ten point scale. The statistical analysis was descriptive. The magnitude of the treatment effect observed was clinically significant. The procedure was well tolerated and improved skin brightness and turgor and reduced roughness in the periorbital region (Succi, da Silva et al., 2012).

3.3 Justification for the Clinical Investigation

This study will serve to assess the effectiveness and safety of Princess® RICH in a prospectively designed clinical trial investigating effect of the device in correction of fine lines (Lateral Canthal Lines and Perioral Rhytids) and in impro tone and elasticity.

A prospective, open label, non-comparative design was selected because it allows for the most efficient collection of clinical data on the investigational device, in a manner which is appropriate to address the purpose and objectives of the present investigation. In the absence of spontaneous improvement of volume loss and moisture, tone and elasticity in the aging skin, it is reasonable to assume that the treatment effect can be adequately assessed by comparing the post-treatment observations versus baseline, eliminating the need for a control group.

The primary performance endpoint is based on evaluation using the Global Aestheic Improvement Scale (GAIS), a widely-used 5-point scale for assessment of aesthetic improvement after correction of ,and is set at eight weeks, following triple administration of the device. Total follow-up is, however, extended to 52 weeks, to get additional information on longer-term effects and duration of aesthetic effect.

Up to 100 subjects will be included in this investigation to obtain week 8 performance and safety data from at least 93 of them. With a sample size of 93, a two-sided 95% confidence interval for a single proportion using the large sample normal approximation will extend 0.10 from the observed proportion for an expected proportion of 0.60. Thus, a robust estimation of the response rate at week 8 can be derived.

4 Risks and Benefits of the IMD and Clinical Investigation

4.1 Anticipated Clinical Benefits

This study will provide prospectively collected data on the effectiveness and safety of Princess® RICH [redacted] will also assess the ability of Princess® RICH to improve skin hydration, tone and elasticity to treated areas of the skin. The study will also provide data on the duration of these effects and subject satisfaction with the clinical results. At the same time the treatment with Princess® RICH may remove or reduce a distressing aesthetic imperfection in subjects with severe LCLs or PRs, thereby improving their psychological and social wellbeing.

4.2 Anticipated Adverse Device Effects

Cosmetic facial soft-tissue injection procedures, in general, have a very good safety profile. Short-term effects, such as mild pain, redness, swelling, and bruising are relatively common and an expected consequence of the injections themselves, but true complications are rare, especially with hyaluronic acid formulations (Alam and Dover, 2001) (Requena et al., 2011) (Daines and Williams, 2013) (Ozturk et al., 2013). In a recent five-year retrospective review of 2,089 injectable soft-tissue facial filler treatments performed at a single center in the United States (including 1,047 with HA-based formulations), true complications were reported in less than 1% of procedures (four cases of inflammation, seven cases of nodule or granuloma [redacted] (Daines and Williams, 2013).

Complications were particularly uncommon among the patients receiving hyaluronic acid-based treatment, with only two events (0.2% of procedures) reported (one nodule/granuloma [redacted] (Daines and Williams, 2013). An additional advantage of non-permanent filler materials is that any complications are likely to be less persistent and easier to treat (Ozturk et al., 2013). Severe complications are extremely rare with these procedures (Alam and Dover, 2001) (Requena et al., 2011) (Daines and Williams, 2013) (Ozturk et al., 2013).

In a review of over 4,500,000 procedures (using formulations based on non-permanent, semi-permanent or permanent filler materials) over a two year period from 2010 to 2011 in the United States, only five severe complications were reported which accounted for 0.0001% of procedures (which comprised soft tissue necrosis, filler embolism, visual impairment and anaphylaxis (Ozturk et al., 2013).

Very few adverse hypersensitivity reactions have been reported after injection of hyaluronic acid-based filler formulations (Requena et al., 2011). As this compound has no organ or species specificity, there is a low theoretical risk of allergic reaction (Requena et al., 2011). Reported outbreaks of cutaneous mycobacterial infections associated with various cosmetic procedures, including mesotherapy, appear to be related to inappropriate cleansing of equipment with contaminated tap water or other sources, rather than contamination of the injection solution itself (Wong et al., 2012).

Most of the reported adverse events are procedure-related. Succi et al. (2012) conclude that the papules and edema are "an expected consequence of a volume applied in a very shallow location; thus their presence is considered inherent to the procedure. Hematoma is also expected when injecting a needle in a region that has richly vascularized, fine, loose tissue." This is supported by the observation of Succi et al. (2012) that "the presence, intensity, and

duration of adverse events decreased throughout the study" reflect the dexterity of the application technique acquired by researchers over time."

4.3 Possible Interactions with Concomitant Medical Treatments

Anticoagulant and antiplatelet drugs may increase the risk of bleeding or bruising, so the subject should be asked about use of such medications, and the prescribing physician should be consulted to appropriately assess the risk level.

Sodium hyaluronate is incompatible with quaternary ammonium compounds such as benzalkonium chloride solutions. The device should never be placed in contact with these substances or with medical-surgical instruments that have been in contact with these substances.

4.4 Risk Mitigation Strategy

The safety risks will be mitigated by careful selection of the subjects and exclusion of those who may have an increased risk of developing certain types of AEs, proper injection technique (described in Section 6.2.2), appropriate training of the investigators to ensure correct application of the device, and regular follow-up visits over the following 52 weeks, which will allow for timely recognition and management of potential AEs. Furthermore, the subjects will be instructed to immediately contact the investigator in case of occurrence of any AE between the scheduled visits.

4.5 Risk-to-Benefit Rationale

Hyaluronic acid-based dermal fillers are generally considered very safe and effective, and have been widely used for soft tissue augmentation worldwide. There is also no scientific evidence demonstrating adverse events of fillers or hyaluronidase in pregnant women. Observed adverse effects are mainly related to the injection procedure, are transient and mostly mild. While few serious adverse effects have been reported, these are very rare and not expected to occur when the device is correctly applied.

Princess® RICH is CE-marked since 2009. From 2009 up to date more than 1,312,484 units of the product have been released. The complaint ratio of 0.0286% confirms the favourable risk/benefit ratio for the device. The safety profile of the device is well established and based on a high number of treatments. Thus, the results confirm the favourable risk/benefit ratio for the device. Commonly reported adverse events and the literature search from benchmark devices support the acceptability of risks and undesirable effects. Therefore the results show acceptability of the benefit/risk profile according to current knowledge/state of the art in the medical fields concerned and according to available medical alternatives.

Considering the potential benefits of correction, in particular the immediate and long lasting improvement of distressing aesthetic defect, and the low risk of the treatment when used appropriately by an experienced user, the benefits clearly outweigh the potential risks.

5 Objectives and Hypotheses of the Clinical Investigation

5.1 Objectives

To assess the effectiveness of Princess® RICH to correct fine lines on the face including

To assess safety

To assess the ability of Princess® RICH to improve skin hydration, skin tone and skin elasticity in the treatment areas

To assess subject satisfaction with treatment

To assess the aesthetic effect of Princess® RICH

5.2 Hypotheses

This is a non-comparative study and does not entail any hypothesis testing.

5.3 Claims and Intended Performance of the IMD to be verified

Princess® RICH has been approved for the replenishment of hyaluronic acid loss due to aging, to improve hydration, tone and elasticity of the skin and to act as a filler for small lines such as . The approval was based on clinical experience with similar devices. The present investigation is undertaken to support these claims by providing evidence of Princess® RICH performance and safety in subjects undergoing up to three treatments with the device and followed for a total of 52 weeks. All subjects will be evaluated by the treating physician, at their initial clinic visit. Subjects deemed by treating physician to have sufficient severity to merit treatment of either their LCL or PR or both will be enrolled in the study. At the same time, measurements for skin hydration, tone and elasticity will be done. All AEs and device deficiencies occurring during the investigation will be collected and reported.

5.4 Risks and Anticipated Adverse Device Effects to Assess

The safety profile of hyaluronic acid dermal fillers is well established. Based on the equivalence of Princess® RICH with these products and available non-clinical safety data, it is anticipated that it will share the same safety profile, described in Section 4.2. All AEs and device deficiencies occurring during the investigation will be collected and reported.

6.1.1.7 Visit 7 Week 24 (± 7 days)

- Urine pregnancy test
- Photography
- Evaluation of improvement of the severity of their LCL and/or PR using GAIS
- Measurement of skin hydration, tone and elasticity
- Subject satisfaction
- Assessment of aesthetic effect
- Concomitant medication
- Adverse events

6.1.1.8 Visit 8 Week 36 (± 7 days)

- Urine pregnancy test
- Photography
- Evaluation of improvement of the severity of their LCL and/or PR using GAIS
- Measurement of skin hydration, tone and elasticity
- Subject satisfaction
- Assessment of aesthetic effect
- Concomitant medication
- Adverse events

6.1.1.9 Visit 9 Week 52 (± 7 days)

- Urine pregnancy test
- Photography
- Evaluation of improvement of the severity of their LCL and/or PR using GAIS
- Measurement of skin hydration, tone and elasticity
- Subject satisfaction
- Assessment of aesthetic effect
- Concomitant medication
- Adverse events

More details on the specific tasks are provided in Section 6.4 Assessments and Procedures.

6.1.2 Primary performance endpoint

Percentage of responders at week 8 after initial treatment point. Responder is defined as at

(Appendix 1), based on the investigator assessment.

6.1.3 Secondary performance endpoints

assessment, at weeks 12, 16, 24, 36 and 52 after initial treatment.
Change from baseline at weeks 3, 6, 8, 12, and 16, 24, 36 and 52 in skin hydration assessed with the corneometer device.

Changes from baseline at weeks 3, 6, 8, 12, 16, 24, 36 and 52 in tone assessed with the cutometer device.
Change from baseline at weeks 3, 6, 8, 12, 16, 24, 36 and 52 in and elasticity as assessed with the cutometer device.
Subject satisfaction with treatment at weeks 8, 12, 16, 24, 36 and 52 using one of the

(Appendix 1)
Percentage of subjects having an an aesthetic effect at weeks 24, 36 and 52 based on the investigator's life assessment

6.1.4 Safety endpoints:

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

Occurrence and frequency of adverse events.

6.2 IMD Handling and Administration

6.2.1 Packaging, Labelling and Storage

The IMD will be obtained from the commercial manufacturing batch.

Each device will be provided in a folding box containing two sterile single use needles (30G and the IFU. A set of two labels showing the batch number is situated at the bottom of the box. One of these labels should be attached to the subject s file.

An additional label, indicating that the device is exclusively for use in a clinical investigation, will be placed on the outer commercial package of each investigational device, if required by national regulations.

The IMD must be stored in the original box, at 2-25°C in a dry place, protected from light, heat and frost. The investigator must ensure that upon receipt of the investigational device and other study supplies, these are kept in an appropriate and secure location, with access limited to authorized individuals.

6.2.2 Methods of Use

The IMD will be administered to eligible subjects at Visit 1(Day 0), Visit 2 (Week 3) and Visit 3 (Week 6)

Preparation for administration

The skin to be treated should be thoroughly cleaned and disinfected prior to injection of the device and appropriate aseptic technique should be employed throughout the procedure. Sensitive skin may be pre-treated with a local anesthetic patch or cream. If anesthetic is used, the type of anesthetic and exact time of application will be recorded in the electronic Case Report Form (eCRF).

Prior to use of the device, the luer-lock adapter should be held securely and the tip cap should be removed by twisting and pulling carefully, which should prevent formation of bubbles. The syringe should be held and the enclosed needle firmly attached. The needle should be secured tightly by twisting clockwise. The syringe is held correctly if the backstop opens at the back, toward the hand in which it is held. These steps are illustrated in the IFU.

Injection technique

Princess® RICH is indicated to be injected into the superficial dermal tissue. The treating physician will select the technique to be used for applying the device. The device may be injected using the multipuncture technique which is used in superficial wrinkle treatment. This technique consists in administering multiple injections alongside the wrinkle.

Completion of administration

After treatment, the patient should be requested to stay in the office for ten minutes after completion of treatment, to detect for possible blanching caused by arterial occlusions. After this time the investigator should check the subject for any adverse event and confirm that there are no any adverse event prior the subject leave the office.

Application of ice packs for 5-10 min. post injection is optional and may reduce redness and swelling.

6.2.3 Applied Volume of the Device

The amount of the device injected will depend on the condition to be treated and will be selected by the investigator. The actual volume injected will be read off the syringe by the investigator and recorded in the eCRF, area of application, date, and exact start time and end time of injection.

6.2.4 Precautions

- This device must only be administered by a doctor who is familiar with superficial dermal injections
- The device must not be used in areas presenting cutaneous, inflammatory and/or infectious processes (e.g. acne, herpes).
- Sensitive skin may be pre-treated using a local anaesthetic patch or cream.
- Do not use an automated injection system to inject this product.
- Patients should be advised not to apply any make-up for 12 hours after the injection and to avoid prolonged exposure to sunlight and UV or using saunas or Turkish baths for one week after the injection.
- To avoid a possible risk of product mobility, the patient should be advised not to massage the treatment site for a few days following the injection.
- There are incompatibilities between sodium hyaluronate and quaternary ammonium compounds such as benzalkonium chloride solutions. Therefore the device should never be placed in contact with these substances or with medical-surgical instruments that have been in contact with these substances.
- The device should only be used with the needle and syringe provided by the manufacturer.
- The needle must not be manipulated or bent, if the needle is blocked, pressure on the plunger rod should not be increased, instead injection should be stopped and the needle replaced.
- After use the syringe, needle and remaining contents should be disposed appropriately and the device should never be re-used.

There are no available clinical data (efficacy, tolerance) about injecting the device into an area which has already been treated with any other filling product.

6.2.5 Rescue Medication

In case of overcorrection or occurrence of nodules or vascular compromise, a commercially available hyaluronidase injection (e.g., Hylase® or equivalent
discretion.

6.2.6 IMD Accountability

The IMD must not be used outside the context of this CIP.

Documentation on IMD receipt, dispensing/use in individual subjects, and return must be maintained by the investigator or his/her designee. Appropriate forms will be provided by the Sponsor or their representative to facilitate the IMD accountability.

At the end of the clinical investigation, all remaining supplies of investigational devices will be returned to the Sponsor. Empty or used syringes will not be returned to the Sponsor, but will be destroyed at the investigation site, in line with their routine procedure for medical waste disposal after drug accountability has been performed. Used needles shall be disposed immediately after the use as per routine procedure for medical waste disposal at the site.

6.3 Subjects

6.3.1 Number of Subjects and Duration of the Clinical Investigation

Up to 100 subjects will be enrolled. Each subject will take part in the investigation for up to sixteen weeks. The study is anticipated to last for up to seven months.

6.3.2 Recruitment Strategy

The study subjects will be recruited by the investigator, among subjects with evidence of hyaluronic acid loss due to aging and who deemed by treating physician to have sufficient severity to merit treatment of either their LCL or PR or both and would benefit from improvements in skin hydration, tone or elasticity and who attend the investigation site seeking the corrective treatment. The investigator may also offer participation in the study to potential candidates identified in their subject database. In case of an unexpectedly low recruitment rate, the investigation may be advertised.

6.3.3 Subject Identification

clinical practice, the Regulation (EU) 2016/679 (General Data Protection Regulation) and other applicable international and national requirements.

A unique 5-digit subject identification code will be assigned to each subject at screening (e.g., 01-001), where the first two digits identify the investigation site and the last three digits identify the subject.

6.3.4 Inclusion Criteria

A subject must meet **ALL** of the following criteria to be eligible for the study:

1. Male or female, 18 years of age or older.
2. Subjects deemed by the treating physcian to have LCL and/or PR of sufficient baseline severity to merit treatment with Princess® RICH to be corrected.

3. A negative urine pregnancy test at Visit 1 and commitment to use an adequate method of birth control for the duration of the clinical investigation (for women of childbearing potential only)
4. Healthy skin in the facial area and free of diseases that could interfere in cutaneous aging evaluation.
5. Willingness to abstain from any aesthetic or surgical procedures in the treatment area for the duration of the clinical investigation.
6. Written signed and dated informed consent

6.3.5 Exclusion Criteria

A subject who meets **ANY** of the following criteria is **NOT** eligible for the study:

1. Subjects who tend to develop hypertrophic scars, have pigment disorders or have susceptibility to keloid formation.
2. Subjects with a history of autoimmune disease or who are receiving therapy for modification of immune response, e.g. biologics, systemic corticosteroids, cytostatic drugs.
3. Subjects who are known to be hypersensitive to hyaluronic acid or glycerol.
4. Subjects who have previously received permanent fillers in the areas to be treated.
5. Subjects who are pregnant or breast feeding.
6. Subjects who are anticoagulated or with history of bleeding disorder.
7. Subjects receiving daily treatment with platelet aggregation inhibitors (e.g. acetylsalicytic acid) unless previously cleared by their primary care physician.
8. Subjects who have cutaneous, inflammatory and/or infectious processes (e.g.acne, herpes) present at V0, recurrent herpes simplex or (pre) cancerous lesions in the areas to be treated.
9. Subjects with known Diabetes mellitus or uncontrolled systemic diseases in the assessment of the investigator.
10. Subjects who have had or are planning to undergo laser therapy, chemical peeling, dermabrasion or botulin toxin treatment in the area to be treated within less than three months prior to and during the course of the study.
11. Current participation in another clinical investigation
12. Subjects whose participation in clinical trials is prohibited by the Austrian Medical Devices Act (e.g, persons with a legal custodian appointed due to mental disability, prisoners, soldiers and other members of the armed forces, civil servants)

6.3.6 Withdrawal Criteria and Procedures

The subject may be withdrawn from the investigation for any of the following reasons:

1. Occurrence of an AE which requires a premature termination of the treatment or precludes follow-up of the subject
2. A major CIP deviation, which may interfere with evaluation of the treatment outcome (e.g., use of prohibited treatments or medication, or similar)
3. ____ reasons
4. Informed consent withdrawal
5. In case it is observed by the investigator that at a given visit no aesthetic effect is any more visible in approximately 75 % of the subjects participating the follow-up period of 52 weeks

A subject is free to withdraw the consent and leave the investigation at any time with no obligation to specify the reason for withdrawal. Efforts should be made, however, to get in touch with subjects who did not attend the scheduled visit and clarify the reason for default.

Reasons, circumstances and findings related to early withdrawal should be fully described in the eCRF respecting the subject. Attempts should be made to perform an early termination visit, which should consist of the assessments planned for the Week 8 visit. If withdrawal is caused by an AE, the procedures stated in Section 14 must be followed.

6.3.7 Replacement of subjects

Subjects withdrawn from the investigation or lost for follow-up will not be replaced.

6.3.8 Life-style and other Restrictions

Contraception

The safety of Princess® RICH for use during pregnancy has not been established, so women of childbearing potential should use contraception or avoid unprotected sexual intercourse throughout the clinical investigation. Any pregnancy occurring in study subjects during the investigation should be reported as an AE and followed-up as described in Section 14.6.

Other restrictions

The following restrictions apply to all subjects:

- Make-up should not be applied for 12 hours after injection;
- Subjects must keep their facial skin care and makeup regimen constant over the study duration and must not apply any of those in the measured area on the day of corneometer and cutometer meadurements. This includes the first day, so subjects must be informed in advance;
- Prolonged exposure to sunlight or ultraviolet radiation must be avoided for one week after the injection; subjects should abstain from frequent solarium visits;
- To avoid a risk of implant mobility, the treatment site should not be massaged or exposed to pressure for few days following the injection;
- Use of saunas or Turkish baths is prohibited for one week after the injection.

A standardized procedure described in the respective manual, for this equipment, will be provided to the investigators, as well, as an appropriate training in the use of this device.

The investigator will do three repeated measurements in each LCL (right and left) approximately at 1 centimetre from ending of the eye, to a constant pressure on the skin for about 1, 5 seconds.

Followed by three repeated measurements, in the PR area, at one centimetre left and one centimetre right from the Philtrum.

Each results from the respective measurement will be collected as summarized below:

Site	Value #1 (a.u.)	Value #2 (a.u.)	Value #3 (a.u.)
LCL right			
LCL left			
PR right			
PR left			

6.4.5.2 Skin tone and elasticity

For determination of skin tone and elasticity the Cutometer MPA 580 will be used. Negative pressure is created in the device and the skin is drawn into the aperture of the probe and after a defined time released again. Inside the probe, the penetration depth is determined by a non-contact optical measuring system. This optical measuring system consists of a light source and a light receptor, as well as two prisms facing each other, which project the light from transmitter to receptor. The light intensity varies due to the penetration depth of the skin. The resistance of the skin to the negative pressure (tone) and its ability to return into its original position (elasticity) are displayed as curves in real time during the measurement. The measurement is monitored as live curves on the screen with units measured in millimetre penetration depths.

A standardized procedure described in the respective manual, for this equipment, will be provided to the investigators, as well, as an appropriate training in the use of this device. The investigator will do three repeated measurements in each LCL (right and left) approximately at 1 centimetre from ending of the eye, to a constant pressure on the skin.

Followed by three repeated measurements, in the PR area, at one centimetre left and one centimetre right from the Philtrum.

Each results from the respective measurement will be collected as summarized below:

Site	Value #1	Value #2	Value #3
LCL right			
LCL left			
PR right			
PR left			

corrections or clarifications are made in appropriate manner, according to GCP. In case of any other observed default, the monitor will inform the investigator, and the Sponsor when appropriate, will discuss and agree with the investigator suitable corrective actions, and will follow-up their implementation and resolution.

remaining investigation supplies, including the IMD, are disposed of, and that all previously identified issues have been resolved.

The investigator and their institution must permit the monitoring of the investigation, and must provide the monitor a direct access to those portions of the subject
which directly concern this clinical investigation. Furthermore, key study personnel must be available to assist the monitor during the monitoring visits.

7 Statistical Considerations

Planned statistical analyses are briefly summarized below. Data analyses will be described in detail in the Statistical Analysis Plan (SAP).

7.1 Sample Size

Approximately 100 subjects will be enrolled in order to obtain week 8 performance and safety data from at least 93 of them.

With a sample size of 93, a two-sided 95% confidence interval for a single proportion using the large sample normal approximation will extend 0.10 from the observed proportion for an expected proportion of 0.60. Thus, a robust estimation of the response rate at week 8 can be derived.

7.2 Analysis Data Sets

All performance analyses will be done in the Intent-to-Treat population, defined as all subjects who received the investigational device and have at least one post-treatment assessment. All safety analyses will be based on the safety analysis set, defined as all subjects who received the investigational device.

7.3 Missing data

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

7.4 Methods of Analysis

In general, collected data will be listed and descriptive statistics will be performed, with all repeating measurements being tabulated by the visit. For continuous variables, descriptive statistics will include the number of observations, minimum, maximum, mean, standard deviation, median, and interquartile range. For discrete variables, summary statistics will include the total number of observations, frequency and percentages. All percentages will be calculated based on the number of non-missing observations.

Demographic data, use of additional anaesthetic and amount of the filler applied will be listed and summarized using descriptive statistics. Descriptive analysis of other data collected will be described in the SAP.

7.5 Formal Interim Analysis and Final Analysis

An interim analysis (IA) will be performed on ITT and PP population after all subjects have completed the follow-up visit at Week 16.
Final analysis will be done after completion of the investigation by all subjects. All analyses will be considered exploratory.

Endpoints will be analysed in the following manner.

7.5.1 Performance endpoints:

7.5.1.1 Primary performance endpoint:

Percentage of responders at week 8 after initial treatment point. Responder is defined as at PR as assessed with the GAIS (Appendix 1), based on the investigator assessment.

7.5.1.2 Secondary performance endpoints:

the fine lines of the LCL or PR, as assessed with
assessment, at weeks 12, 16, 24, 36, 52 after initial treatment.
Change from baseline at weeks 3, 6, 8, 12, 16, 24, 36 and 52 in skin hydration assessed with the corneometer device. The change from baseline in skin hydration will be analyzed by visit using basic statistics.
Change from baseline at weeks 3, 6, 8, 12,16, 24, 36 and 52 in tone assessed with the cutometer device. The change from baseline in skin hydration will be analyzed by visit using basic statistics.
Change from baseline at weeks 3, 6, 8, 12, 16, 24, 36 and 52 in and elasticity as assessed with the cutometer device. The change from baseline in skin hydration will be analyzed by visit using basic statistics.
Subject satisfaction with treatment at weeks 8, 12, 16, 24, 36 and 52 using one of the

(Appendix 1)
Percentage of subjects demonstrating an aesthetic effect at weeks 24, 36 and 52 based on the investigator's assessment.

7.5.2 Safety endpoints
AEs will be coded by the Medical Dictionary for Regulatory Activities (MedDRA) and listed by subject. Incidence of AEs will be summarized by preferred term (PT) and system organ class (SOC), and by seriousness, intensity, relationship to the IMD or procedure, respectively, and outcome. Each subject will be counted only once within a SOC or a PT by using the event with the greatest severity or judged to have the closest causal relationship, respectively, within each category.

8 Data Management

8.1 Source Documents and Other Records Maintained by the Investigator

medical file, such as the dates of informed consent and enrolment into the clinical investigation, medical history, prior and concomitant medications, visit dates, clinical observations including AEs, results of all assessments including clinical photographs, information related to medical

Any form completed by the subject is also considered as a source document and must be kept
ile.

In addition, the investigator must maintain all other essential documents pertaining to the clinical investigation as defined by ISO 14155:2011 and applicable regulatory requirements.

8.2 Case Report Forms

Data on each subject enrolled in the investigation will be recorded in the web-based CRF, which is designed to accommodate the specific features of the study design and complies with regulatory requirements on electronic data transfer.

The investigator and their authorized designees only are allowed to make entries in the eCRF. This will be regulated by appropriate reading and writing access. Completed eCRFs will be

electronically signed by the investigator or their authorized designee. Any change, deletion or addition will be recorded by an audit trail system.

The investigator must assure that all data are entered promptly, completely, and accurately according to the eCRF instructions, and is ultimately responsible for conformance of eCRF entries with source documents.

8.3 Data Management Procedures

All data management activities will be conducted by the Sponsor's representative following their standard operating procedures. They will build the database and handle the data cleaning process, including logical checks, medical checks, and query process. Details on data handling will be described in the Data Management Plan.

Computerized validation check programs on completeness, correctness, plausibility (such as range checks, cross-checks) will verify the data according to the Data Validation Plan. All identified discrepancies will be queried using eCRF-sytem and addressed to the investigator. The investigator or their designee must carefully answer any query issued by Data Management. Self-evident correction will be done with paper CRF.

Upon completion of data collection and all data cleaning activities, i.e., when the database is considered complete and accurate, it will be soft locked and reviewed by the Sponsor. The database will be hard locked after
trail. Clean data set will be exported for statistical analysis.

8.4 Data Retention

The investigator shall retain all study records (including all subject-related and device-related records, study-
file) during the clinical investigation and for the period required by the applicable regulatory requirements, or for at least 15 years after the premature termination or completion of the clinical investigation, whichever is longer. In any case, the investigator must contact the Sponsor in writing prior to destruction of any records pertaining to the clinical investigation, to get confirmation that these no longer need to be retained. In addition, the Sponsor should be informed in writing if the investigator plans to leave the site or chooses to store the records at a different physical address than the site address, to ensure traceability of the records and appropriate arrangements for the transfer of custody.

The medical files of study participants must be retained in accordance with local legislation and the maximum period permitted by the hospital, institution or private practice.

8.5 Report of the Clinical Investigation

There will be two reports throughout the study. An Interim Report will be generated after all subjects have completed the follow-up visit at Week 16. The Clinical Investigation Report will be generated following the completion of the overall clinical investigation. Both reports will include a summary of all available data, statistical measures, tabulated results, graphical results, and interpretations. A complete list of all adverse events will be enclosed. Both reports will be submitted to relevant authorities as appropriate, within the timeframes defined per national regulation or by the EC.

9 Amendments to the Clinical Investigation Plan

Any change of this CIP can only be made in form of a written amendment. Such amendment has to be discussed, agreed upon and signed by the Sponsor and the investigator before implementation.

Any amendment which may affect the validity of the data or information resulting from original CIP, the risk-benefit ratio for the subject, the scientific soundness of the investigation, or the rights, safety or welfare of study subjects will also have to be reviewed and approved by the EC and regulatory authorities, if applicable, prior to implementation.

Amendments with impact on study procedures to be performed, risk-benefit ratio for the subject and/or the well-being of the subjects require additional informed consent, which has to be given in writing by all subjects enrolled in the clinical investigation who are affected by the amendment.

10 Deviations from the Clinical Investigation Plan

A CIP deviation is a failure to follow, intentionally or unintentionally, the requirements of the CIP. As required by national regulation or guidelines, requests for deviations and reports of deviations will be provided to the EC if the deviation affects subject -being, or the scientific integrity of the clinical investigation.

Under emergency circumstances, deviations from the CIP may proceed without prior approval by the Sponsor and favorable opinion of the EC if the rights, safety and well-being of human subjects need to be protected. Such deviations will be documented and reported to the Sponsor and the EC as soon as possible in accordance with national regulations.

All CIP deviations will be listed and their impact on evaluability of respective subjects will be discussed in a data review meeting prior to the hard data base lock.

11 Device Accountability

Investigational device accountability is described in Section 6.2.6

12 Statements of Compliance

This clinical investigation will be conducted in compliance with the Clinical Investigation Plan (CIP) and the following standards and regulatory requirements:

- International Standard ISO 14155:2011: Clinical investigation of medical devices for human subjects - Good clinical practice;
- Declaration of Helsinki, in its currently adopted version;
- Applicable sections of the national medical device law.

By acting in accordance with this CIP, the investigators and the study site personnel fulfil the requirements of the International Standard ISO 14155:2011.

The clinical investigation will not commence until a favourable opinion from the respective EC has been received. All additional requirements imposed by the EC will be followed.

A prior regulatory approval will also be sought, if required by national regulations.

Insurance coverage for damages emerging from the clinical investigation will be provided according to applicable legal requirements.

13 Informed Consent Process

Written informed consent must be obtained from each subject prior to initiation of any of the investigation-specific procedures.

The investigator or their authorized designee must give each subject complete and adequate verbal and written information about the investigation. The investigator must ensure that the subject is fully informed about the aims, procedures, potential risks, any discomforts, and expected benefits of the clinical investigation. It must be emphasized that participation is voluntary and that the subject has the right to withdraw from the clinical investigation at any time without any justification and without prejudice. They also must be informed that the quality of their medical care will not be adversely affected if they decline to participate in the investigation or in case of subsequent consent withdrawal. Before consenting, the subject must be left with ample time to consider and ask questions. The subject must then sign and date the Informed Consent prior to the conduct of any study procedures. The person obtaining the consent (the investigator or their designee) must sign and date the Informed Consent as well.

A signed and dated copy of the Subject Information Sheet and Informed Consent will be given to the subject for their records.

may be affected by amendment to the CIP (e.g. a change in any procedure), the Subject Information Sheet and the Informed Consent must be amended accordingly, and the subject must sign the amended Informed Consent indicating that they re-consent to participate in the clinical investigation.

14 Adverse Events, Adverse Device Effects and Device Deficiencies

14.1 Definitions

Adverse Event (AE) is 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 study subjects this definition includes events related to the procedures involved, as well pregnancy in females.

For users or other persons this definition is restricted to events related to the IMD.

Adverse Device Effect (ADE): is an AE related to the use of the IMD.

This includes any AE resulting from insufficiencies or inadequacies in the IFU, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. In addition, this includes any event that is a result of a use error or intentional misuse.

Serious Adverse Event (SAE) is an AE that led to any of the following conditions:

Death;

Serious deterioration in the health of the subject that either resulted in:

- A life-threatening illness or injury, or
- A permanent impairment of a body structure or a body function, or
- In-patient or prolonged hospitalization, or
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function;

Foetal distress, foetal death, a congenital abnormality or birth defect.

Planned hospitalization for pre-existing condition or a procedure required by the CIP without a serious deterioration in health is not considered a SAE.

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) is defined as an SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the

Device deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use errors, and inadequate labelling.

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.

14.2 Method of Detecting AEs

AEs will be detected at each visit by observation and by asking the subject about the occurrence of AEs. Care should be taken not to introduce bias when eliciting AE information from the subject. Open-ended and non-leading verbal questioning is the preferred method and appropriate questions include:

ation since

In addition, the subjects will be instructed to immediately contact the investigator/study site in case of occurrence of any untoward event between visits.

14.3 AE/SAE Documentation

For each AE the following must be reported:

- description of the event (event term);
- seriousness;
- start date;
- start time (for events occurring on the treatment day);
- severity;
- action taken;
- outcome;
- end date (if applicable);
- the relationship to the investigational device and procedure, respectively.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such case, the diagnosis will be documented as the AE/SAE and not the individual symptoms and signs.

Each AE should be reported separately. The investigator will record all AEs in the Adverse Events the eCRF. For SAEs, the Serious Adverse Event Form must also be completed. Complete description of all AEs should be also available in source documents.

Any changes in the health of subjects occurring after provision of informed consent and prior to application of the IMD will be recorded as part of the medical history. Any medical condition that is present at screening should also be considered as medical history and not recorded as an AE. If such condition, however, deteriorates after the IMD administration, at any time during the investigation, it should be reported as an AE.

If the severity or seriousness of an AE changes over time, the most severe intensity or seriousness of the AE will be recorded and included in the analysis. No separate AEs will be recorded for each severity level.

Changes in causality assessment (the relationship to the IMD or procedure) should also be clearly documented.

page of the eCRF.

14.4 AE/SAE Assessment

All AEs will be assessed in terms of:

- seriousness (yes or no, based on SAE definition provided in Section 14.1);
- severity;
- relationship to the IMD or study procedures;
- outcome.

14.4.1 Severity Assessment

The severity of an AE/SAE will be graded as follows:

Mild: The AE is easily tolerated and does not interfere with daily activity.

Moderate: The AE interferes with daily activity but the subject is still able to function.

Severe: The AE is incapacitating and/or requires medical intervention.

14.4.2 Causality Assessment

The investigator is obligated to estimate the relationship between each AE/SAE and the IMD or study procedure. Clinical judgement should be used and relevant documents like IFU or Investigators Brochure consulted. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered. The relationship should be determined using one of the following causality levels:

Definite: The AE/SAE is associated with the investigational device or with procedures beyond reasonable doubt when it is a known side effect of the product category the device belongs to, or of similar devices and procedures; has a temporal relationship with investigational device use/application or procedures; involves a body-site or organ that the investigational device or procedures are applied to or have an effect on; follows a known response pattern to the medical device (if the response pattern is previously known); the discontinuation of medical device application (or reduction of the level of exposure), when clinically feasible, and reintroduction of its use (or increase of the level of exposure) impact on the event; other possible causes (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; and/or harm to the subject is due to error in use.

Probable: The relationship with the use of the investigational device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.

Possible: The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained, should also be classified as possible.

Unlikely: The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

Not related: Relationship to the device or procedures can be excluded when the AE/SAE is not a known side effect of the product category the device belongs to or of similar devices and procedures; has no temporal relationship with the use of the investigational device or the procedures; does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; the discontinuation of medical device application or the reduction of the level of exposure, when clinically feasible, and reintroduction of its use (or increase of the level of exposure) do not impact on the event; involves a body-site or an organ not expected to be affected by the device or procedure; can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); and/or harm to the subject are not clearly due to use error.

14.4.3 Outcome Assessment

The outcome of an AE will be assessed as follows:

Resolved: The subject has fully recovered from the event, or the condition has returned to the level observed at baseline.

Ongoing: The event is ongoing at the time of reporting and the subject has still not recovered.

Resolved with sequelae: As a result of the AE, the subject suffered persistent and significant disability/ incapacity (e.g. became blind, deaf or paralyzed).

Fatal: The subject died due to the event.

Unknown: If outcome is not known or not reported.

14.5 AE/SAE Reporting Requirements and Contact Details

For any AE (including a SAE) all appropriate sections of the eCRF must be completed.

Any SAE must be reported by the investigator to the within 24 hours of awareness of the event via fax. Contact details are as follows:

FGK Pharmacovigilance GmbH
Heimeranstr. 35, DE-80339 Munich, Germany
eFax number: +43 1 3580072
Email address: sae7532.rich@fgk-pv.com

This also applies to any significant AE, which in the investigator ion could affect the safety of the study subjects or the conduct of the study.

Information about an SAE will be collected and recorded on the SAE Form. The investigator will be requested to supply as much detailed information as possible regarding the SAE that is available at the time of the initial contact. The investigator should also complete missing or requested information and submit follow-up reports until the SAE has resolved or, in the case of permanent impairment, until the SAE has stabilized.

SAEs without undue delay after receipt of the respective SAE report from the investigator.

Reporting to ECs and regulatory authorities will follow pertinent national legislation.

At the end of the study, a reconciliation of all reported SAEs will take place and be enclosed as a list in the Report of the Clinical Investigation (see Section 8.5).

14.6 AE/SAE Follow-up

The investigator will take all appropriate and necessary measures required for resolution of the AE.

All AEs must be followed-up by the investigator until recovery, or until the investigator , or until the last day of the clinical investigation at the site, whichever occurs first.

Any pregnancy must be notified to *FGK Pharmacovigilance GmbH* within the same timelines as an SAE (within 24 hours after being made aware of the pregnancy) on a Pregnancy Notification Form. The pregnant subject should be withdrawn immediately from the clinical investigation upon confirmation.

Any pregnancy must be followed-up until the pregnancy outcome. If it is still on-going at the end of the clinical investigation, follow-up will be continued outside of the context of clinical investigation and pregnancy outcome (including pregnancy duration and health status of a newborn or cause of premature termination, as applicable) will be reported to the Sponsor.

All SAEs judged to be related to the IMD (SADEs) must be followed by the investigator until the subject has recovered, recovered with sequelae, died, or until the investigator determines

14.7 Foreseeable AEs and Anticipated ADEs

Foreseeable AEs and anticipated ADEs are listed in Section 4.2 Anticipated adverse device effects.

14.8 Device Deficiency Reporting Requirements

All investigational medical device deficiencies will be recorded on a Device Deficiency Report Form.

Device deficiencies should be reported by the investigator to the representative within 24 hours after the site became aware of the device deficiency. Contact information is provided in Section 14.5.

The representative will forward the deficiency report to the Sponsor within 24 hours after receipt of the respective report from the investigator.

If a device deficiency is associated with an AE, the corresponding AE documentation procedures must be adhered to as well.

14.8.1 Handling of Deficient Medical Devices

Any medical device alleged to be deficient must not be used by the investigator and must be returned to the Sponsor.

14.9 Data Monitoring Committee

Not applicable.

15 Vulnerable Populations

Vulnerable populations will not be included in this clinical investigation.

16 Suspension or Premature Termination of the Clinical Investigation

The Sponsor reserves the right to terminate the clinical investigation for any reason (e.g. safety, new data on the risk/benefit, ethical or administrative reasons). Written notice, outlining the reasons for the termination, will be submitted to the investigators in advance of such termination. The Sponsor will provide instructions if assessments beyond the regular per protocol procedures should be necessary.

The Sponsor may suspend enrolment or terminate the study at a specific site for reasons including, but not limited to, inadequate data collection, low subject enrolment rate, achievement of the total enrolment, or non-compliance with the CIP or other clinical research requirements.

The investigator, EC, or regulatory authority (if applicable) may also suspend or prematurely terminate the clinical investigation at the investigational sites for which they are responsible.

If the clinical investigation is prematurely terminated, the Sponsor or the Sponsor's representative will promptly inform the relevant authority (if applicable) of the termination and its reason(s); the investigator or the Sponsor (or representative) will promptly inform the EC, as specified in applicable regulations.

In case it is observed by the investigator that at a given visit no aesthetic effect is any more visible in approximately 75 % of the subjects participating the follow-up period of 52 weeks, the study can be terminated at an earlier time point.

17 Publication Policy

This CIP, other study documentation, data, and all other information generated will be held in strict confidence. No information concerning the clinical investigation or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

The results of the clinical investigation may be published and/or presented at scientific meetings. The results, however, should not be published without prior written consent by the Sponsor and such consent will not be unreasonably withheld. All manuscripts and abstracts, which refer to data originating from the clinical investigation, must be submitted to the Sponsor for comments at least 90 days prior to submission for publication.

If the proposed publication contains any invention related to the clinical investigation, the Sponsor is entitled to file respective patent applications and - on this ground - to delay the submission for publication or presentation of medical results for at least 6 months after receipt of the manuscript or abstract.

18 Bibliography

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Ethikkommission

Medizinische Universität Graz

Auenbruggerplatz 2, A-8036 Graz
ethikkommission@medunigraz.at
Tel.: +43 / 316 / 385-13928, Fax: -14348

FOLGEVOTUM

gültig bis 05.07.2020

EK-Nummer:	30-397 ex 17/18
Studientitel:	A Prospective Open-label, Multicenter Study Evaluating Princess® RICH in Correction of Fine Lines
Prüfer:	Ao. Univ.-Prof. Dr. Daisy Kopera Med. Uni. Graz Klinikum für Dermatologie und Venerologie
Sponsor:	Croma-Pharma GmbH
Ansprechpartner:	Dr. Sonja Höller, A-2100 Leobendorf, Industriezeile 6, A-2100
CRO:	bioskin GmbH
Ansprechpartner:	Dr. Fabian Albrecht, 20095 Hamburg, Burchardstraße 17
Antragsteller:	bioskin GmbH
Ansprechpartner:	Dr. Fabian Albrecht, 20095 Hamburg, Burchardstraße 17

Die o.a. Studie wurde von der Ethikkommission erstmals in der Sitzung 09-17/18 am 11.06.2018 behandelt.
Die Ethikkommission ist zu folgendem Schluss gekommen:

Es besteht kein Einwand gegen die Durchführung der Studie in der vorliegenden Form.

Stimmberechtigte bzw. anwesende Mitglieder bei der Behandlung waren: Siehe beiliegende Liste vom 11.06.2018.

Kommissionsmitglieder, die für diesen Tagesordnungspunkt als befangen anzusehen waren und daher gemäß Geschäftsordnung an der Entscheidungsfindung und Abstimmung nicht teilgenommen haben: keine

Zur Beurteilung vorliegende Dokumente:

Dokumente eingegangen am 18.05.2018, begutachtet in der Sitzung 09-17/18 am 11.06.2018

✓	Cover Letter CPH-401-201364_Anlage 01_Anschreiben EK Graz_20180518_signed 1.0	18.05.2018
✓	Antragsformular ECS	18.05.2018
	Originalprotokoll CPH-401-201364_Anlage 04_CIP RICH_V1.0_20180515_signed 1.0	15.05.2018
	Informed Consent Form CPH-401-201364_Anlage 03_Probandeninformation_V1.0_20180517 1.0	17.05.2018
✓	Conflict of Interest Erklärung CPH-401-201364_Anlage 11_03_FD Kopera_20180514_signed 1.0	14.05.2018
✓	Conflict of Interest Erklärung CPH-401-201364_Anlage 11_01_CoI Kopera_20180514_signed 1.0	14.05.2018
✓	Conflict of Interest Erklärung CPH-401-201364_Anlage 11_04_FD Schaunig_20180516_signed 1.0	16.05.2018
✓	Conflict of Interest Erklärung CPH-401-201364_Anlage 11_02_CoI Schaunig_20180515_signed 1.0	15.05.2018
✓	Case Report Form CPH-401-201364_Anlage 02_CRF Draft_V0.1_20180515 0.1	15.05.2018
✓	Versicherungsbestätigung Zürich-Versicherungs-Aktiengesellschaft 25620677-3	01.01.2014
✓	Versicherungsbestätigung Zürich-Versicherungs-Aktiengesellschaft 25620677-3	18.05.2018
✓	Versicherungsbestätigung Zürich-Versicherungs-Aktiengesellschaft 25620677-3	01.01.2014

19 Appendix 1 EVALUATION INSTRUMENTS

19.1 Global Aesthetic Improvement Scale (GAIS)

Category	Description
Very much improved	Optimal aesthetic result for the implant in this patient.
Much improved	Marked improvement in appearance from the initial condition, but not completely optimal for this patient. A Touch-up would slightly improve the result.
Improved	Obvious improvement in appearance from the initial condition, but a Touch-up or retreatment is indicated.
No change	The appearance is essentially the same as the original condition.
Worse	The appearance is worse than the original condition.

19.2 Subject's Treatment Satisfaction Questionnaire

Very satisfied
Satisfied
Neither satisfied nor unsatisfied
Unsatisfied
Very unsatisfied

✓	Versicherungsbestätigung Zürich-Versicherungs-Aktiengesellschaft 25620677-3	01.01.2015
✓	CV CPH-401-201364_Anlage 10_01_CV Kopera_20180218_signed 1.0	18.02.2018
✓	CV CPH-401-201364_Anlage 10_02_CV Kopera_20180514_signed 1.0	14.05.2018
✓	CV CPH-401-201364_Anlage 10_03_CV Schaunig_20180515_signed 1.0	15.05.2018
✓	Investigator's Brochure CPH-401-201364_Anlage 05_IB Princess RICH_V1.0_20180516_signed 1.0	16.05.2018
✓	Sonstiges: CPH-401-201364_Anlage 06_01_Konformitätserklärung Princess RICH_20170131_signed 1.0	31.01.2017
✓	Sonstiges: CPH-401-201364_Anlage 12_Prüfarztvertrag Kopera_V1.0_20180517 1.0	17.05.2018
✓	Sonstiges: CPH-401-201364_Anlage 14_LoA_20180515_signed 1.0	15.05.2018
✓	Sonstiges: CPH-401-201364_Anlage 08_Liste Normen_V1.0_20180517 1.0	17.05.2018
✓	Sonstiges: CPH-401-201364_Anlage 07_RMR Princess RICH_20171130_signed 1.0	30.11.2017
✓	Sonstiges: CPH-401-201364_Anlage 13_Mustertext Rekrutierungsmaßnahmen_V1.0_201805017 1.0	17.05.2018
✓	Sonstiges: CPH-401-201364_Anlage 06_03_Zertifikat QM System_20160722_signed 1.0	22.07.2016
✓	Sonstiges: CPH-401-201364_Anlage 06_02_Gebrauchsanweisung Princess RICH_20161013 1.0	13.10.2016
Dokumente eingegangen am 24.05.2018, begutachtet in der Sitzung 09-17/18 am 11.06.2018		
✓	Originalprotokoll CPH-401-201364 1.0	15.05.2018
Dokumente eingegangen am 30.05.2018, begutachtet in der Sitzung 09-17/18 am 11.06.2018		
✓	Cover Letter	30.05.2018
✓	Antragsformular Unterschriftenseite	30.05.2018
	Informed Consent Form Zentrum Rappl 2.0	29.05.2018
	Informed Consent Form Zentrum Kopera 2.0	29.05.2018
✓	CV Prüfer Rappl	23.04.2018
✓	CV Mitarbeiter May, Zentrum Rappl	23.05.2018
✓	Financial Disclosure: May	20.05.2018
✓	Financial Disclosure: Rappl	20.05.2018
✓	Prüfervertrag 1.0	15.05.2018
✓	Antrag Teil B PDF (Rappl)	16.05.2018
✓	Antrag Teil B ECS unterschrieben (Kopera	22.05.2018
Dokumente eingegangen am 26.06.2018, begutachtet im 'expedited Review' am 05.07.2018		
✓	Cover Letter	26.06.2018
✓	Informed Consent Form Zentrum Rappl 3.0	15.06.2018
✓	Informed Consent Form Zentrum Kopera 3.0	15.06.2018
✓	Zahlungsbeleg	14.06.2018
✓	Konformitätserklärung (CE) Princess Rich - full qualitiy assurance	27.04.2018
✓	Konformitätserklärung (CE) Design Examination (of product)	21.12.2016
✓	Konformitätserklärung (CE) Princess Rich	07.05.2018
Dokumente eingegangen am 19.07.2018, begutachtet im 'expedited Review' am 24.07.2018		
✓	Cover Letter	19.07.2018
✓	Informed Consent Form Zentrum Rappl 4.0	10.07.2018
✓	Informed Consent Form Zentrum Kopera 4.0	10.07.2018
Dokumente eingegangen am 25.09.2018, begutachtet im 'expedited Review' am 05.10.2018		
✓	Cover Letter	25.09.2018
✓	Originalprotokoll 2.0	19.09.2018
✓	Fragebögen Subject Treatment Satisfaction 1.0	14.08.2018
Dokumente eingegangen am 13.11.2018, begutachtet im 'expedited Review' am 22.11.2018		
✓	Cover Letter	13.11.2018
✓	CV Mitarbeiter Cuno	12.11.2018

Dokumente eingegangen am 29.03.2019 (in der nächsten Begutachtung mitbegutachtet)	
✓ Cover Letter	29.03.2019
✓ Originalprotokoll 3.0	26.03.2019
Informed Consent Form Addendum, Zentrum Rappl 1.0	26.03.2019
Informed Consent Form Addendum, Zentrum Kopera 1.0	26.03.2019
✓ Versicherungsbestätigung Zurich 25620677-3	18.05.2018
Dokumente eingegangen am 02.04.2019 (in der nächsten Begutachtung mitbegutachtet)	
✓ Originalprotokoll mit Unterschriften 3.0	26.03.2019
Dokumente eingegangen am 10.04.2019, begutachtet im 'expedited Review' am 26.04.2019	
✓ Informed Consent Form Addendum, Zentrum Rappl 2.0	10.04.2019
✓ Informed Consent Form Addendum, Zentrum Kopera 2.0	10.04.2019
Dokumente eingegangen am 24.06.2019, begutachtet im 'expedited Review' am 27.06.2019	
✓ Cover Letter	24.06.2019
✓ Zwischenbericht	24.06.2019

Datum Erstvotum: 05.07.2018

Die Ethikkommission geht – rechtlich unverbindlich – davon aus, dass es sich um eine klinische Prüfung nach MPG (mit CE-Zeichen innerhalb der Zweckbestimmung) handelt und macht darauf aufmerksam, dass vor Beginn der Prüfung ein ordnungsgemäßer Antrag auf Genehmigung an das Bundesamt für Sicherheit im Gesundheitswesen zu stellen ist.

Das Votum der Ethikkommission berührt in keiner Weise die alleinige Verantwortung der Prüferin / des Prüfers / der Prüfer für die ordnungsgemäße Durchführung der Studie unter Einhaltung aller einschlägiger gesetzlicher Bestimmungen und Richtlinien.

Weiters machen wir darauf aufmerksam, dass der Kommission unverzüglich zu melden sind:

- Abweichungen vom Protokoll aus Sicherheitsgründen oder Protokolländerungen

- Änderungen, die das Risiko der Teilnehmer/-innen erhöhen oder die Durchführung der Studie wesentlich beeinflussen

- Mutmaßliche unerwartete schwerwiegende Nebenwirkungen - SUSARs (AMG-Studien ab 1.5.2004) oder schwerwiegende unerwünschte Ereignisse - SAEs (andere Studien)

- Jegliche Information über sonstige Umstände, die die Sicherheit der Teilnehmer/-innen oder die Durchführung der Studie beeinträchtigen können

Graz, 27. Juni 2019

Univ.Prof.DI Dr.Josef Haas
Vorsitzender

Univ.Prof.Dr.Hans Dimai
Stv. Vorsitzender

Achtung: Bitte bei allen das Projekt betreffende Schreiben oder telefonischen Anfragen die EK-Nummer angeben!

Bundesamt für
Sicherheit im
Gesundheitswesen
BASG

BASG/AGES
Institute Surveillance
Traisengasse 5, 1200 Vienna

Dear applicant,

The Federal Office for Safety in Healthcare herewith notifies you about the conclusion of procedure BASG reference 11936919 regarding the clinical investigation:

Title: ☐A Prospective Open-label, Multicenter Study Evaluating Princess® RICH ii Correction of Fine Lines☐

Protocol No.: CPH-401-201364

There are no objections from the Austrian Competent Authority to the conduct of the clinical investigation as amended. The substantial amendment can be implemented upon availability of positive Ethics Committee opinions for all trial sites.

BASG approval should be published within the next five working days, available at https://abstimmungen.basg.gv.at/abstimmung

To find the information on the trial, please enter the BASG reference in the field ☐Betrachtugsobjekt☐. If you are unable to find the publication of approval on our website after the next five working days or have further questions, please do not hesitate to contact us.

This letter should be filed in the Trial Master File and Investigator Site Files together with the confirmation of formal completeness and a screenshot of the BASG website documenting the date of approval.

On behalf of the Austrian Competent Authority

Zmuda Violetta
am 14.5.2019

BUNDESAMT FÜR SICHERHEIT IM GESUNDHEITSWESEN
@ AMTSSIGNATUR

Dieses Dokument wurde amtssigniert.
Informationen zur Prüfung der elektronischen Signatur und des Ausdrucks finden Sie unter http://www.basg.gv.at/amtssignatur.

Bundesamt für Sicherheit im Gesundheitswesen
Traisengasse 5, 1200 Wien

Signaturwert

irrThpAktmSDebSfSb/BI5TnWSP
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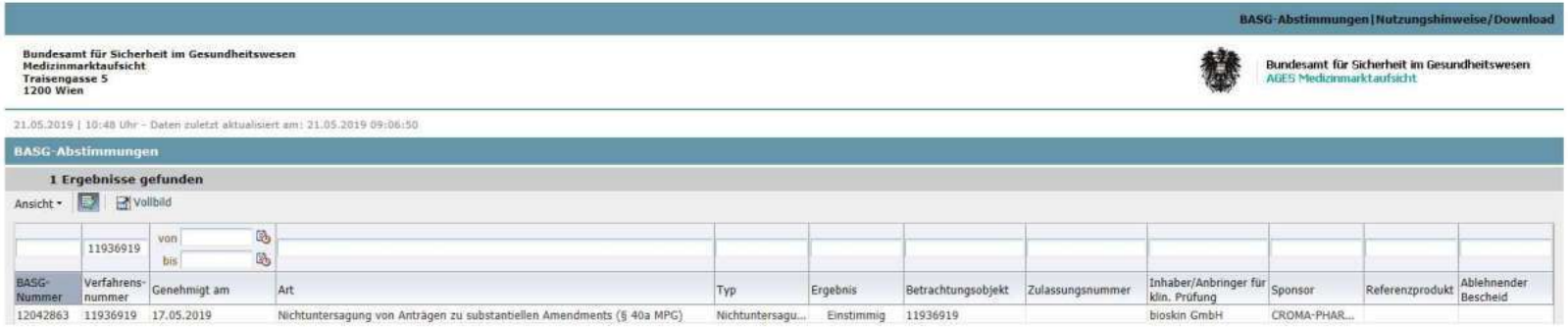
croma

DOC Code	Valid from	Valid until	Print date
C_CT_CER_005_05	09.03.2020	08.06.2025	09.04.2020



BASG-Abstimmungen | Nutzungshinweise/Download

Bundesamt für Sicherheit im Gesundheitswesen
Medizinmarktaufsicht
Traisengasse 5
1200 Wien

Bundesamt für Sicherheit im Gesundheitswesen
AGES Medizinmarktaufsicht

21.05.2019 | 10:48 Uhr – Daten zuletzt aktualisiert am: 21.05.2019 09:06:50

BASG-Abstimmungen

1 Ergebnisse gefunden

Ansicht | Vollbild

	11936919	von / bis									
BASG-Nummer	Verfahrens-nummer	Genehmigt am	Art	Typ	Ergebnis	Betrachtungsobjekt	Zulassungsnummer	Inhaber/Anbringer für klin. Prüfung	Sponsor	Referenzprodukt	Ablehnender Bescheid
12042863	11936919	17.05.2019	Nichtuntersagung von Anträgen zu substantiellen Amendments (§ 40a MPG)	Nichtuntersagu...	Einstimmig	11936919		bioskin GmbH	CROMA-PHAR...		

Clinical Investigation Report

Sponsor:	**CROMA-PHARMA GmbH**
Clinical investigation plan (CIP) identification:	CPH-401-201364 RICH
Title:	A Prospective Open-label, Multicentre Study Evaluating Princess® RICH in Correction of Fine Lines
Investigational medical device (IMD):	Princess® RICH [1.8% Sodium Hyaluronate with 2% Glycerol i.d.]
Classification:	Class III medical device
Coordinating investigator (CI):	Univ. Prof. Dr. Daisy Kopera Medical University Graz- Dermatology and Venerology Clinic Auenbruggerplatz 8, 8036 Graz, Austria Phone general: +43 316 385 12423 Fax: +43 316 385 12466 Email: daisy.kopera@medunigraz.at
Sponsor	CROMA-PHARMA GmbH Industriezeile 6, 2100 Leobendorf, Austria Phone: +43 2262 684 680 Email: office@croma.at
Biostatistician	Agnes Himmelmann, M.S. bioskin GmbH Messberg 4, 20095 Hamburg, Germany
Author of the report	Ragna Williams, M.S. bioskin GmbH Messberg 4, 20095 Hamburg, Germany
Clinical investigation period	25OCT2018 (first subject in, Visit 1/Screening) to 22OCT2019 (last subject last Week 36 visit, Visit 8)
Date of report:	03MAR2020

The clinical investigation was conducted in compliance with Good Clinical Practice [GCP], in accordance with the currently valid revision of the Declaration of Helsinki, ISO 14155-2011(E) and any applicable national laws and regulations.

Table of Contents

page

List of in-text tables

page

Summary

Title

A Prospective Open-label, Multicentre Study Evaluating Princess® RICH in Correction of Fine Lines

Purpose

1. To assess the effectiveness of Princess® RICH to correct fine lines on the face including lateral canthal lines (LCL) also
2. To assess safety
3. To assess the ability of Princess® RICH to improve skin hydration, skin tone and skin elasticity in the treatment areas
4. To assess subject satisfaction with treatment
5. To assess the aesthetic effect of Princess® RICH

Introduction

Princess® RICH has been approved in 2009 for the replenishment of hyaluronic acid (HA) loss due to aging, to improve hydration, tone and elasticity of the skin and to act as a filler for small lines such as lateral canthal lines and perioral rhytids . The approval was based on clinical experience with equivalent and similar devices. The present investigation was undertaken to support these claims by providing evidence of Princess® RICH performance and safety in subjects undergoing up to three treatments with the device and followed for a total of 36 weeks.

The intended use of Princess® RICH was updated in April 2019 as follows: The device is a viscoelastic solution to replenish the loss of hyaluronic acid due to ageing, to improve hydration, tone and elasticity of the skin.

Design and methodology

This was an open label, single treatment arm study.

All subjects were evaluated by the treating physician, at their initial clinic visit. Subjects deemed by treating physician to have sufficient severity to merit treatment of either their LCL or PR or both were enrolled in this investigation. At the same time, measurements for skin hydration, tone and elasticity were done.

1. Once selected, and prior to receiving any treatment, all subjects were photographed using a frontal and two lateral (left and right) views to establish a baseline for LCL and/or PR. Measurements for skin hydration, tone and elasticity were taken using the corneometer and cutometer devices to assess baseline status.
2. Subjects then received treatment of either their LCL or PR or both, based on the judgment of the treating physician, with Princess® RICH. This visit was referred to as Study Visit 1.
3. At Week 3 (Visit 2) following injection, all subjects returned to the clinic and were photographed, as above, evaluated for improvement of the severity of their LCL and/or PR using the Global Aesthetic Improvement Scale (GAIS), and measurements for skin hydration, tone and elasticity were done using the corneometer and cutometer devices.

   At this visit, assessment of concomitant medication and

Design and methodology (continued)

adverse events was done. The subjects then received the 2nd treatment, as per instructions for use.

4. At Week 6 (Visit 3), all subjects returned to the clinic and were photographed, as above, and evaluated for the improvement of the severity of their LCL and/or PR using the GAIS. Measurements for skin hydration, tone and elasticity were taken prior to next injection. An assessment for concomitant medication and adverse events was done. The subjects then received the 3rd treatment, as per instructions for use.
5. At Week 8 (Visit 4, primary endpoint assessment), all subjects returned to the clinic and were photographed, as above, as well as evaluated by the treating physician to assess the following parameters:
   a. Assessment of improvement in the severity of their LCL and/or PR using GAIS.
   b. Measurements for skin hydration, tone and elasticity, using the corneometer and cutometer devices.
   c. Each subject was asked to grade their satisfaction with the treatment using the Subject Treatment Satisfaction Questionnaire listed in Appendix 1 of the Clinical investigation plan (CIP), V3.0.
   d. Assessment of concomitant medication and adverse events was done.
6. At Week 12 (Visit 5), all subjects returned to the clinic and were photographed, as above, as well as evaluated by the treating physician to assess the following parameters:
   a. Assessment of improvement in the severity of their LCL and/or PR using GAIS.
   b. Measurements for skin hydration, tone and elasticity using the corneometer and cutometer devices.
   c. Each subject was asked to grade their satisfaction with the treatment using the Subject Treatment Satisfaction Questionnaire.
   d. Concomitant medication and adverse events assessment were performed.
7. At Week 16 (Visit 6), all subjects returned to the clinic and were photographed, as above, as well as evaluated by the treating physician to assess the following parameters:
   a. Assessment of the improvement in the severity of their LCL and PR using GAIS.
   b. Measurements for skin hydration, tone and elasticity using the corneometer and cutometer devices.
   c. Each subject was asked to grade their satisfaction with the treatment using the Subject Treatment Satisfaction Questionnaire.
   d. Concomitant medication and adverse events assessment were done.

Design and methodology (continued)	8. At Weeks 24 (Visit 7) and 36 (Visit 8), subjects who consented in the participation of a follow-up period of 36 weeks returned to the clinic. Subjects were photographed, as above, and were evaluated by the treating physician to assess the following parameters: a. Assessment of the improvement in the severity of their LCL and PR using GAIS. b. Measurements for skin hydration, tone and elasticity using the corneometer and cutometer devices. c. Each Subject was asked to grade their satisfaction with the treatment using the Subject Treatment Satisfaction Questionnaire. d. Assessment of the aesthetic effect of Princess® RICH as assessed by the investigator. e. Concomitant medication and adverse events assessment were done. 9. At the end of the investigation (independent of whether the subject participates in the 36-Week follow-up period), all necessary investigation closeout procedures were performed and the subjects were discharged from the investigation. Formal interim analysis: An interim analysis was performed after all subjects had completed the follow-up visit at Week 16. The interim report V1.0 dated 28OCT2019 was based on all 3 investigation sites and is filed in the trial master file (TMF). End of Investigation: The duration of the clinical investigation was planned for 52 weeks at a maximum. As it was observed by the investigator that at Week 36 (Visit 8) no aesthetic effect was any more visible in approximately 75 % of the subjects participating the follow-up period, the investigation was terminated at Week 36.
Population (planned/analysed)	100 male and female subjects aged 18 years or older were planned to be included; 102 subjects were screened and enrolled in this clinical investigation. However, the data collected at site 03 were excluded from this clinical investigation report (CIR) (see Section 3.4.). Therefore, data of only 59 subjects were valid for the safety-analysis-set. Data of 58 subjects were valid for intent-to-treat-population (ITT). For the remaining subject, the primary exclusionary reason [redacted] suffered from familial catastrophes and discontinued the investigation after Visit 1.

Population (planned/analysed, continued)	47 subjects were included in the per-protocol (PP) population (valid cases set = VCS). 12 subjects in total were excluded from PP population. (patient suffers fr with protocol deviation interfering with the evaluation for GAIS at 1 of the 11 subjects withdrew from the investigation after Visit 4/Week 8 due to personal reasons. The 2 subjects with premature discontinuation after Visit 4 and Visit 1 were the only 2 dropouts in this investigation.
Results and conclusions	The performance results of Princess® RICH clearly showed high effectiveness in the correction of fine lines on the face either on LCL or PR alone or for both areas (LCL and PR) combined as assessed by investigators. The investigator ratings using the global aesthetic improvement score (GAIS) showed high responder rates at the primary assessment visit Week 8 (100% for LCL, PR and for at least one test area [LCL or PR]) and still substantial responder rates at Weeks 12 and 16 (for LCL and PR) and at Week 24 (for PR only). Afterwards, the responder rates declined to 0% for LCL to 33.3% for PR (28.6% for LCL or PR) at Week 36. These results were supported by the results seen in the subject ratings was demonstrated at Week 8 with the majority of the subjects The remaining At Weeks 12, 16, 24 and 36, most of the subjects (91.1%, 73.7%, 58.3% and 71.4 at any assessment time point. The ability of Princess® RICH to improve skin tone and skin elasticity in the treatment areas was confirmed by cutometry. The cutometric measurements revealed mean lower R0 values (skin tone) and mean higher R2 ratios compared to baseline following IMD treatment, indicating an improvement in skin tone and skin elasticity in the treatment areas. Over the investigational period, the greatest decrease in R0 was noted at Week 8 for LCL and at Week 36 for PR. The greatest increase in skin elasticity was noted for LCL at Week 12 and for PR at Week 36.

Results and conclusions (continued)	In comparison to approximately 80% described in literature (Succi et al., 2012; Uth, Elberg and Zachariae, 2016), only 1 of the subjects (2%) in this clinical investigation presented swelling. corresponding to other HA described in literature (Abduljabbar and shoulder operation). 7 subjects took a medication for treatment of AE. None of the subjects took a rescue medication. 52.5%, 45.2%, and 53.7% took an additional anaesthetic medication on Day 0, Week 3 and Week 6, respectively. Furthermore, no device deficiencies were reported in this clinical investigation. On the basis of the present results no specific risks or precautions are required to be mentioned over those already known and described. There were no safety concerns based on the results of this clinical investigation. Overall, the IMD poses a well-tolerated, safe and effective alternative to current use of other comparable dermal fillers in the treatment of LCL and PR. Princess® RICH as a hyaluronic dermal injectable convinced with its performance on improving skin tone and elasticity and to act as a filler for small lines such as LCL and PR lasting for a satisfactory duration.
Initiation/completion date of investigation	25OCT2018 (first subject in, Visit 1/Screening) 22OCT2019 (last subject last Week 36 visit, Visit 8)

Results and conclusions (continued)

The assessment of skin hydration using corneometry demonstrated only minor changes over the investigational period until Week 8 based on mean corneometric values of 51.8 i.u. for LCL and 53.2 i.u. for PR at baseline. As of Week 12, a trend to an increase was noted for LCL and PR. At Week 24, the greatest increase was noted for both LCL and PR (15.1 and 10.9 i.u., respectively). 12 weeks later at Week 36, still a considerable skin hydration (9.8 i.u.) was noted for LCL, while the skin hydration had decreased to the minimum value of -4.6 i.u. for PR. An improvement of skin hydration was seen at Weeks 24 (LCL: 69.0 i.u. and PR: 61.4 i.u.) and 36 (LCL only: 83.6 i.u.) as the corneometric values were within the values known for well hydrated skin (range between 60 und 85 i.u.; in the eye area generally higher as perioral).

In summary, the performance results of this clinical investigation demonstrate the benefit of the non-cross-linked, glycerol-added HA product Princess® RICH correcting fine lines in both treatment areas providing rejuvenation and an aesthetic effect lasting for a satisfactory duration.

The outcome of the primary performance analyses on the ITT population was supported by the analyses the PP population showing overall similar results.

The safety variables of this investigation demonstrated the safety and tolerability of Princess® RICH when either LCL or PR or both areas combined were treated and no new safety concerns were identified during this investigation. The safety results are consistent with the known safety profile of other HA fillers and show that the safety profile of Princess® RICH is typical for a natural HA (Baspeyras et al., 2013; Succi et al., 2012).

In total, 36 treatment-emergent adverse events (TEAEs) were reported in 24 subjects (41%). 2 of the TEAEs were SAEs (Neuropathia vestibularis right and meniscus partial rupture left knee), which were considered to be unlikely or not related to IMD or procedure, respectively. All other TEAEs were non-serious TEAEs, mostly located at treatment area or just around treatment area (25 TEAES in 18 subjects) and considered to be related to study

causal relationship to IMD was considered to be probable for 1 TEAE

Local injection related side effects were expected in this clinical investigation (Lafaille and Benedetto, 2010; Gabriele F-H et al 2014):

compared to other HA fillers. For a natural, non-cross-linked glycerol-added HA gel (Mesolis plus) 76% haematoma was seen (N = 20, Succi et al., 2012); for Restylane, a cross-linked product the incidence was: 93% of subjects showing injection site reactions and slightly over 50% of the subjects showing bruising (Cohen 2008).

1. Introduction

Facial aging is a natural and progressive process, driven by intrinsic and extrinsic factors. This gradual process of structural weakening of the face begins during the third decade of life and over time (DeFatta and Williams, 2009). Skin aging is characterized by 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 (Sjerobabski-Masnec and Situm, 2010). Due to reduced elasticity, the repeated muscle action produces prominent wrinkles and creases in the mimetic areas of the face, while concomitant involution of facial fat deposits and bone atrophy contribute to skin laxity, facial volume loss and volume redistribution, resulting in aged face (DeFatta and Williams, 2009, Newman, 2009). It is nowadays recognized that volume deficit, rather than vertical descent or ptosis alone, is a critical component of facial aging (Tan and Kontis, 2015).

Typical clinical signs of facial aging include flaccidity of the skin and subcutaneous tissue, wrinkles expression in the upper third of the face, accentuation of tear troughs and nasolabial folds, drop of angles of the mouth, loss of definition in the mandibular border and changes in skin pigmentation (Goldman and Wollina, 2010).

At cellular level a reduced capacity of proliferation from the fibroblast has been observed and, as consequence, a decreased synthesis of collagen and elastin. This entails an alteration in the organization of the elastic fibre network, thus skin remains with reduced resilience and elasticity (Hwang et al., 2011).

Perception of age and health is critical in the judgment of attractiveness. Young faces are generally perceived to be more attractive than old faces, and estimated age is negatively correlated with perceived attractiveness (Porcheron et al., 2014, Samson et al., 2010). 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 well-being of people who elect to undergo such procedures. Common positive changes include increased satisfaction with self-appearance, reduced depression or anxiety, improved emotional well-being and increased self-confidence (Sadick, 2008).

Native HA is a linear polysaccharide composed of disaccharide units containing N-acetylglucosamine and glucuronic acid (Scott, 1995). It is one of the main constituents of the extracellular matrix and is therefore indispensable for the cellular framework (Fraser et al., 1997).

Since HA is present in the connective tissue of the skin, cartilage, bone and synovial fluid, injectable products containing HA are extensively used for soft tissue regeneration due to their unique chemical-physical properties, biocompatibility, biodegradability and versatility. HA has a superior safety profile and many complications of HA can be easily corrected with hyaluronidase (Cohen, 2008). With injection of native HA it is possible to promote skin rejuvenation and fibroblast activation (Iorizzo et al., 2008). Over the last years, HA injectable dermal fillers have become the most popular agents for soft tissue countering and volumizing.

In order to find a consensus regarding use, aims of treatment, indications and limitations of treatment with native HA, an expert conference took place. The conclusion from the expert evaluation was that the treatment with native HA is a useful method for the extensive superficial

treatment of the skin with the goal of improving elasticity, surface structure, moisture and turgor (Wiest and Kerscher, 2008).

Several clinical studies have been carried out in order to support the above mentioned

HA filler (Glytone) on skin elasticity and complexion radiance (Baspeyras et al., 2013). Moreover, a recent clinical study has demonstrated the rejuvenation of the periorbital region of the face, using a treatment with natural HA and glycerol, a product equivalent to Princess® RICH (Succi et al., 2012).

Princess® RICH is a viscoelastic solution used to replenish the loss of HA due to aging to improve hydration, tone and elasticity of the skin and to act as a filler for lateral canthal lines (LCL) also called

Further information about Princess® RICH can be found in the investigator´s brochure (IB) (Princess® RICH V2.0, dated 14JUN2019).

This clinical investigation was performed in compliance with GCP, in accordance with the currently valid revision of the Declaration of Helsinki, ISO 14155-2011(E) and any applicable national laws and regulations.

2. Investigational medical device (IMD) and methods

Details of the IMD are given in Table 1.

Table 1: Details of the IMD

Brand name	Princess® RICH
Formulation	Hyaluronic Acid
Functional components	Sodium hyaluronate (17.72 mg/mL) as Active ingredient Citric acid monohydrate (0.06 mg/mL) as Buffer salt Glycerol (21.16 mg/mL) as Stabilizer Di-sodiumhydrogen phosphate dodecahydrate (1.31 mg/mL) as Buffer salt Water for injection (970.76 mg/mL) as Solvent
Shelf life	36 months
Intended use	Initial intended use: To replenish the loss of HA due to aging to improve hydration, tone and elasticity of the skin and to act as a filler for LCL also called The intended use was updated in April 2019 as follows: To replenish the loss of hyaluronic acid due to ageing, to improve hydration, tone and elasticity of the skin.
Amount per unit	1 mL per syringe
Packaging	A folding box containing two sterile single use instructions for use (IFU)
Storage	2 25 °C / 36 77°F
Manufacturer	Princess® RICH is manufactured by CROMA-PHARMA GmbH, Industriezeile 6, 2100 Leobendorf, Austria. Enclosed needles are manufactured by TERUMO Europe N.V., Interleuvenlaan 40, 3001 Leuven, Belgium.

The IMD was labelled according to the requirements of local law and legislation.

All IMDs used during the investigation were stored at the investigation site in accordance with instructions given, and were inaccessible to unauthorized personnel.