3. Clinical investigation plan (CIP)

3.1 Clinical investigation objectives

The objective of the clinical investigation was

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

3.2 Clinical investigation design

3.2.1 Overall clinical investigation design and plan - description

The present clinical investigation was designed as an open label, prospectively designed trial using a single investigational product, Princess® RICH, for the treatment of small lines such as hydration, tone and elasticity. The clinical investigation was performed in 102 male or female subjects (all sites) or in 59 female subjects (excl. site 03) respectively, with a single investigational product, Princess® RICH.

The data collected at site 03 were excluded from this clinical investigation report (CIR) (see Section 3.4).

All subjects were evaluated by the 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 the investigation. Documentation of the evaluation was done by photographs taken with the 3D LifeViz micro camera-Quantificare, and measurements for skin hydration, tone and elasticity was done using the corneometer and cutometer devices (Courage & Khazaka). Subjects were to be treated with the investigational product, Princess® RICH at Weeks 0, 3 and 6.

At Weeks 3, 6, 8, 12, 16, 24 and 36 (with Week 8 being the primary endpoint) all subjects were to be assessed by the treating physician for improvement of the severity of their LCL and/or PR using the Global Aesthetic Improvement Scale (GAIS). The documentation of the evaluation was to be done by photographs taken with the 3D LifeViz micro camera-Quantificare, followed by measurements of skin hydration, tone and elasticity using the corneometer and cutometer devices (Courage & Khazaka).

A subject treatment satisfaction questionnaire was to be collected at Weeks 8, 12, 16, 24 and 36.

Adverse events were collected at all time points within the investigation.

At the end of the investigation, all necessary investigation closeout procedures were performed and the subjects were discharged from the investigation.

3.2.2 Efficacy / performance and safety variables

3.2.2.1 Primary efficacy variable / Primary performance endpoint:

Primary efficacy assessment was:

- Percentage of responders at Week 8 after initial treatment point. Responder was defined
  the PR as assessed with the GAIS, based on the investigator assessment.

3.2.2.2 Secondary efficacy variable / Secondary performance endpoints:

Secondary efficacy assessments were:

- Percentage of responders. Responder was
  in the fine lines of the LCL on both sides and/or PR, as assessed with the GAIS and based
  Weeks 12, 16, 24 and 36 after initial treatment.
- Change from baseline at Weeks 3, 6, 8, 12, 16, 24 and 36 in skin hydration assessed with the corneometer device.
- Changes from baseline at Weeks 3, 6, 8, 12, 16, 24 and 36 in skin tone assessed with the cutometer device.
- Change from baseline at Weeks 3, 6, 8, 12, 16, 24 and 36 in skin elasticity as assessed with the cutometer device.
- Subject satisfaction with treatment at Weeks 8, 12, 16, 24 and 36 using one of the
  her unsatisfied nor
  .
- Percentage of subjects demonstrating an aesthetic effect at Weeks 24 and 36 based on the investigator's assessment.

3.2.2.3 Safety variables

Medical and aesthetic history and demographic data

Medical and aesthetic history was collected at Visit 1. Special attention had been paid to previous cosmetic and surgical procedures of the face, and diseases/conditions relevant for exclusion criteria. Information on year of birth, gender and race was collected as well.

Adverse events (AEs)

All AEs were assessed in terms of seriousness (yes/no), severity, relationship to the IMD or clinical investigation procedures, and outcome (for details see CIP V3.0, Section 14.4
serious adverse event [SAE]

The severity of an AE/SAE was graded as: mild, moderate or severe.

The relationship was determined using one of the following causality levels: definite, probable, possible, unlikely, or not related.

The outcome of an AE was assessed as: resolved, ongoing, resolved with sequelae, fatal, unknown.

Laboratory variables

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

Safety endpoints

The safety of the investigational device was evaluated using the following endpoint:

Occurrence and frequency of adverse events.

A schedule of clinical investigation procedures is provided in Table 2.

Table 2: Clinical investigation flow chart

Procedures	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) [i] **Week 24** (±7 days)	VISIT 8 (optional) [i] **Week 36** (±7 days)
Informed consent	x*							
Informed consent addendum[i]						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
Eligibility check [d]	x*							
Photography [e]	x*	x*	x*	x	x	x	x	x
Investigator assessment (GAIS) [f]		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
Subject satisfaction [h]				x	x	x	x	x
Assessment of aesthetic effect by the investigator							x	x
Adverse events	x**	x	x	x	x	x	x	x
Concomitant medication	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 were postmenopausal for less than 12 months. Urine dipstick test was used.

[d] Investigator evaluation to determine baseline status of subj

[e] Photography was to 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] Optional visits (only applicable for subjects willing to participate in the prolonged follow-up): The duration of the clinical investigation was planned for 52 Weeks at a maximum. As it was observed by the investigator that at 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.

3.2.2.4 Assessments/Measurements

Effectiveness of Princess® RICH to correct fine lines on the face (LCL and/or PR) was assessed by means of the following performance measures:

- Measures of skin hydration, skin tone and skin elasticity
- Subj
- Aesthetic effect assessed by the investigator

Aesthetic improvement/GAIS assessment

Aesthetic improvement was evaluated by the investigator using the GAIS (Narins et al., 2003), a widely-used instrument presented in Table 3.

Table 3: 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.

Skin hydration

For determination of the hydration level of the skin, the Corneometer CM 825 was used, which measures the capacitance at low frequency (40-75 KHz) in arbitrary units (a.u.). This instrument is able to measure values from 0 to 150 arbitrary units.

The skin capacitance values were documented by 3-fold repeated measurements per test site (LCL right, LCL left, PR right, PR left) for each subject and visit.

Skin tone and skin elasticity

For determination of skin tone and skin elasticity the Cutometer MPA 580 was used. The resistance of the skin to the negative pressure (tone) and its ability to return into its original position (elasticity) were displayed as curves in real time during the measurement.

The skin tone was assessed by the maximal amplitude of the curve in millimetres (R0). The skin elasticity was assessed by R2, the ratio of complete relaxation after the pressure was cut off in millimetres divided by R0.

Results for R0 and R2 were documented as 3-fold repeated measurements per test site (LCL right, LCL left, PR right, PR left) for each subject and visit.

Each subject was asked to grade their satisfaction with the treatment using one of the following

Aesthetic effect

The investigator assessed whether the aesthetic effect was still present in the subject via live-

Visit. The presence of the aesthetic effect was

3.2.2.5 Photographic documentation

Photographic documentation was performed on Visit 1 to Visit 8.

Clinical photographs were taken by the investigator or their designee using the 3D LifeViz micro camera with dual beamer pointers (Quantificare). This camera produces life-like high quality 3D reconstructions.

A standardized procedure for study photography, which was described in a separate *Photo Manual*, was provided to the investigators. This *Photo Manual* ensured consistency of the background, camera settings, lighting, and subject position between the visits and across the sites. Obtained photographs were immediately uploaded to a secure storage system and a backup copy was kept in the investigator physician's computer.

3.2.2.6 Measurement of safety parameters

Relevant medical history and aesthetic history, and adverse events were recorded. Laboratory parameters were not controlled during the course of the clinical investigation.

Adverse events were recorded with duration, intensity and probability of correlation with the IMD and procedure.

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

3.3 Ethical considerations

Taking into account the risks and benefits as outlined in the CIP V3.0, 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
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 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 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 are 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 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 investigation.

il 17JUL2019 at MaRa-Medical Aesthetic Research Academy, Dr. Thomas Rappl (site 03). The following conclusion was drawn in the inspection report dated 09JAN2020:

Due to critical deviations that occurred at this site during the conduct of this clinical investigation regarding, among others, the manipulation of dates and subject signatures the conduct of the investigation was not considered to be in accordance with the Austrian Medical Devices Act) and EN ISO 14155: 2011 and the investigation data collected at site 03 are regarded as untrustworthy. Hence, the data collected at site 03 were excluded from this clinical investigation report (CIR).

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 investigation 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 make-up regimen constant over the investigation 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 enrolment

Enrolment was performed competitively between the sites.

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

Digits 1 and 2: investigational site (01, 02, 03)

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

The site 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 anaesthetic patch or cream. If anaesthetic was used, the type of anaesthetic and exact time of application would have been recorded in the 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 have been used in areas presenting cutaneous, inflammatory and/or infectious processes (e.g. acne, herpes).
- Sensitive skin might have been 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 ultra-violet light 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
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
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 2 optional further visits (Weeks 24 and 36).

Initially a third optional visit at Week 52 was planned but according to Section 16 of CIP V3.0, the investigation was considered completed as planned (75% of the subjects included in the extension of the investigation without aesthetic effect) at Week 36.

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 investigation and did 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 have extended 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 have been derived.

However, the data collected at site 03 were excluded from this CIR (see Section 3.4).

3.9.3 Analysis sets and type of analysis

All performance analyses were done in the intent-to-treat (ITT) 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 ITT population, who completed the trial without any protocol deviation (PD) that interfered 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 investigation;
- who had taken any medication or procedure interfering with the performance evaluation;
- whose 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 was 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 resulted in noteworthy study protocol violations.

The assignment of subjects to the PP population was finalised 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.

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

3.9.4.2 Discontinuations and dropouts

Subjects discontinuing the investigation are listed in Section 4.3 of this CIR with reason for discontinuation and last investigation day given.

3.9.4.3 Performance analyses

3.9.4.3.1 Hypotheses

This was a non-comparative clinical investigation and did 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 ITT population. Additionally, the performance analyses were presented for the per-protocol population.

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

with the GAIS by investigator assessment at Weeks 8, 12, 16, 24 and 36 after initial treatment. was sufficient for

subjects with LCL and PR treated.

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

with the GAIS and based on the inves .

The secondary performance outcome measures

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

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

For the secondary performance outcome measures

- of the LCL on both sides and/or the PR, as assessed with the GAIS and based on the
- Subject satisfaction with treatment at Weeks 8, 12, 16, 24 and 36,
- Aesthetic effect assessed by investigator at Weeks 24 and 36

frequency tables are given.

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 AEs.

3.9.4.4.1 Extent of exposure to investigational device

The extent of exposure to investigational product is 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 are presented.

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

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, interim analysis with version 22.0 from March 2019) and listed by subject.

Summaries of AEs are provided for seriousness, severity, duration, causal relationship to the device and causal relationship to procedure. These summaries are 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 eCRF, while non-local AEs were accredited to an individual IMD dose, if the start of the AE was 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 is 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 device effects (ADEs), SAEs, serious adverse devices effects (SADEs) and subjects who prematurely discontinued the investigation due to AEs are given.

3.9.4.4.3 Laboratory analyses

Outcomes of the urine pregnancy tests are listed.

4. Results

The results section is restricted to the results of sites 01 and 02 (see Section 3.4).

The first subjects were screened, gave informed consent, and received initial treatment on 25OCT2018 at the site Yuvell fine aesthetics. The last subject was enrolled at the site Dermatology and venerology clinic on 15FEB2019. The last subject completed the Week 36 Visit on 22OCT2019.

4.1 Deviations from the CIP

Major deviations from the CIP

In total 19 major deviations from the CIP were reported in 14 subjects (see Appendix B, Listing 2.1).

subjects. These subjects had either a missed visit or the visit (including phone contact) was out of window. 2 of the subjects (subject ID nos. 01-003 and 01-022) dropped out after Visit 4 or Visit 1, respectively (see also Section 4.2).

Table 4:

Subject ID No.	Major PD description,
01-002	Visit 2: Visit missed.
01-003	Visit 2: Patient missed the visit.
	Visit 4: was not done 52 to 60 days after Visit 1; difference 78 days.
01-005	Visit 4: was not done 52 to 60 days after Visit 1; difference 78 days.
01-015	Visit 3: Visit missed.
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.

PD = protocol deviation

Source: Appendix B, Listing 2.1

The next frequently noted PD category was 6 PDs in 3 subjects; in these 3 subjects the IMD treatment was not administered as per protocol.

Table 5:

Subject ID No.	
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.

AE = adverse event, PD = protocol deviation

Source: Appendix B, Listing 2.1

Table 6: Major protocol deviations with PD ca

Subject ID No.	
01-008*	Investigator did not sign and date informed consent V4.0 10JUL2018
01-009	Investigator did not sign and date informed consent V2.0 10APR2019

PD = protocol deviation
Source: Appendix B, Listing 2.1

1 PD reported in 1 of 2 subjects each belonged to the PD categories

Table 7:

Subject ID No.	
01-001	Subject was randomized although prohibited medication was used (immunosuppressant Arava) before and during the study.

PD = protocol deviation
Source: Appendix B, Listing 2.1

Table 8: Major protocol

Subject ID No.	
01-008	Visit 1: right lateral canthus photography done after IMD administration.

IMD = investigational medicinal product, PD = protocol deviation
Source: Appendix B, Listing 2.1

12 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 might thus have interfered with the evaluation for GAIS at Week .

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 analysed

A summary of subject enrolment 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
assessed by the treating physicians and were enrolled across 3 sites in this clinical investigation.

The enrolment per site was follows:

Site 01 Dermatology and venerology clinic: 25 subjects
Site 02 Yuvell fine aesthetics: 34 subjects
Site 03 Mara Graz: 43 subjects

However, the data collected at site 03 were excluded from this CIR (see Section 3.4.).

Hence, only 59 subjects were included in the safety analysis set.

58 subjects were included in the ITT population; 1 subject (site 01) was excluded (primary exclusionary reason: other [patient suffers from familial catastrophes]).

47 subjects were included in the PP population.

12 subjects (site 01: 11 subjects and site 02: 1 subject) were excluded from the PP population. The exclusionary reason for these subject was
for 1 subject and
Wee 11 subjects. 1 of the 11 subjects withdrew from the investigation after Visit 4/Week 8 due to personal reasons (see below and Section 4.1)

There were 2 dropouts (both at site 01):

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:

d ther (subject suffered from family catastrophes), respectively.

4.3 Dropouts and missing data

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

5 of the 12 subjects included in the extension of the investigation (up to Week 36) discontinued the clinical investigation as no aesthetic effect was noted at Week 24 (Visit 7) and 5 further subjects as no aesthetic effect was noted at Week 36 (Visit 8). Therefore, no aesthetic effect was observed for 83% of the subjects included in the extension phase at Week 36 (Visit 8) and the investigation was considered completed as planned according to Section 16 of CIP V3.0 (75% of the subjects included in the extension of the investigation without aesthetic effect). Hence, the investigation was also considered completed for the 2 remaining subjects in the extension phase.

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.

4.5 Demographic and other baseline characteristics

A summary of subject demographic characteristics can be found in Table 9 and in Appendix A, Table 1.4. The individual demographic data can be found in Appendix B, Listing 4.

All 59 subjects were female, between 28 to 77 years old and white.

All 59 subjects had sufficient severity of either their LCL or PR or both as assessed by treating investigator.

Table 9: Summary of subject demographic and baseline characteristics

	Safety analysis set	Intent-to-treat population	Per-protocol population
Number of subjects	N=59	N=58	N=47
Age[1] [years]			
N	59	58	47
Mean ± SD	52.6 ± 9.0	52.6 ± 9.1	52.5 ± 9.7
Median	53.0	53.0	52.0
Min, max	28, 77	28, 77	28, 77
Sex			
N	59	58	47
Female	59 (100%)	58 (100%)	47 (100%)
Male	0 (0%)	0 (0%)	0 (0%)
Race			
N	59	58	47
White	59 (100%)	58 (100%)	47 (100%)

[1]

max = Maximum, Min = Minimum, SD = standard deviation
Source: Appendix A, Table 1.4

Medical history

Medical history findings were reported in 35 subjects: in 21 subjects menopausal symptoms, in 11 subjects thyroid disorders (including thyroid dysfunction or ectomy, hypotherosis and benign neoplasm of thyroid gland), in 4 subjects hypertension, in 3 subjects breast cancer (excision), in 2 subjects each hysterectomy and in 1 subject each ovariectomy, rheumatoid arthritis, female sterilisation, metrorrhagia, depression, aortic arteriosclerosis, osteoporosis and panic attack.

Previous and concomitant therapies

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

18 subjects used a therapy for any medical history.

7 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 subjects 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:
Desloratadine for birch allergy, gastrozol for acid reflux, and meniscus surgery left knee

1 subject: Prednisolone for neuropathia vestibularis right arm

1 subject: Mexalen and Novalgin and Pantoloc for planned shoulder OP right arm

Additional anaesthetic and rescue medication

As can be seen in Table 10, a comparable share of subjects took additional anaesthetic medication on Day 0 and at Week 6 (52.5% and 53.7%, respectively), somewhat less subjects (45.2%) at Week 3. None of the subjects took the rescue medication hyaluronidase.

Table 10: Additional anaesthetic and rescue medication

(N_{SES} = 59)	Additional anaesthetics used	Rescue medication hyaluronidase
Day 0		
N	59	59
No	28 (47.5%)	59 (100%)
Yes	31 (52.5%)	0 (0.0%)
Week 3		
N	42	42
No	23 (54.8%)	42 (100%)
Yes	19 (45.2%)	0 (0.0%)
Week 6		
N	41	41
No	19 (46.3%)	41 (100%)
Yes	22 (53.7%)	0 (0.0%)
Overall		
N	59	59
No	27 (45.8%)	59 (100%)
Yes	32 (54.2%)	0 (0.0%)

SES = Safety-evaluation-set

Source: Appendix A, Table 3.2

4.6 CIP compliance

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

4.7 Performance results

A summary of the performance results is presented in Appendix A, Tables 2.1-2.12. The performance results can be found in Appendix B, Listings 15-19.

4.7.1 Primary performance results

The performance/effectiveness of Princess® RICH to correct fine lines on the face, including LCL and/or PR,
wrinkle severity using the GAIS.

The primary performance endpoint in this clinical investigation was:

Percentage of responders at Week 8 after initial treatment point

The responders regarding GAIS are given in Appendix A, Tables 2.3 (ITT) and 2.4 (PP) and the results of the GAIS assessment by the investigator are given in Appendix A, Tables 2.1 (ITT) and 2.2 (PP) as well as in Appendix B, Listing 15.

both side

All of the of subjects (100%) of the ITT and the PP population were found to be responders for IMD treatment of fine lines either of LCL, PR or both areas at Week 8 (see Table 11):

Table 11: 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} = 58)			
N	25	51	58
No improvement	0 (0.0%)	0 (0.0%)	0 (0.0%)
Improvement	25 (100%)	51 (100%)	58 (100%)
Limits of 95% CI for percentage of responders	--	--	--
PP (N_{PP} = 47)			
N	16	42	47
No improvement	0 (0.0%)	0 (0.0%)	0 (0.0%)
Improvement	16 (100%)	42 (100%)	47 (100%)
Limits of 95% CI for percentage of responders	--	--	-

[1] Subjects responding on both test areas counted once

CI = confidence interval, GAIS = Global Aesthetic Improvement Scale, ITT = Intent-to-treat, LCL = Lateral Canthal Lines, PP = Per-protocol, PR = Perioral rhytids

Source: Appendix A, Table 2.3 and 2.4

all of the subjects of the ITT population uch frequently (LCL left and right: 52.0%, PR: 51.0%), (LCL left and right: 28.0%, PR: 37.3%), (LCL left and right: 20.0%, PR: 11.8%, see Table 12). Neither nor ere rated for any treatment area in any of the subjects.

Similar results were obtained for the PP population (see Table 12).

Table 12: 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} = 58)			
N	25	25	51
Very much improved	7 (28.0%)	7 (28.0%)	19 (37.3%)
Much improved	13 (52.0%)	13 (52.0%)	26 (51.0%)
Improved	5 (20.0%)	5 (20.0%)	6 (11.8%)
No change	0 (0.0%)	0 (0.0%)	0 (0.0%)
Worse	0 (0.0%)	0 (0.0%)	0 (0.0%)
PP (N_{PP} = 47)			
N	16	16	42
Very much improved	6 (37.5%)	6 (37.5%)	18 (42.9%)
Much improved	8 (50.0%)	8 (50.0%)	21 (50.0%)
Improved	2 (12.5%)	2 (12.5%)	3 (7.1%)
No change	0 (0.0%)	0 (0.0%)	0 (0.0%)
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, ITT = Intent-to-treat, LCL = Lateral Canthal Lines, PP = Per-protocol, PR = Perioral rhytids

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 to 36 after initial treatment

The responders regarding GAIS are given in Appendix A, Tables 2.3 (ITT) and 2.4 (PP) and the results of the GAIS assessment by the investigator are given in Appendix A, Tables 2.1 (ITT) and 2.2 (PP) as well as in Appendix B, Listing 15.

At Week 12, nearly all of the subjects were still found to be responders (see Table 13), i.e., the proportion of responders (ITT population) was almost the same for LCL and/or PR when compared to Week 8 (see Table 11) (LCL: 95.7%, PR: 98.0%, at least 1 test area: 98.2%). Only one subject per treatment area showed no improvement.

Similar results were seen for the PP population with nearly all of the subjects still being responders at Week 12 (LCL: 93.3%, PR: 97.6%, at least 1 test area: 97.8%) and only one subject per treatment area showing no improvement.

After further 4 weeks at Week 16, the proportion of responders (ITT population) had declined but the majority of the subjects were still responders (ITT: 62.5%, 80.0% and 80.7% for LCL, PR and at least 1 test area, respectively (PP: 68.8%, 85.7% and 85.1%, respectively).

At Week 24, the proportion of responders of the 12 (ITT) or 11 (PP) subjects included in the extension of the investigation had further decreased to 28.6%, 54.5% and 58.3% for LCL, PR and at least 1 test area, respectively (PP: 33.3%, 60.0% and 63.6%, respectively).

The proportion of responders (ITT population) had decreased for LCL, PR and at least 1 test area to 0.0%, 33.3% and 28.6%, respectively (PP: 0.0%, 33.3% and 28.6%, respectively) for the remaining subjects at Week 36. Hence, the investigation was considered completed as planned according to Section 16 of CIP V3.0 (75% of the subjects included in the extension of the investigation without aesthetic effect).

Table 13: Responders regarding GAIS (ITT)

Responders regarding GAIS (N_{ITT} = 58)	LCL	PR	At least one test area (LCL or PR)[1]
Week 3			
N	23	49	56
No improvement	0 (0.0%)	0 (0.0%)	0 (0.0%)
Improvement	23 (100%)	49 (100%)	56 (100%)
Limits of 95% CI for percentage of responders	--	--	-
Week 6			
N	24	50	56
No improvement	0 (0.0%)	0 (0.0%)	0 (0.0%)
Improvement	24 (100%)	50 (100%)	56 (100%)
Limits of 95% CI for percentage of responders	--	--	-
Week 8			
N	25	51	58
No improvement	0 (0.0%)	0 (0.0%)	0 (0.0%)
Improvement	25 (100%)	51 (100%)	58 (100%)
Limits of 95% CI for percentage of responders	--	--	-
Week 12			
N	23	49	56
No improvement	1 (4.3%)	1 (2.0%)	1 (1.8%)
Improvement	22 (95.7%)	48 (98.0%)	55 (98.2%)
Limits of 95% CI for percentage of responders	(87.3%, 100%)	(94.0%, 100%)	(94.7%, 100%)
Week 16			
N	24	50	57
No improvement	9 (37.5%)	10 (20.0%)	11 (19.3%)
Improvement	15 (62.5%)	40 (80.0%)	46 (80.7%)
Limits of 95% CI for percentage of responders	(43.1%, 81.9%)	(68.9%, 91.1%)	(70.5%, 90.9%)
Week 24			
N	7	11	12
No improvement	5 (71.4%)	5 (45.5%)	5 (41.7%)
Improvement	2 (28.6%)	6 (54.5%)	7 (58.3%)
Limits of 95% CI for percentage of responders	(0.0%, 62.0%)	(25.1%, 84.0%)	(30.4%, 86.2%)
Week 36			
N	2	6	7
No improvement	2 (100%)	4 (66.7%)	5 (71.4%)
Improvement	0 (0.0%)	2 (33.3%)	2 (28.6%)
Limits of 95% CI for percentage of responders	--	(0.0%, 71.1%)	(0.0%, 62.0%)

[1] Subjects responding on both test areas counted once

CI = confidence interval, GAIS = Global Aesthetic Improvement Scale, ITT = Intent-to-treat, LCL = Lateral Canthal Lines, PR = Perioral rhytids

Source: Appendix A, Table 2.3

Table 14: GAIS by investigator (ITT)

Global aesthetic improvement score (GAIS) by investigator[1] (N_{ITT} = 58)	Right LCL	Left LCL	PR
Week 3			
N	23	23	49
Very much improved	1 (4.3%)	1 (4.3%)	2 (4.1%)
Much improved	14 (60.9%)	13 (56.5%)	29 (59.2%)
Improved	8 (34.8%)	9 (39.1%)	18 (36.7%)
No change	0 (0.0%)	0 (0.0%)	0 (0.0%)
Worse	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 6			
N	24	24	50
Very much improved	5 (20.8%)	4 (16.7%)	12 (24.0%)
Much improved	16 (66.7%)	17 (70.8%)	32 (64.0%)
Improved	3 (12.5%)	3 (12.5%)	6 (12.0%)
No change	0 (0.0%)	0 (0.0%)	0 (0.0%)
Worse	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 8			
N	25	25	51
Very much improved	7 (28.0%)	7 (28.0%)	19 (37.3%)
Much improved	13 (52.0%)	13 (52.0%)	26 (51.0%)
Improved	5 (20.0%)	5 (20.0%)	6 (11.8%)
No change	0 (0.0%)	0 (0.0%)	0 (0.0%)
Worse	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 12			
N	23	23	49
Very much improved	3 (13.0%)	3 (13.0%)	17 (34.7%)
Much improved	14 (60.9%)	14 (60.9%)	27 (55.1%)
Improved	5 (21.7%)	5 (21.7%)	4 (8.2%)
No change	1 (4.3%)	1 (4.3%)	1 (2.0%)
Worse	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 16			
N	24	24	50
Very much improved	2 (8.3%)	2 (8.3%)	12 (24.0%)
Much improved	5 (20.8%)	5 (20.8%)	21 (42.0%)
Improved	8 (33.3%)	8 (33.3%)	7 (14.0%)
No change	9 (37.5%)	9 (37.5%)	10 (20.0%)
Worse	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 24			
N	7	7	11
Very much improved	0 (0.0%)	0 (0.0%)	1 (9.1%)
Much improved	1 (14.3%)	1 (14.3%)	4 (36.4%)
Improved	1 (14.3%)	1 (14.3%)	1 (9.1%)
No change	5 (71.4%)	5 (71.4%)	5 (45.5%)
Worse	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 36			
N	2	2	6
Very much improved	0 (0.0%)	0 (0.0%)	0 (0.0%)
Much improved	0 (0.0%)	0 (0.0%)	0 (0.0%)
Improved	0 (0.0%)	0 (0.0%)	2 (33.3%)
No change	2 (100%)	2 (100%)	4 (66.7%)
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, ITT = Intent-to-treat, LCL = Lateral Canthal Lines, PR = Perioral rhytids
Source: Appendix A, Table 2.1

As can be seen in Table 14, at Week 12, the investigator still rated
in the vast majority of the subjects for right and left LCL and PR (Week 8: 100% each for right and left LCL and PR, Week 12: both right and left LCL: 96%, PR: 98%
uch improved

both right and left

At Week 24, the investigator rated no change for the majority of the subjects (LCL: 71.4% both, PR: 45.5% Much imp
were rated for both right and left LCL in 1

each and much improved for the remaining 4 subjects (36.4%).

At Week 36, the investigator rated
for 100% of the subjects for both right and left LCL and for 66.7% of the subjects for PR. mproved
the PR of the remaining 2 subjects (33.3%).

No worsening was observed for any area in any subject at any assessment time point.

Similar ratings were reported for the PP population (see Appendix A, Table 2.2).

4.7.2.2 Measures of skin hydration, skin tone and skin elasticity

Change in skin hydration assessed with the corneometer device from baseline at Weeks 3, 6, 8, 12, 16, 24, and 36

The results of the skin hydration assessment are given in Appendix A, Tables 2.7.1 and 2.7.2 (ITT) and in Tables 2.8.1 and 2.8.2 (PP) as well as in Appendix B, Listing 17.1.

As can be seen in Table 15 (ITT), 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).

Table 15: Corneometer Measurements [I.U.] (ITT)

	Skin hydration [I.U.]	
Corneometer measurements[1] (N_{ITT} = 58)	**LCL**	**PR**
Baseline (Day 0)		
N	25	49
Mean ± SD	51.8 ± 14.0	53.2 ± 15.6
95% Confidence interval for mean	46.0 , 57.6	48.8 , 57.7
Median	49.7	53.0
Q1 , Q3	45.5 , 63.3	41.0 , 61.1
Min, max	20.9 , 75.9	23.4 , 90.7
Mean Changes from Baseline (Day 0)		
Week 3		
N	21	46
Mean Change from Baseline (Day 0)± SD	-2.6 ± 12.6	-0.4 ± 12.8
95% Confidence interval for mean	-8.3 , 3.2	-4.2 , 3.4
Median Change from Baseline (Day 0)	-1.3	0.9
Q1 , Q3	-7.3 , 6.1	-8.2 , 6.5
Min, max	-27.5 , 20.4	-26.6 , 31.1
Week 6		
N	24	48
Mean Change from Baseline (Day 0)± SD	-1.6 ± 15.2	-0.8 ± 15.4
95% Confidence interval for mean	-8.0 , 4.8	-5.2 , 3.7
Median Change from Baseline (Day 0)	-0.6	-0.9
Q1 , Q3	-13.9 , 4.8	-11.3 , 5.7
Min, max	-22.3 , 38.1	-25.9 , 51.7
Week 8		
N	23	48
Mean Change from Baseline (Day 0)± SD	1.5 ± 11.5	0.6 ± 15.6
95% Confidence interval for mean	-3.4 , 6.5	-4.0 , 5.1
Median Change from Baseline (Day 0)	0.7	0.8
Q1 , Q3	-2.2 , 5.5	-11.5 , 10.7
Min, max	-18.8 , 37.3	-26.8 , 42.8
Week 12		
N	22	47
Mean Change from Baseline (Day 0)± SD	4.2 ± 14.5	5.4 ± 15.6
95% Confidence interval for mean	-2.3 , 10.6	0.8 , 10.0
Median Change from Baseline (Day 0)	1.1	3.2
Q1 , Q3	-5.3 , 12.5	-4.9 , 14.7
Min, max	-19.5 , 37.8	-32.0 , 41.8
Week 16		
N	24	48
Mean Change from Baseline (Day 0)± SD	3.9 ± 13.0	5.4 ± 12.8
95% Confidence interval for mean	-1.6 , 9.4	1.7 , 9.1
Median Change from Baseline (Day 0)	4.3	3.7
Q1 , Q3	-7.0 , 12.4	-5.7 , 15.9
Min, max	-16.5 , 40.3	-16.4 , 29.3
Week 24		
N	5	8
Mean Change from Baseline (Day 0) ± SD	15.1 ± 15.6	10.9 ± 17.3
95% Confidence interval for mean	-4.3 , 34.5	-3.5 , 25.4
Median Change from Baseline (Day 0)	12.4	9.4
Q1 , Q3	7.7 , 21.7	-1.5 , 23.7
Min, max	-3.9 , 37.6	-13.1 , 37.5
Week 36		
N	1	4
Mean Change from Baseline (Day 0) ± SD	9.8	-4.6 ± 13.3
95% Confidence interval for mean	- , -	-25.8 , 16.5
Median Change from Baseline (Day 0)	9.8	-6.0
Q1 , Q3	9.8 , 9.8	-15.0 , 5.7
Min, max	9.8 , 9.8	-18.4 , 12.0

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

ITT = Intent-to-treat, LCL = Lateral Canthal Lines, max = Maximum, Min = Minimum, Q1 = 1st quartile, Q3 = 3rd quartile, PR = Perioral rhytids, SD = standard deviation

Source: Appendix A, Table 2.7.1

Changes in skin tone assessed with the cutometer device from baseline at Weeks 3, 6, 8, 12, 16, 24, and 36

The results of the skin tone assessment are given in Appendix A, Tables 2.9.1 to 2.9.3 and Figures 1 and 3 (ITT), in Tables 2.10.1 to 2.10.3, Figures 5 and 7 (PP) as well as in Appendix B, Listing 18.1.

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 36 (statistically significant at $p < 0.05$ at Weeks 3 to 24 for LCL and at Weeks 3 to 16 and 36 for PR). The greatest decrease in R0 was noted at Week 8 for LCL (mean change = -0.117 mm) and at Week 36 for PR (mean change = -0.120 mm [see Table 16]).

Similar results were reported for the PP population.

Table 16: Cutometer Measurements, Skin Tone [mm] (ITT)

Cutometer measurements[1] (N_{ITT} = 58)	LCL, Skin tone R0 [mm]	PR, Skin tone R0 [mm]
Day 0		
N	24	50
Mean ± SD	0.206 ± 0.072	0.205 ± 0.090
95% Confidence interval for mean	0.175 , 0.237	0.180 , 0.231
Median	0.201	0.200
Q1 , Q3	0.149 , 0.244	0.133 , 0.280
Min, max	0.087, 0.392	0.040, 0.393
Mean Changes from Baseline (Day 0)		
Week 3		
N	21	48
Mean Change from Baseline (Day 0) ± SD	-0.044 ± 0.080	-0.037 ± 0.052
95% Confidence interval for mean	-0.080 , -0.007	-0.052 , -0.022
Median Change from Baseline (Day 0)	-0.031	-0.026
Q1 , Q3	-0.065 , -0.009	-0.065 , -0.002
Min, max	-0.277, 0.073	-0.206, 0.049
Week 6		
N	23	48
Mean Change from Baseline (Day 0) ± SD	-0.094 ± 0.070	-0.063 ± 0.052
95% Confidence interval for mean	-0.124 , -0.064	-0.079 , -0.048
Median Change from Baseline (Day 0)	-0.084	-0.056
Q1 , Q3	-0.135 , -0.046	-0.101 , -0.034
Min, max	-0.242, 0.043	-0.217, 0.035
Week 8		
N	23	50
Mean Change from Baseline (Day 0) ± SD	-0.117 ± 0.072	-0.088 ± 0.052
95% Confidence interval for mean	-0.149 , -0.086	-0.103 , -0.073
Median Change from Baseline (Day 0)	-0.108	-0.081
Q1 , Q3	-0.173 , -0.065	-0.112 , -0.049
Min, max	-0.295, 0.007	-0.245, 0.018
Week 12		
N	20	47
Mean Change from Baseline (Day 0) ± SD	-0.089 ± 0.087	-0.077 ± 0.080
95% Confidence interval for mean	-0.130 , -0.048	-0.101 , -0.053
Median Change from Baseline (Day 0)	-0.113	-0.085
Q1 , Q3	-0.154 , -0.017	-0.134 , -0.036
Min, max	-0.227, 0.095	-0.259, 0.144
Week 16		
N	23	49
Mean Change from Baseline (Day 0) ± SD	-0.038 ± 0.074	-0.083 ± 0.084
95% Confidence interval for mean	-0.070 , -0.006	-0.107 , -0.059
Median Change from Baseline (Day 0)	-0.036	-0.091
Q1 , Q3	-0.100 , 0.014	-0.146 , -0.019
Min, max	-0.172, 0.094	-0.259, 0.093
Week 24		
N	5	9
Mean Change from Baseline (Day 0) ± SD	-0.062 ± 0.046	-0.012 ± 0.104
95% Confidence interval for mean	-0.120 , -0.005	-0.092 , 0.068
Median Change from Baseline (Day 0)	-0.086	-0.024
Q1 , Q3	-0.097 , -0.013	-0.100 , 0.073
Min, max	-0.104 , -0.012	-0.156 , 0.125
Week 36		
N	1	5
Mean Change from Baseline (Day 0) ± SD	-0.093	-0.120 ± 0.047
95% Confidence interval for mean	- , -	-0.179 , -0.061
Median Change from Baseline (Day 0)	-0.093	-0.108
Q1 , Q3	-0.093 , -0.093	-0.128 , -0.092
Min, max	-0.093 , -0.093	-0.198 , -0.076

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

ITT = Intent-to-treat, LCL = Lateral Canthal Lines, max = Maximum, Min = Minimum, Q1 = 1st quartile, Q3 = 3rd quartile, PR = Perioral rhytids, SD = standard deviation

Source: Appendix A, Table 2.9.1

Table 17: Cutometer Measurements, Skin Elasticity [ratio] (ITT)

Cutometer measurements[1] (N_{ITT} = 58)	LCL, Skin elasticity R2 [ratio]	PR, Skin elasticity R2 [ratio]
Day 0		
N	24	50
Mean ± SD	0.835 ± 0.046	0.887 ± 0.051
95% Confidence interval for mean	0.815 , 0.854	0.872 , 0.901
Median	0.838	0.892
Q1 , Q3	0.812 , 0.872	0.866 , 0.916
Min, max	0.731, 0.909	0.609, 0.955
Mean Changes from Baseline (Day 0)		
Week 3		
N	23	49
Mean Change from Baseline (Day 0)± SD	0.000 ± 0.044	-0.005 ± 0.058
95% Confidence interval for mean	-0.019 , 0.019	-0.022 , 0.011
Median Change from Baseline (Day 0)	-0.009	-0.020
Q1 , Q3	-0.039 , 0.037	-0.034 , 0.019
Min, max	-0.078, 0.067	-0.139, 0.265
Week 6		
N	23	48
Mean Change from Baseline (Day 0)± SD	0.035 ± 0.055	-0.004 ± 0.060
95% Confidence interval for mean	0.011 , 0.059	-0.021 , 0.014
Median Change from Baseline (Day 0)	0.036	-0.002
Q1 , Q3	-0.006 , 0.068	-0.030 , 0.025
Min, max	-0.083, 0.154	-0.138, 0.272
Week 8		
N	23	50
Mean Change from Baseline (Day 0)± SD	0.023 ± 0.047	0.004 ± 0.052
95% Confidence interval for mean	0.003 , 0.044	-0.011 , 0.018
Median Change from Baseline (Day 0)	0.019	0.004
Q1 , Q3	-0.008 , 0.063	-0.027 , 0.031
Min, max	-0.064, 0.102	-0.090, 0.246
Week 12		
N	20	47
Mean Change from Baseline (Day 0)± SD	0.043 ± 0.060	0.009 ± 0.073
95% Confidence interval for mean	0.015 , 0.071	-0.013 , 0.030
Median Change from Baseline (Day 0)	0.037	0.014
Q1 , Q3	-0.002 , 0.083	-0.017 , 0.047
Min, max	-0.086, 0.147	-0.232, 0.287
Week 16		
N	23	49
Mean Change from Baseline (Day 0)± SD	0.028 ± 0.064	0.003 ± 0.067
95% Confidence interval for mean	-0.000 , 0.055	-0.016 , 0.022
Median Change from Baseline (Day 0)	0.031	0.010
Q1 , Q3	-0.023 , 0.049	-0.029 , 0.040
Min, max	-0.090, 0.183	-0.217, 0.237
Week 24		
N	5	9
Mean Change from Baseline (Day 0)± SD	-0.020 ± 0.070	0.008 ± 0.045
95% Confidence interval for mean	-0.107 , 0.067	-0.026 , 0.043
Median Change from Baseline (Day 0)	0.013	0.017
Q1 , Q3	-0.026 , 0.017	-0.027 , 0.046
Min, max	-0.139 , 0.034	-0.055 , 0.067
Week 36		
N	1	5
Mean Change from Baseline (Day 0)± SD	0.020	0.035 ± 0.031
95% Confidence interval for mean	- , -	-0.004 , 0.074
Median Change from Baseline (Day 0)	0.020	0.026
Q1 , Q3	0.020 , 0.020	0.014 , 0.051
Min, max	0.020 , 0.020	0.003 , 0.081

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

ITT = Intent-to-treat, LCL = Lateral Canthal Lines, max = Maximum, Min = Minimum, Q1 = 1st quartile, Q3 = 3rd quartile, PR = Perioral rhytids

Source: Appendix A, Table 2.9.1

Change in skin elasticity as assessed with the cutometer device from baseline at Weeks 3, 6, 8, 12, 16, 24, and 36

The results of the skin elasticity assessment are given in Appendix A, Tables 2.9.1 to 2.9.3 and Appendix A, Figures 2 and 4 (ITT), in Tables 2.10.1 to 2.10.3 and Appendix A, Figures 6 and 8 (PP) as well as in Appendix B, Listing 18.1.

Slightly higher mean values compared to baseline (change from baseline) were reported for the parameter R2 over the investigational period until Week 16 and at Week 36 (LCL) or from Week 8 to 36 (PR), respectively (statistically significant at $p < 0.05$ at Weeks 6 to 12 for LCL). This reflects an increase in skin elasticity as the closer the R2 ratio is to 1, the higher the skin elasticity. At Week 24, the R2 ratio was decreased compared to baseline for LCL but increased again at Week 36. However, at Week 36 only a single subject was left in the ITT population for LCL. The greatest mean changes were noted for LCL at Week 12 (mean change = 0.043) and for PR at Week 36 (mean change = 0.035) (see Table 17).

Similar results were reported for the PP population.

4.7.2.3

Subject satisfaction with treatment at Weeks 8, 12, 16, 24, and 36 using one of the following

The results of the subject satisfaction assessment are given in Appendix A, Table 2.5 (ITT) and in Table 2.6 (PP) as well as in Appendix B, Listing 16.

At Week 8, the majority of the subjects (93.1
treatment (see Table 18 was rated by 6.9%.

Similar results were observed four weeks later at Week 12 with 91.1% of the subjects continued being
rated by 8.9%.

After further 4 weeks at Week 16, a decreased percentage of subjects (73.7%) were still

rated by 26.3%.

8 weeks later at Week 24, still more than half of the subjects included in the extension of the investigation (58.3

was rated by an increased percentage of subjects (71.4%) compared to Week 24. However, only 7 subjects were left in the ITT population at this assessment time point. The remaining 28.6%

time point

(see Table 18).

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

4.7.2.4 Aesthetic effect in follow-up phase

Percentage of subjects demonstrating an aesthetic effect at Weeks 24 and 36 based on the investigator's assessment

The results of the assessment of the aesthetic effect are given in Appendix A, Table 2.11 (ITT) and in Table 2.12 (PP) as well as in Appendix B, Listing 19.

The investigator assessed whether the aesthetic effect was still present in the subject via live-

Visit. The presence o

58.3% of the subjects of the ITT population still showed an aesthetic effect at Week 24 (PP: 63.6%) while 41.7% (PP: 36.4%) of the subjects discontinued the clinical investigation as no aesthetic effect was noted.

At Week 36, an aesthetic effect was still noted for 16.7% of the subjects (PP: 18.2%) while 41.7% (PP: 45.5%) of the subjects included in the extension phase discontinued the clinical investigation as no aesthetic effect was noted anymore (see Table 19). Therefore, no aesthetic effect was observed for 83% of the subjects included in the extension phase at Week 36 (Visit 8) and the investigation was considered completed as planned according to Section 16 of CIP V3.0 (75% of the subjects included in the extension of the investigation without aesthetic effect). Hence, the investigation was also considered completed for the 2 remaining subjects in the extension phase.

Table 19: Aesthetic effect in follow-up phase (ITT and PP)

Any aesthetic effects present?	Week 24	Week 36
ITT		
N	12	7
Yes	7 (58.3%)	2 (16.7%)
No	5 (41.7%)	5 (41.7%)
PP		
N	11	7
Yes	7 (63.6%)	2 (18.2%)
No	4 (36.4%)	5 (45.5%)

ITT = Intent-to-treat, PP = Per-protocol

Source: Appendix A, Table 2.11 and 2.12

Table 18:

	ITT = 58)
Week 8	
N	58
Very satisfied	36 (62.1%)
Satisfied	18 (31.0%)
Neither satisfied nor unsatisfied	4 (6.9%)
Unsatisfied	0 (0.0%)
Very unsatisfied	0 (0.0%)
Week 12	
N	56
Very satisfied	29 (51.8%)
Satisfied	22 (39.3%)
Neither satisfied nor unsatisfied	5 (8.9%)
Unsatisfied	0 (0.0%)
Very unsatisfied	0 (0.0%)
Week 16	
N	57
Very satisfied	31 (54.4%)
Satisfied	11 (19.3%)
Neither satisfied nor unsatisfied	15 (26.3%)
Unsatisfied	0 (0.0%)
Very unsatisfied	0 (0.0%)
Week 24	
N	12
Very satisfied	5 (41.7%)
Satisfied	2 (16.7%)
Neither satisfied nor unsatisfied	5 (41.7%)
Unsatisfied	0 (0.0%)
Very unsatisfied	0 (0.0%)
Week 36	
N	7
Very satisfied	4 (57.1%)
Satisfied	1 (14.3%)
Neither satisfied nor unsatisfied	2 (28.6%)
Unsatisfied	0 (0.0%)
Very unsatisfied	0 (0.0%)

ITT = Intent-to-treat

Source: Appendix A, Table 2.5

4.8 Safety results

Injection volume

The injection volumes are given in Appendix A, Table 3.1 as well as in Appendix B, Listing 13.

IMD treatment was performed in all 59 enrolled subjects at sites 01 and 02 on Day 0: in the majority of the subjects in the PR area (52 subjects [88%]), in less subjects in the left and right LCL area (26 subjects each [44%]).

69% of the subjects: in about four-fifths of the subjects in the PR area, in about a half 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 6.0 mL (mean = 2.09 mL) for PR and between 0.3 to 1.7 mL (mean = 0.91 mL) for left LCL, and 0.3 to 1.6 mL (mean = 0.90 mL) for right LCL.

The total amount ranged between 0.5 and 6.0 mL (mean = 2.64 mL).

Table 20: Injection volume (SES)

Injected volume [mL] (N_{SES} = 59)	Left LCL	Right LCL	PR	Total
Day 0				
N	26	26	52	59
Mean ± SD	0.36 ± 0.15	0.35 ± 0.15	0.98 ± 0.65	1.17 ± 0.49
Median	0.30	0.30	1.00	1.00
Min, max	0.3, 1.0	0.3, 1.0	0.2, 2.8	0.2, 2.8
Week 3				
N	21	21	35	42
Mean ± SD	0.33 ± 0.09	0.33 ± 0.10	0.79 ± 0.59	0.99 ± 0.46
Median	0.30	0.30	0.50	1.00
Min, max	0.2, 0.5	0.1, 0.5	0.2, 3.0	0.2, 3.0
Week 6				
N	19	19	32	41
Mean ± SD	0.38 ± 0.17	0.38 ± 0.17	0.95 ± 0.54	1.10 ± 0.43
Median	0.30	0.30	1.00	1.00
Min, max	0.2, 1.0	0.2, 1.0	0.4, 2.3	0.4, 2.3
Overall				
N	26	26	52	59
Mean ± SD	0.91 ± 0.27	0.90 ± 0.26	2.09 ± 1.46	2.64 ± 1.11
Median	0.90	0.90	1.80	2.60
Min, max	0.3, 1.7	0.3, 1.6	0.3, 6.0	0.5, 6.0

LCL= Lateral Canthal Lines, max = Maximum, Min = Minimum, PR = Perioral rhytids, SD = standard deviation, SES = Safety-evaluation-set

Source: Appendix A, Table 3.1

Adverse events (AEs)

A summary of AE characteristics can be found in Table 21 and in Appendix A, Table 3.3.1. The adverse events by trial sites are given in Appendix A, Table 3.3.2. A listing of AEs by subject can be found in Appendix B, Listing 20. The adverse events by MedDRA class, seriousness, severity, duration and/or causal relationship to the device or procedure are listed in Appendix A, Tables 3.4 to 3.9.

In total, 36 treatment-emergent adverse events (TEAEs) were reported in 24 subjects (41%).

2 of the TEAEs were 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

34 of the TEAEs were non-serious. The location of 25 non-serious TEAEs reported in 18 subjects was related to test fields, i.e., at treatment area or just around treatment area.

The location of 11 TEAEs (including both SAEs) reported in 8 subjects was not related to test fields.

The causal relationship to IMD was considered to be not or unlikely related for 33 of the 36 TEAEs, probable for 1 TEAE, and definite for 2 TEAEs.

The causal relationship to procedure was found to be not or unlikely related for 12 TEAEs, probable for 1 TEAE, and definite for 23 TEAEs.

The intensity of most of the TEAEs was assessed as mild (81%). 17% of the TEAEs were assessed as moderate (including 1 SAE, see above), and 1 TEAE was assessed as severe (SAE, see above).

The disposition of the TEAEs was lower for site 01 compared to site 02:

Site 1: 4 of 25 subjects with TEAEs (16%)
Site 2: 20 of 34 subjects with TEAEs (59%), incl. both SAEs

The most frequently reported SOC according to MedDRA class (see Table 22) was general
17 subjects (29
23 TEAEs in 17 subjects [29%]). Furthermore,
swelling
once in 1 subject.
12%)
5
reported

Further SOCs such as

the PTs

The duration of the TEAEs was in most cases > 7 days (SOC general disorders and administration site condit 13 subjects; SOC subjects),
7 days (SOC
4 subjects; SOC 3 subjects). Particularly, the TEAEs with location
3 TEAEs) showed these longer
durations (see Appendix A, Table 3.7).

7 subjects took a medication for treatment of AE. None of the subjects took a rescue medication.

noted for 2 TEAEs each (PTs: gastrooesophageal reflux disease and seasonal allergy; PTs: oral herpes and shoulder operation).

Table 21: Summary of AE characteristics (SES)

Adverse event characteristics (N_{SES} = 59)	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]	24 (41%)	18 (31%)	8 (14%)
Number of adverse events reported	36	25	11
Serious AEs			
No	34 (94%)	25 (100%)	9 (82%)
Yes	2 (6%)	0 (0%)	2 (18%)
Intensity			
Mild	29 (81%)	21 (84%)	8 (73%)
Moderate	6 (17%)	4 (16%)	2 (18%)
Severe	1 (3%)	0 (0%)	1 (9%)
Causal relationship to investigational device			
Definite	2 (6%)	2 (8%)	0 (0%)
Probable	1 (3%)	1 (4%)	0 (0%)
Possible	0 (0%)	0 (0%)	0 (0%)
Unlikely	2 (6%)	1 (4%)	1 (9%)
Not related	31 (86%)	21 (84%)	10 (91%)
Causal relationship to procedure			
Definite	23 (64%)	23 (92%)	0 (0%)
Probable	1 (3%)	1 (4%)	0 (0%)
Possible	0 (0%)	0 (0%)	0 (0%)
Unlikely	2 (6%)	1 (4%)	1 (9%)
Not related	10 (28%)	0 (0%)	10 (91%)
Duration[4]			
	2 (6%)	0 (0%)	2 (18%)
	1 (3%)	0 (0%)	1 (9%)
	10 (28%)	6 (24%)	4 (36%)
> 7 days	21 (58%)	19 (76%)	2 (18%)
missing	2 (6%)	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
AE = adverse event, SES = Safety-evaluation-set, TEAE = treatment-emerged adverse event

Source: Appendix A, Table 3.3.1

Table 22: Subjects with adverse events by MedDRA class (SES)

Subjects with adverse events by MedDRA class (N_{SES} = 59)	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 (2%)	0 (0%)	1 (2%)
Gastrooesophageal reflux disease	1 (2%)	0 (0%)	1 (2%)
General disorders and administration site conditions	17 (29%)	17 (29%)	0 (0%)
Injection site haematoma	17 (29%)	17 (29%)	0 (0%)
Injection site swelling	1 (2%)	1 (2%)	0 (0%)
Immune system disorders	1 (2%)	0 (0%)	1 (2%)
Seasonal allergy	1 (2%)	0 (0%)	1 (2%)
Infections and infestations	7 (12%)	1 (2%)	6 (10%)
Gastroenteritis	1 (2%)	0 (0%)	1 (2%)
Nasopharyngitis	3 (5%)	0 (0%)	3 (5%)
Oral herpes	1 (2%)	1 (2%)	0 (0%)
Sinusitis	2 (3%)	0 (0%)	2 (3%)
Vestibular neuronitis	1 (2%)	0 (0%)	1 (2%)
Injury, poisoning and procedural complications	1 (2%)	0 (0%)	1 (2%)
Meniscus injury	1 (2%)	0 (0%)	1 (2%)
Surgical and medical procedures	1 (2%)	0 (0%)	1 (2%)
Shoulder operation	1 (2%)	0 (0%)	1 (2%)

[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.
MedDRA = Medical Dictionary for Regulatory Activities, SES = Safety-evaluation-set, TEAE = treatment-emerged adverse event
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 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 for satisfaction with IMD

eeks 12, 16, 24 and 36, most of the

by any subject 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.

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 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

[23 TEAEs in 17 subjects]
swelling [1 TEAE in 1 subject]). The causal relationship to IMD was considered to be probable for 1 TEAE (injection site swelling), and definite for 2 TEAEs

Local injection related side effects were expected in this clinical investigation (Lafaille and Benedetto, 2010; Gabriele F-H et al 201
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 (Cohen 2008).

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.

within 1 to 2 weeks in most cases, corresponding to other HA described in literature (A

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.

6 Abbreviated terms and definitions

ADE	Adverse Device Effect
AE	Adverse event
BASG	Bundesamt fuer Sicherheit im Gesundheitswesen
CI	Coordinating investigator
CIP	Clinical investigation plan
CRO	Clinical Research Organisation
DRM	Data review meeting
eCRF	Electronic case report form
GAIS	Global Aesthetic Improvement Scale
GCP	Good clinical practice
HA	Hyaluronic acid
IB	
IFU	Instructions for use
i.e	*id est*
IMD	Investigational medical device
ISO	International organization for standardization
ITT	Intent-to-treat
LCL	Lateral Canthal Lines
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
PD	Protocol deviation
PP	Per-protocol
PR	Perioral rhytids
PT	Preferred term
SADE	Serious adverse device effect
SAE	Serious adverse event
SAS	Statistical analysis system
SES	Safety-evaluation-set
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TMF	Trial master file
VCS	Valid-cases-set

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:

Ethikkommission der Medizinischen Universitaet Graz

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Participating Ethics Committees:

Ethikkommission des Landes Steiermark

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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 investigation 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 23: Administrative structure of the investigation

Role	Title/Name	Address
Sponsor	**CROMA-PHARMA GmbH** *Clinical Project Managers:* - Marivic Narciso, M.Sc. (June 2018 . November 2019) - 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. (November 2018 . January 2020) - _ nfeld, Ph.D. (November 2017-November 2018)	Industriezeile 6 2100 Leobendorf, Austria
Coordinating investigator and Principal investigator Investigational site 01	Univ. Prof. Dr. Daisy Kopera	Medical University Graz Dermatology and venerology clinic Auenbruggerplatz 8 8036 Graz, Austria
Principal investigator Investigational site 02	Dr. Monika Sulovsky	YUVELL® fine aesthetics Weihburggasse 22/1 1010 Wien, Austria
Principal investigator Investigational site 03	Dr. Thomas Rappl	MaRa-Medical Aesthetic Research Academy Kaiser Franz Josef Kai 48 8010 Graz, Austria
Clinical Research Organisation (CRO)	**bioskin GmbH** *Head Clinical Trial Management:* - Kirstin Michaelis-Wittern, M.D. *Clinical Trial Manager:* - Fabian Ecke, Ph.D. (until 31OCT2019) - Annika Wisnowsky, Ph.D. (as of 01NOV2019) *Medical monitor:* - Yi-Ling von Mackensen, M.D. *Biostatistician:* - Agnes Himmelmann, M.S. *Data Manager:* - Stefanie Felscher *Head Medical Writing* - Ragna Williams, M.S.	Messberg 4 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 - Sponsor

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 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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Appendix A

Statistical Report

Abbreviations

AE	adverse event
ATC	anatomical therapeutic chemical
GAIS	global aesthetic improvement scale
ITT	Intent-to-treat
LCL	—
Max	maximum
MedDRA	medical dictionary for regulatory activities
Min	minimum
PP	per-protocol
PR	—
PT	preferred term
Q1	1st quartil
Q3	3rd quartil
SD	standard deviation
SES	safety analysis set
SOC	system organ class
TEAE	treatment emergent adverse event

Table of Contents

Table 1.1: Summary of subject enrollment and evaluability
(Part 1 of 1)

	Dermatology and venerology clinic	Yuvell fine aesthetics	Mara Graz	Total
Number of subjects enrolled	25	34	43	102
Subjects excluded from safety analysis set	0	0	43	43
Subjects included in safety analysis set	25	34	0	59
Subjects excluded from intent-to-treat population	1	0	43	44
Subjects included in intent-to-treat population	24	34	0	58
Subjects excluded from per-protocol population	11	1	43	55
Subjects included in per-protocol population	14	33	0	47

Additional partial exclusions from statistical analysis:
Corneometer and Cutometer measurements for per-protocol population due to deviation from required climatic conditions:
Day 0 (2 subjects), Week 3 (2 subjects), Week 6 (1 subjects), Week 12 (16 subjects), Week 16 (18 subjects), Week 24 (5 subjects)

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 1.2: Summary of subject completion / discontinuation
(Part 1 of 1)

	N
Number of subjects enrolled	102
Number of subjects with trial completion at Week 16	88 (86.3%)
Number of subjects discontinued before Week 16	2 (2.0%)
Reasons for discontinuation	
Adverse Event	0 (0.0%)
Death	0 (0.0%)
Lost to follow-up	0 (0.0%)
Physician decision	0 (0.0%)
Pregnancy	0 (0.0%)
Protocol violation	0 (0.0%)
Screening failure	0 (0.0%)
Site terminated by sponsor	0 (0.0%)
Study terminated by sponsor	0 (0.0%)
Withdrawal by subject	1 (1.0%)
Other	1 (1.0%)
Number of subjects enrolled into extension phase	12 (11.8%)
Reasons for discontinuation	
Adverse Event	0 (0.0%)
Death	0 (0.0%)
Lost to follow-up	0 (0.0%)
Physician decision	0 (0.0%)
Pregnancy	0 (0.0%)
Protocol violation	0 (0.0%)
Screening failure	0 (0.0%)
Site terminated by sponsor	0 (0.0%)
Study terminated by sponsor	0 (0.0%)
Withdrawal by subject	0 (0.0%)
Other	12 (11.8%)

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 1.3: Subjects excluded from the analysis populations
(Part 1 of 1)

	N
Number of subjects enrolled	102
Subjects excluded from the safety analysis set	43 (42%)
Primary exclusionary reason / protocol deviation[1]	
Screen failure (not met inclusion/met exclusion criteria)	0 (0%)
Subject did not receive the investigational device	0 (0%)
Subject at site with inspection findings	43 (42%)
Subjects excluded from the intent-to-treat population	44 (43%)
Primary exclusionary reason / protocol deviation[1]	
Screen failure (not met inclusion/met exclusion criteria)	0 (0%)
Subject did not receive the investigational device	0 (0%)
Subject has no post treatment assessment	0 (0%)
Other	1 (1%)
Subject at site with inspection findings	43 (42%)
Subjects excluded from the per-protocol population	55 (54%)
Primary exclusionary reason[1]	
Screen failure (not met inclusion/met exclusion criteria)	0 (0%)
Subject did not receive any IMP	0 (0%)
Subject has no post treatment assessment	0 (0%)
Subject with inclusion / exclusion criteria violation	0 (0%)
Subject with protocol deviation interfering with the evaluation for GAIS at Week 8	11 (11%)
Subject used medication or procedure interfering with the performance evaluation	0 (0%)
Subject with missing primary performance endpoint[2]	0 (0%)
Subject withdrawal	0 (0%)
Other	1 (1%)
Subject at site with inspection finding	43 (42%)

[1] In case of multiple reasons for exclusion, only the primary is given;
[2] Except the primary effectiveness outcome is a missing for a treatment related reason, e.g. discontinuation of assessments due to adverse events at least possibly related to investigational device.

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 1.4: Subject demographic and baseline characteristics
(Part 1 of 1)

	Safety analysis set	Intent-to-treat population	Per-protocol population
Number of subjects	N=59	N=58	N=47
Age[1] [years]			
N	59	58	47
Mean ± SD	52.6 ± 9.0	52.6 ± 9.1	52.5 ± 9.7
Median	53.0	53.0	52.0
Min, max	28, 77	28, 77	28, 77
Sex			
N	59	58	47
Female	59 (100%)	58 (100%)	47 (100%)
Male	0 (0%)	0 (0%)	0 (0%)
Race			
N	59	58	47
White	59 (100%)	58 (100%)	47 (100%)

[1] _____ ____

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 1.5: Oversight on subject treated areas
(Part 1 of 1)

	Day 0 (N_{SES} = 59)
Number of subjects with treatment of LCL only	7 (11.9%)
Number of subjects with treatment of PR only	33 (55.9%)
Number of subjects with treatment of LCL and PR	19 (32.2%)

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.1: Global aesthetic improvement score (GAIS) by investigator (Intent-to-treat population)
(Part 1 of 2)

Global aesthetic improvement score (GAIS) by investigator[1] (N_{ITT} = 58)	Right LCL	Left LCL	PR
Week 3			
N	23	23	49
Very much improved	1 (4.3%)	1 (4.3%)	2 (4.1%)
Much improved	14 (60.9%)	13 (56.5%)	29 (59.2%)
Improved	8 (34.8%)	9 (39.1%)	18 (36.7%)
No change	0 (0.0%)	0 (0.0%)	0 (0.0%)
Worse	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 6			
N	24	24	50
Very much improved	5 (20.8%)	4 (16.7%)	12 (24.0%)
Much improved	16 (66.7%)	17 (70.8%)	32 (64.0%)
Improved	3 (12.5%)	3 (12.5%)	6 (12.0%)
No change	0 (0.0%)	0 (0.0%)	0 (0.0%)
Worse	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 8			
N	25	25	51
Very much improved	7 (28.0%)	7 (28.0%)	19 (37.3%)
Much improved	13 (52.0%)	13 (52.0%)	26 (51.0%)
Improved	5 (20.0%)	5 (20.0%)	6 (11.8%)
No change	0 (0.0%)	0 (0.0%)	0 (0.0%)
Worse	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 12			
N	23	23	49
Very much improved	3 (13.0%)	3 (13.0%)	17 (34.7%)
Much improved	14 (60.9%)	14 (60.9%)	27 (55.1%)
Improved	5 (21.7%)	5 (21.7%)	4 (8.2%)
No change	1 (4.3%)	1 (4.3%)	1 (2.0%)
Worse	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 16			
N	24	24	50
Very much improved	2 (8.3%)	2 (8.3%)	12 (24.0%)
Much improved	5 (20.8%)	5 (20.8%)	21 (42.0%)
Improved	8 (33.3%)	8 (33.3%)	7 (14.0%)
No change	9 (37.5%)	9 (37.5%)	10 (20.0%)
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.

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.1: Global aesthetic improvement score (GAIS) by investigator (Intent-to-treat population)
(Part 2 of 2)

Global aesthetic improvement score (GAIS) by investigator[1] (N_{ITT} = 58)	Right LCL	Left LCL	PR
Week 24			
N	7	7	11
Very much improved	0 (0.0%)	0 (0.0%)	1 (9.1%)
Much improved	1 (14.3%)	1 (14.3%)	4 (36.4%)
Improved	1 (14.3%)	1 (14.3%)	1 (9.1%)
No change	5 (71.4%)	5 (71.4%)	5 (45.5%)
Worse	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 36			
N	2	2	6
Very much improved	0 (0.0%)	0 (0.0%)	0 (0.0%)
Much improved	0 (0.0%)	0 (0.0%)	0 (0.0%)
Improved	0 (0.0%)	0 (0.0%)	2 (33.3%)
No change	2 (100%)	2 (100%)	4 (66.7%)
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.

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.2: Global aesthetic improvement score (GAIS) by investigator (Per-protocol population)
(Part 1 of 2)

Global aesthetic improvement score (GAIS) by investigator[1] (N_{PP} = 47)	Right LCL	Left LCL	PR
Week 3			
N	16	16	42
Very much improved	1 (6.3%)	1 (6.3%)	2 (4.8%)
Much improved	10 (62.5%)	10 (62.5%)	25 (59.5%)
Improved	5 (31.3%)	5 (31.3%)	15 (35.7%)
No change	0 (0.0%)	0 (0.0%)	0 (0.0%)
Worse	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 6			
N	16	16	42
Very much improved	5 (31.3%)	4 (25.0%)	11 (26.2%)
Much improved	10 (62.5%)	11 (68.8%)	27 (64.3%)
Improved	1 (6.3%)	1 (6.3%)	4 (9.5%)
No change	0 (0.0%)	0 (0.0%)	0 (0.0%)
Worse	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 8			
N	16	16	42
Very much improved	6 (37.5%)	6 (37.5%)	18 (42.9%)
Much improved	8 (50.0%)	8 (50.0%)	21 (50.0%)
Improved	2 (12.5%)	2 (12.5%)	3 (7.1%)
No change	0 (0.0%)	0 (0.0%)	0 (0.0%)
Worse	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 12			
N	15	15	41
Very much improved	2 (13.3%)	2 (13.3%)	16 (39.0%)
Much improved	10 (66.7%)	10 (66.7%)	22 (53.7%)
Improved	2 (13.3%)	2 (13.3%)	2 (4.9%)
No change	1 (6.7%)	1 (6.7%)	1 (2.4%)
Worse	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 16			
N	16	16	42
Very much improved	2 (12.5%)	2 (12.5%)	12 (28.6%)
Much improved	5 (31.3%)	5 (31.3%)	18 (42.9%)
Improved	4 (25.0%)	4 (25.0%)	6 (14.3%)
No change	5 (31.3%)	5 (31.3%)	6 (14.3%)
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.

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.2: Global aesthetic improvement score (GAIS) by investigator (Per-protocol population)
(Part 2 of 2)

Global aesthetic improvement score (GAIS) by investigator[1] (N_{PP} = 47)	Right LCL	Left LCL	PR
Week 24			
N	6	6	10
Very much improved	0 (0.0%)	0 (0.0%)	1 (10.0%)
Much improved	1 (16.7%)	1 (16.7%)	4 (40.0%)
Improved	1 (16.7%)	1 (16.7%)	1 (10.0%)
No change	4 (66.7%)	4 (66.7%)	4 (40.0%)
Worse	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 36			
N	2	2	6
Very much improved	0 (0.0%)	0 (0.0%)	0 (0.0%)
Much improved	0 (0.0%)	0 (0.0%)	0 (0.0%)
Improved	0 (0.0%)	0 (0.0%)	2 (33.3%)
No change	2 (100%)	2 (100%)	4 (66.7%)
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.

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.3: Responders regarding GAIS (Intent-to-treat population)
(Part 1 of 1)

Responders regarding GAIS[1] (N_{ITT} = 58)	LCL	PR	At least one test area (LCL or PR)[2]
Week 3			
N	23	49	56
No improvement	0 (0.0%)	0 (0.0%)	0 (0.0%)
Improvement	23 (100%)	49 (100%)	56 (100%)
Limits of 95% CI for percentage of responders	--	--	--
Week 6			
N	24	50	56
No improvement	0 (0.0%)	0 (0.0%)	0 (0.0%)
Improvement	24 (100%)	50 (100%)	56 (100%)
Limits of 95% CI for percentage of responders	--	--	--
Week 8			
N	25	51	58
No improvement	0 (0.0%)	0 (0.0%)	0 (0.0%)
Improvement	25 (100%)	51 (100%)	58 (100%)
Limits of 95% CI for percentage of responders	--	--	--
Week 12			
N	23	49	56
No improvement	1 (4.3%)	1 (2.0%)	1 (1.8%)
Improvement	22 (95.7%)	48 (98.0%)	55 (98.2%)
Limits of 95% CI for percentage of responders	(87.3%, 100%)	(94.0%, 100%)	(94.7%, 100%)
Week 16			
N	24	50	57
No improvement	9 (37.5%)	10 (20.0%)	11 (19.3%)
Improvement	15 (62.5%)	40 (80.0%)	46 (80.7%)
Limits of 95% CI for percentage of responders	(43.1%, 81.9%)	(68.9%, 91.1%)	(70.5%, 90.9%)
Week 24			
N	7	11	12
No improvement	5 (71.4%)	5 (45.5%)	5 (41.7%)
Improvement	2 (28.6%)	6 (54.5%)	7 (58.3%)
Limits of 95% CI for percentage of responders	(0.0%, 62.0%)	(25.1%, 84.0%)	(30.4%, 86.2%)
Week 36			
N	2	6	7
No improvement	2 (100%)	4 (66.7%)	5 (71.4%)
Improvement	0 (0.0%)	2 (33.3%)	2 (28.6%)
Limits of 95% CI for percentage of responders	--	(0.0%, 71.1%)	(0.0%, 62.0%)

[1] with the GAIS,
[2] Subjects responding on both test areas counted once

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.4: Responders regarding GAIS (Per-protocol population)
(Part 1 of 1)

Responders regarding GAIS[1] (N_{PP} = 47)	LCL	PR	At least one test area (LCL or PR)[2]
Week 3			
N	16	42	47
No improvement	0 (0.0%)	0 (0.0%)	0 (0.0%)
Improvement	16 (100%)	42 (100%)	47 (100%)
Limits of 95% CI for percentage of responders	--	--	--
Week 6			
N	16	42	47
No improvement	0 (0.0%)	0 (0.0%)	0 (0.0%)
Improvement	16 (100%)	42 (100%)	47 (100%)
Limits of 95% CI for percentage of responders	--	--	--
Week 8			
N	16	42	47
No improvement	0 (0.0%)	0 (0.0%)	0 (0.0%)
Improvement	16 (100%)	42 (100%)	47 (100%)
Limits of 95% CI for percentage of responders	--	--	--
Week 12			
N	15	41	46
No improvement	1 (6.7%)	1 (2.4%)	1 (2.2%)
Improvement	14 (93.3%)	40 (97.6%)	45 (97.8%)
Limits of 95% CI for percentage of responders	(80.7%, 100%)	(92.8%, 100%)	(93.6%, 100%)
Week 16			
N	16	42	47
No improvement	5 (31.3%)	6 (14.3%)	7 (14.9%)
Improvement	11 (68.8%)	36 (85.7%)	40 (85.1%)
Limits of 95% CI for percentage of responders	(46.0%, 91.5%)	(75.1%, 96.3%)	(74.9%, 95.3%)
Week 24			
N	6	10	11
No improvement	4 (66.7%)	4 (40.0%)	4 (36.4%)
Improvement	2 (33.3%)	6 (60.0%)	7 (63.6%)
Limits of 95% CI for percentage of responders	(0.0%, 71.1%)	(29.6%, 90.4%)	(35.2%, 92.1%)
Week 36			
N	2	6	7
No improvement	2 (100%)	4 (66.7%)	5 (71.4%)
Improvement	0 (0.0%)	2 (33.3%)	2 (28.6%)
Limits of 95% CI for percentage of responders	--	(0.0%, 71.1%)	(0.0%, 62.0%)

[1] with the GAIS,
[2] Subjects responding on both test areas counted once.

Source: CPH-401-201364_AppA_30JAN20.rtf

-to-treat population)

(Part 1 of 1)

	JTT = 58)
Week 8	
N	58
Very satisfied	36 (62.1%)
Satisfied	18 (31.0%)
Neither satisfied nor unsatisfied	4 (6.9%)
Unsatisfied	0 (0.0%)
Very unsatisfied	0 (0.0%)
Week 12	
N	56
Very satisfied	29 (51.8%)
Satisfied	22 (39.3%)
Neither satisfied nor unsatisfied	5 (8.9%)
Unsatisfied	0 (0.0%)
Very unsatisfied	0 (0.0%)
Week 16	
N	57
Very satisfied	31 (54.4%)
Satisfied	11 (19.3%)
Neither satisfied nor unsatisfied	15 (26.3%)
Unsatisfied	0 (0.0%)
Very unsatisfied	0 (0.0%)
Week 24	
N	12
Very satisfied	5 (41.7%)
Satisfied	2 (16.7%)
Neither satisfied nor unsatisfied	5 (41.7%)
Unsatisfied	0 (0.0%)
Very unsatisfied	0 (0.0%)
Week 36	
N	7
Very satisfied	4 (57.1%)
Satisfied	1 (14.3%)
Neither satisfied nor unsatisfied	2 (28.6%)
Unsatisfied	0 (0.0%)
Very unsatisfied	0 (0.0%)

Source: CPH-401-201364_AppA_30JAN20.rtf

-protocol population)

(Part 1 of 1)

	PP = 47)
Week 8	
N	47
Very satisfied	32 (68.1%)
Satisfied	11 (23.4%)
Neither satisfied nor unsatisfied	4 (8.5%)
Unsatisfied	0 (0.0%)
Very unsatisfied	0 (0.0%)
Week 12	
N	46
Very satisfied	27 (58.7%)
Satisfied	15 (32.6%)
Neither satisfied nor unsatisfied	4 (8.7%)
Unsatisfied	0 (0.0%)
Very unsatisfied	0 (0.0%)
Week 16	
N	47
Very satisfied	29 (61.7%)
Satisfied	8 (17.0%)
Neither satisfied nor unsatisfied	10 (21.3%)
Unsatisfied	0 (0.0%)
Very unsatisfied	0 (0.0%)
Week 24	
N	11
Very satisfied	5 (45.5%)
Satisfied	2 (18.2%)
Neither satisfied nor unsatisfied	4 (36.4%)
Unsatisfied	0 (0.0%)
Very unsatisfied	0 (0.0%)
Week 36	
N	7
Very satisfied	4 (57.1%)
Satisfied	1 (14.3%)
Neither satisfied nor unsatisfied	2 (28.6%)
Unsatisfied	0 (0.0%)
Very unsatisfied	0 (0.0%)

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.7.1: Corneometer measurements [I.U.] (Intent-to-treat population)
(Part 1 of 4)

	Skin hydration [I.U.]	
Corneometer measurements[1] (N_{ITT} = 58)	**LCL**	**PR**
Day 0		
N	25	49
Mean ± SD	51.8 ± 14.0	53.2 ± 15.6
95% Confidence interval for mean	46.0 , 57.6	48.8 , 57.7
Median	49.7	53.0
Q1 , Q3	45.5 , 63.3	41.0 , 61.1
Min, max	20.9 , 75.9	23.4 , 90.7
Week 3		
N	21	48
Mean ± SD	52.5 ± 12.5	53.2 ± 15.5
95% Confidence interval for mean	46.8 , 58.2	48.7 , 57.7
Median	51.5	53.2
Q1 , Q3	41.5 , 61.6	40.9 , 65.4
Min, max	35.6 , 82.0	29.3 , 96.9
Change from Baseline (Day 0)		
N	21	46
Mean ± SD	-2.6 ± 12.6	-0.4 ± 12.8
95% Confidence interval for mean	-8.3 , 3.2	-4.2 , 3.4
Median	-1.3	0.9
Q1 , Q3	-7.3 , 6.1	-8.2 , 6.5
Min, max	-27.5 , 20.4	-26.6 , 31.1
Week 6		
N	24	50
Mean ± SD	50.2 ± 17.0	52.7 ± 17.4
95% Confidence interval for mean	43.1 , 57.4	47.8 , 57.7
Median	49.0	50.7
Q1 , Q3	37.6 , 57.9	40.3 , 61.1
Min, max	22.1 , 90.7	22.0 , 110.9
Change from Baseline (Day 0)		
N	24	48
Mean ± SD	-1.6 ± 15.2	-0.8 ± 15.4
95% Confidence interval for mean	-8.0 , 4.8	-5.2 , 3.7
Median	-0.6	-0.9
Q1 , Q3	-13.9 , 4.8	-11.3 , 5.7
Min, max	-22.3 , 38.1	-25.9 , 51.7

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

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.7.1: Corneometer measurements [I.U.] (Intent-to-treat population)
(Part 2 of 4)

	Skin hydration [I.U.]	
Corneometer measurements[1] (N_{ITT} = 58)	**LCL**	**PR**
Day 0		
N	25	49
Mean ± SD	51.8 ± 14.0	53.2 ± 15.6
95% Confidence interval for mean	46.0 , 57.6	48.8 , 57.7
Median	49.7	53.0
Q1 , Q3	45.5 , 63.3	41.0 , 61.1
Min, max	20.9 , 75.9	23.4 , 90.7
Week 8		
N	23	50
Mean ± SD	52.4 ± 13.3	53.5 ± 15.8
95% Confidence interval for mean	46.7 , 58.2	49.0 , 58.0
Median	52.3	51.3
Q1 , Q3	42.1 , 61.4	42.6 , 64.5
Min, max	30.2 , 79.0	19.7 , 97.2
Change from Baseline (Day 0)		
N	23	48
Mean ± SD	1.5 ± 11.5	0.6 ± 15.6
95% Confidence interval for mean	-3.4 , 6.5	-4.0 , 5.1
Median	0.7	0.8
Q1 , Q3	-2.2 , 5.5	-11.5 , 10.7
Min, max	-18.8 , 37.3	-26.8 , 42.8
Week 12		
N	22	49
Mean ± SD	56.4 ± 11.9	58.7 ± 18.4
95% Confidence interval for mean	51.1 , 61.7	53.4 , 64.0
Median	54.5	57.6
Q1 , Q3	49.0 , 59.4	47.6 , 67.2
Min, max	40.9 , 85.4	22.8 , 97.7
Change from Baseline (Day 0)		
N	22	47
Mean ± SD	4.2 ± 14.5	5.4 ± 15.6
95% Confidence interval for mean	-2.3 , 10.6	0.8 , 10.0
Median	1.1	3.2
Q1 , Q3	-5.3 , 12.5	-4.9 , 14.7
Min, max	-19.5 , 37.8	-32.0 , 41.8

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

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.7.1: Corneometer measurements [I.U.] (Intent-to-treat population)
(Part 3 of 4)

	Skin hydration [I.U.]	
Corneometer measurements[1] (N_{ITT} = 58)	**LCL**	**PR**
Day 0		
N	25	49
Mean ± SD	51.8 ± 14.0	53.2 ± 15.6
95% Confidence interval for mean	46.0 , 57.6	48.8 , 57.7
Median	49.7	53.0
Q1 , Q3	45.5 , 63.3	41.0 , 61.1
Min, max	20.9 , 75.9	23.4 , 90.7
Week 16		
N	24	50
Mean ± SD	56.5 ± 11.5	58.2 ± 17.0
95% Confidence interval for mean	51.6 , 61.3	53.3 , 63.0
Median	58.6	54.4
Q1 , Q3	46.2 , 61.3	47.5 , 63.3
Min, max	35.1 , 80.3	30.3 , 104.9
Change from Baseline (Day 0)		
N	24	48
Mean ± SD	3.9 ± 13.0	5.4 ± 12.8
95% Confidence interval for mean	-1.6 , 9.4	1.7 , 9.1
Median	4.3	3.7
Q1 , Q3	-7.0 , 12.4	-5.7 , 15.9
Min, max	-16.5 , 40.3	-16.4 , 29.3
Week 24		
N	5	9
Mean ± SD	69.0 ± 5.7	61.4 ± 10.0
95% Confidence interval for mean	61.9 , 76.1	53.7 , 69.0
Median	69.8	58.4
Q1 , Q3	68.4 , 71.0	53.4 , 66.2
Min, max	60.0 , 75.6	51.3 , 81.6
Change from Baseline (Day 0)		
N	5	8
Mean ± SD	15.1 ± 15.6	10.9 ± 17.3
95% Confidence interval for mean	-4.3 , 34.5	-3.5 , 25.4
Median	12.4	9.4
Q1 , Q3	7.7 , 21.7	-1.5 , 23.7
Min, max	-3.9 , 37.6	-13.1 , 37.5

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

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.7.2: Corneometer measurements [I.U.] - baseline by visit (Intent-to-treat population)
(Part 1 of 4)

	Skin hydration [I.U.]	
Corneometer measurements[1] (N_{ITT} = 58)	**LCL**	**PR**
Baseline to Week 3		
N	21	46
Mean ± SD	55.1 ± 12.3	53.8 ± 15.1
95% Confidence interval for mean	49.5 , 60.7	49.3 , 58.2
Median	51.0	53.3
Q1 , Q3	47.5 , 64.4	42.0 , 61.1
Min, max	30.8 , 75.9	28.7 , 90.7
Week 3		
N	21	46
Mean ± SD	52.5 ± 12.5	53.4 ± 15.8
95% Confidence interval for mean	46.8 , 58.2	48.7 , 58.1
Median	51.5	53.2
Q1 , Q3	41.5 , 61.6	40.8 , 65.5
Min, max	35.6 , 82.0	29.3 , 96.9
Change from Baseline		
N	21	46
Mean ± SD	-2.6 ± 12.6	-0.4 ± 12.8
95% Confidence interval for mean	-8.3 , 3.2	-4.2 , 3.4
Median	-1.3	0.9
Q1 , Q3	-7.3 , 6.1	-8.2 , 6.5
Min, max	-27.5 , 20.4	-26.6 , 31.1
Baseline to Week 6		
N	24	48
Mean ± SD	51.9 ± 14.3	53.5 ± 15.6
95% Confidence interval for mean	45.8 , 57.9	49.0 , 58.1
Median	49.1	53.3
Q1 , Q3	44.1 , 63.9	41.5 , 61.3
Min, max	20.9 , 75.9	23.4 , 90.7
Week 6		
N	24	48
Mean ± SD	50.2 ± 17.0	52.8 ± 17.7
95% Confidence interval for mean	43.1 , 57.4	47.6 , 57.9
Median	49.0	50.7
Q1 , Q3	37.6 , 57.9	40.1 , 61.7
Min, max	22.1 , 90.7	22.0 , 110.9
Change from Baseline		
N	24	48
Mean ± SD	-1.6 ± 15.2	-0.8 ± 15.4
95% Confidence interval for mean	-8.0 , 4.8	-5.2 , 3.7
Median	-0.6	-0.9
Q1 , Q3	-13.9 , 4.8	-11.3 , 5.7
Min, max	-22.3 , 38.1	-25.9 , 51.7

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

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.7.1: Corneometer measurements [I.U.] (Intent-to-treat population)
(Part 4 of 4)

	Skin hydration [I.U.]	
Corneometer measurements[1] (N_{ITT} = 58)	**LCL**	**PR**
Day 0		
N	25	49
Mean ± SD	51.8 ± 14.0	53.2 ± 15.6
95% Confidence interval for mean	46.0 , 57.6	48.8 , 57.7
Median	49.7	53.0
Q1 , Q3	45.5 , 63.3	41.0 , 61.1
Min, max	20.9 , 75.9	23.4 , 90.7
Week 36		
N	1	5
Mean ± SD	83.6	54.8 ± 4.6
95% Confidence interval for mean	- , -	49.2 , 60.5
Median	83.6	53.1
Q1 , Q3	83.6 , 83.6	51.8 , 59.7
Min, max	83.6 , 83.6	50.0 , 59.8
Change from Baseline (Day 0)		
N	1	4
Mean ± SD	9.8	-4.6 ± 13.3
95% Confidence interval for mean	- , -	-25.8 , 16.5
Median	9.8	-6.0
Q1 , Q3	9.8 , 9.8	-15.0 , 5.7
Min, max	9.8 , 9.8	-18.4 , 12.0

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

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.7.2: Corneometer measurements [I.U.] - baseline by visit (Intent-to-treat population)
(Part 2 of 4)

	Skin hydration [I.U.]	
Corneometer measurements[1] (N_{ITT} = 58)	**LCL**	**PR**
Baseline to Week 8		
N	23	48
Mean ± SD	50.9 ± 13.7	53.1 ± 15.7
95% Confidence interval for mean	44.9 , 56.8	48.5 , 57.6
Median	48.6	52.9
Q1 , Q3	42.6 , 63.3	40.9 , 61.3
Min, max	20.9 , 75.9	23.4 , 90.7
Week 8		
N	23	48
Mean ± SD	52.4 ± 13.3	53.6 ± 16.1
95% Confidence interval for mean	46.7 , 58.2	49.0 , 58.3
Median	52.3	51.3
Q1 , Q3	42.1 , 61.4	42.5 , 64.9
Min, max	30.2 , 79.0	19.7 , 97.2
Change from Baseline		
N	23	48
Mean ± SD	1.5 ± 11.5	0.6 ± 15.6
95% Confidence interval for mean	-3.4 , 6.5	-4.0 , 5.1
Median	0.7	0.8
Q1 , Q3	-2.2 , 5.5	-11.5 , 10.7
Min, max	-18.8 , 37.3	-26.8 , 42.8
Baseline to Week 12		
N	22	47
Mean ± SD	52.2 ± 14.2	53.5 ± 15.8
95% Confidence interval for mean	45.9 , 58.6	48.9 , 58.1
Median	49.9	53.0
Q1 , Q3	45.5 , 63.3	41.0 , 61.5
Min, max	20.9 , 75.9	23.4 , 90.7
Week 12		
N	22	47
Mean ± SD	56.4 ± 11.9	58.9 ± 18.7
95% Confidence interval for mean	51.1 , 61.7	53.4 , 64.4
Median	54.5	59.9
Q1 , Q3	49.0 , 59.4	47.2 , 67.4
Min, max	40.9 , 85.4	22.8 , 97.7
Change from Baseline		
N	22	47
Mean ± SD	4.2 ± 14.5	5.4 ± 15.6
95% Confidence interval for mean	-2.3 , 10.6	0.8 , 10.0
Median	1.1	3.2
Q1 , Q3	-5.3 , 12.5	-4.9 , 14.7
Min, max	-19.5 , 37.8	-32.0 , 41.8

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

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.7.2: Corneometer measurements [I.U.] - baseline by visit (Intent-to-treat population)
(Part 3 of 4)

	Skin hydration [I.U.]	
Corneometer measurements[1] (N_{ITT} = 58)	**LCL**	**PR**
Baseline to Week 16		
N	24	48
Mean ± SD	52.5 ± 13.9	53.5 ± 15.6
95% Confidence interval for mean	46.7 , 58.4	49.0 , 58.0
Median	49.9	53.3
Q1 , Q3	45.6 , 63.9	41.5 , 61.3
Min, max	20.9 , 75.9	23.4 , 90.7
Week 16		
N	24	48
Mean ± SD	56.5 ± 11.5	58.9 ± 16.9
95% Confidence interval for mean	51.6 , 61.3	54.0 , 63.9
Median	58.6	54.6
Q1 , Q3	46.2 , 61.3	48.1 , 63.5
Min, max	35.1 , 80.3	30.3 , 104.9
Change from Baseline		
N	24	48
Mean ± SD	3.9 ± 13.0	5.4 ± 12.8
95% Confidence interval for mean	-1.6 , 9.4	1.7 , 9.1
Median	4.3	3.7
Q1 , Q3	-7.0 , 12.4	-5.7 , 15.9
Min, max	-16.5 , 40.3	-16.4 , 29.3
Baseline to Week 24		
N	5	8
Mean ± SD	53.9 ± 16.3	51.7 ± 12.7
95% Confidence interval for mean	33.7 , 74.1	41.1 , 62.3
Median	54.0	50.2
Q1 , Q3	47.6 , 63.3	44.7 , 60.9
Min, max	30.8 , 73.8	30.6 , 71.5
Week 24		
N	5	8
Mean ± SD	69.0 ± 5.7	62.6 ± 9.9
95% Confidence interval for mean	61.9 , 76.1	54.4 , 70.9
Median	69.8	62.3
Q1 , Q3	68.4 , 71.0	54.1 , 67.1
Min, max	60.0 , 75.6	52.6 , 81.6
Change from Baseline		
N	5	8
Mean ± SD	15.1 ± 15.6	10.9 ± 17.3
95% Confidence interval for mean	-4.3 , 34.5	-3.5 , 25.4
Median	12.4	9.4
Q1 , Q3	7.7 , 21.7	-1.5 , 23.7
Min, max	-3.9 , 37.6	-13.1 , 37.5

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

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.7.2: Corneometer measurements [I.U.] - baseline by visit (Intent-to-treat population)
(Part 4 of 4)

	Skin hydration [I.U.]	
Corneometer measurements[1] (N_{ITT} = 58)	**LCL**	**PR**
Baseline to Week 36		
N	1	4
Mean ± SD	73.8	60.2 ± 9.8
95% Confidence interval for mean	- , -	44.7 , 75.8
Median	73.8	60.9
Q1 , Q3	73.8 , 73.8	54.0 , 66.5
Min, max	73.8 , 73.8	47.7 , 71.5
Week 36		
N	1	4
Mean ± SD	83.6	55.6 ± 4.9
95% Confidence interval for mean	- , -	47.8 , 63.4
Median	83.6	56.4
Q1 , Q3	83.6 , 83.6	51.5 , 59.7
Min, max	83.6 , 83.6	50.0 , 59.8
Change from Baseline		
N	1	4
Mean ± SD	9.8	-4.6 ± 13.3
95% Confidence interval for mean	- , -	-25.8 , 16.5
Median	9.8	-6.0
Q1 , Q3	9.8 , 9.8	-15.0 , 5.7
Min, max	9.8 , 9.8	-18.4 , 12.0

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

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.8.1: Corneometer measurements [I.U.] (Per-protocol population)
(Part 1 of 4)

	Skin hydration [I.U.]	
Corneometer measurements[1] (N_{PP} = 47)	**LCL**	**PR**
Day 0		
N	16	38
Mean ± SD	56.9 ± 12.0	55.3 ± 15.0
95% Confidence interval for mean	50.6 , 63.3	50.4 , 60.3
Median	52.1	54.1
Q1 , Q3	47.3 , 68.4	45.0 , 61.5
Min, max	42.6 , 75.9	28.7 , 90.7
Week 3		
N	16	40
Mean ± SD	55.9 ± 12.2	55.6 ± 14.8
95% Confidence interval for mean	49.4 , 62.4	50.9 , 60.4
Median	53.8	54.7
Q1 , Q3	47.2 , 61.8	44.6 , 65.6
Min, max	41.3 , 82.0	29.3 , 96.9
Change from Baseline (Day 0)		
N	16	38
Mean ± SD	-1.1 ± 13.6	0.4 ± 13.2
95% Confidence interval for mean	-8.3 , 6.2	-4.0 , 4.7
Median	-0.4	1.5
Q1 , Q3	-6.8 , 7.1	-10.3 , 6.6
Min, max	-27.5 , 20.4	-25.9 , 31.1
Week 6		
N	16	41
Mean ± SD	55.4 ± 17.7	55.0 ± 17.4
95% Confidence interval for mean	46.0 , 64.8	49.5 , 60.5
Median	54.1	55.6
Q1 , Q3	42.8 , 64.7	43.1 , 62.4
Min, max	25.3 , 90.7	22.0 , 110.9
Change from Baseline (Day 0)		
N	16	39
Mean ± SD	-1.5 ± 15.5	-0.1 ± 16.3
95% Confidence interval for mean	-9.8 , 6.7	-5.4 , 5.1
Median	2.0	-1.1
Q1 , Q3	-15.2 , 4.8	-11.4 , 6.7
Min, max	-22.3 , 38.1	-25.9 , 51.7

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

Partial exclusions from statistical analysis due to deviation from required climatic conditions: Day 0 (2 subjects), Day 0 (2 subjects), Week 3 (2 subjects), Week 6 (1 subjects), Week 12 (16 subjects), Week 16 (18 subjects), Week 24 (5 subjects)

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.8.1: Corneometer measurements [I.U.] (Per-protocol population)
(Part 2 of 4)

	Skin hydration [I.U.]	
Corneometer measurements[1] (N_{PP} = 47)	**LCL**	**PR**
Day 0		
N	16	38
Mean ± SD	56.9 ± 12.0	55.3 ± 15.0
95% Confidence interval for mean	50.6 , 63.3	50.4 , 60.3
Median	52.1	54.1
Q1 , Q3	47.3 , 68.4	45.0 , 61.5
Min, max	42.6 , 75.9	28.7 , 90.7
Week 8		
N	14	41
Mean ± SD	56.4 ± 13.6	55.4 ± 16.6
95% Confidence interval for mean	48.6 , 64.3	50.2 , 60.6
Median	53.4	52.5
Q1 , Q3	48.6 , 68.5	42.6 , 66.5
Min, max	30.2 , 79.0	19.7 , 97.2
Change from Baseline (Day 0)		
N	14	39
Mean ± SD	0.3 ± 10.3	0.2 ± 15.3
95% Confidence interval for mean	-5.6 , 6.3	-4.7 , 5.2
Median	2.8	1.6
Q1 , Q3	-2.2 , 5.5	-12.2 , 10.5
Min, max	-18.8 , 17.5	-26.8 , 42.8
Week 12		
N	12	27
Mean ± SD	54.7 ± 8.8	58.2 ± 18.3
95% Confidence interval for mean	49.1 , 60.3	50.9 , 65.4
Median	56.0	53.7
Q1 , Q3	47.8 , 58.7	46.6 , 66.0
Min, max	43.3 , 74.4	29.6 , 97.1
Change from Baseline (Day 0)		
N	12	26
Mean ± SD	-1.4 ± 9.9	6.1 ± 12.1
95% Confidence interval for mean	-7.7 , 4.9	1.2 , 10.9
Median	-1.0	3.9
Q1 , Q3	-7.2 , 5.8	-2.3 , 12.5
Min, max	-19.5 , 13.8	-16.9 , 37.8

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

Partial exclusions from statistical analysis due to deviation from required climatic conditions: Day 0 (2 subjects), Day 0 (2 subjects), Week 3 (2 subjects), Week 6 (1 subjects), Week 12 (16 subjects), Week 16 (18 subjects), Week 24 (5 subjects)

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.8.1: Corneometer measurements [I.U.] (Per-protocol population)
(Part 3 of 4)

	Skin hydration [I.U.]	
Corneometer measurements[1] (N_{PP} = 47)	**LCL**	**PR**
Day 0		
N	16	38
Mean ± SD	56.9 ± 12.0	55.3 ± 15.0
95% Confidence interval for mean	50.6 , 63.3	50.4 , 60.3
Median	52.1	54.1
Q1 , Q3	47.3 , 68.4	45.0 , 61.5
Min, max	42.6 , 75.9	28.7 , 90.7
Week 16		
N	15	25
Mean ± SD	56.0 ± 12.4	60.1 ± 17.5
95% Confidence interval for mean	49.2 , 62.9	52.9 , 67.4
Median	58.9	55.5
Q1 , Q3	46.1 , 64.4	51.2 , 62.3
Min, max	35.1 , 80.3	30.3 , 104.5
Change from Baseline (Day 0)		
N	15	25
Mean ± SD	0.2 ± 10.9	8.0 ± 13.3
95% Confidence interval for mean	-5.9 , 6.3	2.5 , 13.5
Median	0.8	6.7
Q1 , Q3	-9.0 , 6.5	-2.8 , 21.3
Min, max	-16.5 , 21.7	-14.7 , 29.2
Week 24		
N	1	4
Mean ± SD	69.8	59.0 ± 8.2
95% Confidence interval for mean	- , -	46.0 , 72.1
Median	69.8	59.3
Q1 , Q3	69.8 , 69.8	51.9 , 66.2
Min, max	69.8 , 69.8	51.3 , 66.2
Change from Baseline (Day 0)		
N	1	3
Mean ± SD	-3.9	5.1 ± 13.7
95% Confidence interval for mean	- , -	-28.9 , 39.2
Median	-3.9	5.8
Q1 , Q3	-3.9 , -3.9	-8.9 , 18.5
Min, max	-3.9 , -3.9	-8.9 , 18.5

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

Partial exclusions from statistical analysis due to deviation from required climatic conditions: Day 0 (2 subjects), Day 0 (2 subjects), Week 3 (2 subjects), Week 6 (1 subjects), Week 12 (16 subjects), Week 16 (18 subjects), Week 24 (5 subjects)

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.8.1: Corneometer measurements [I.U.] (Per-protocol population)
(Part 4 of 4)

	Skin hydration [I.U.]	
Corneometer measurements[1] (N_{PP} = 47)	**LCL**	**PR**
Day 0		
N	16	38
Mean ± SD	56.9 ± 12.0	55.3 ± 15.0
95% Confidence interval for mean	50.6 , 63.3	50.4 , 60.3
Median	52.1	54.1
Q1 , Q3	47.3 , 68.4	45.0 , 61.5
Min, max	42.6 , 75.9	28.7 , 90.7
Week 36		
N	1	5
Mean ± SD	83.6	54.8 ± 4.6
95% Confidence interval for mean	- , -	49.2 , 60.5
Median	83.6	53.1
Q1 , Q3	83.6 , 83.6	51.8 , 59.7
Min, max	83.6 , 83.6	50.0 , 59.8
Change from Baseline (Day 0)		
N	1	4
Mean ± SD	9.8	-4.6 ± 13.3
95% Confidence interval for mean	- , -	-25.8 , 16.5
Median	9.8	-6.0
Q1 , Q3	9.8 , 9.8	-15.0 , 5.7
Min, max	9.8 , 9.8	-18.4 , 12.0

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

Partial exclusions from statistical analysis due to deviation from required climatic conditions: Day 0 (2 subjects), Day 0 (2 subjects), Week 3 (2 subjects), Week 6 (1 subjects), Week 12 (16 subjects), Week 16 (18 subjects), Week 24 (5 subjects)

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.8.2: Corneometer measurements [I.U.] - baseline by visit (Per-protocol population)
(Part 1 of 4)

	Skin hydration [I.U.]	
Corneometer measurements[1] (N_{PP} = 47)	**LCL**	**PR**
Baseline to Week 3		
N	16	38
Mean ± SD	56.9 ± 12.0	55.6 ± 15.1
95% Confidence interval for mean	50.6 , 63.3	50.6 , 60.6
Median	52.1	54.1
Q1 , Q3	47.3 , 68.4	45.0 , 63.5
Min, max	42.6 , 75.9	28.7 , 90.7
Week 3		
N	16	38
Mean ± SD	55.9 ± 12.2	56.0 ± 15.1
95% Confidence interval for mean	49.4 , 62.4	51.0 , 60.9
Median	53.8	55.7
Q1 , Q3	47.2 , 61.8	44.3 , 65.7
Min, max	41.3 , 82.0	29.3 , 96.9
Change from Baseline		
N	16	38
Mean ± SD	-1.1 ± 13.6	0.4 ± 13.2
95% Confidence interval for mean	-8.3 , 6.2	-4.0 , 4.7
Median	-0.4	1.5
Q1 , Q3	-6.8 , 7.1	-10.3 , 6.6
Min, max	-27.5 , 20.4	-25.9 , 31.1
Baseline to Week 6		
N	16	39
Mean ± SD	56.9 ± 12.0	55.4 ± 14.9
95% Confidence interval for mean	50.6 , 63.3	50.5 , 60.2
Median	52.1	53.9
Q1 , Q3	47.3 , 68.4	45.0 , 61.5
Min, max	42.6 , 75.9	28.7 , 90.7
Week 6		
N	16	39
Mean ± SD	55.4 ± 17.7	55.2 ± 17.8
95% Confidence interval for mean	46.0 , 64.8	49.4 , 61.0
Median	54.1	55.6
Q1 , Q3	42.8 , 64.7	41.1 , 62.8
Min, max	25.3 , 90.7	22.0 , 110.9
Change from Baseline		
N	16	39
Mean ± SD	-1.5 ± 15.5	-0.1 ± 16.3
95% Confidence interval for mean	-9.8 , 6.7	-5.4 , 5.1
Median	2.0	-1.1
Q1 , Q3	-15.2 , 4.8	-11.4 , 6.7
Min, max	-22.3 , 38.1	-25.9 , 51.7

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

Partial exclusions from statistical analysis due to deviation from required climatic conditions: Day 0 (2 subjects), Day 0 (2 subjects), Week 3 (2 subjects), Week 6 (1 subjects), Week 12 (16 subjects), Week 16 (18 subjects), Week 24 (5 subjects)

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.8.2: Corneometer measurements [I.U.] - baseline by visit (Per-protocol population)
(Part 2 of 4)

	Skin hydration [I.U.]	
Corneometer measurements[1] (N_{PP} = 47)	**LCL**	**PR**
Baseline to Week 8		
N	14	39
Mean ± SD	56.1 ± 11.6	55.4 ± 14.9
95% Confidence interval for mean	49.4 , 62.8	50.6 , 60.3
Median	52.1	53.9
Q1 , Q3	47.1 , 64.4	45.0 , 63.5
Min, max	42.6 , 75.9	28.7 , 90.7
Week 8		
N	14	39
Mean ± SD	56.4 ± 13.6	55.7 ± 16.9
95% Confidence interval for mean	48.6 , 64.3	50.2 , 61.1
Median	53.4	52.5
Q1 , Q3	48.6 , 68.5	41.8 , 66.8
Min, max	30.2 , 79.0	19.7 , 97.2
Change from Baseline		
N	14	39
Mean ± SD	0.3 ± 10.3	0.2 ± 15.3
95% Confidence interval for mean	-5.6 , 6.3	-4.7 , 5.2
Median	2.8	1.6
Q1 , Q3	-2.2 , 5.5	-12.2 , 10.5
Min, max	-18.8 , 17.5	-26.8 , 42.8
Baseline to Week 12		
N	12	26
Mean ± SD	56.1 ± 12.4	52.3 ± 14.4
95% Confidence interval for mean	48.2 , 64.0	46.5 , 58.1
Median	50.9	52.4
Q1 , Q3	46.6 , 67.9	44.1 , 59.3
Min, max	42.6 , 75.9	28.7 , 90.7
Week 12		
N	12	26
Mean ± SD	54.7 ± 8.8	58.4 ± 18.7
95% Confidence interval for mean	49.1 , 60.3	50.8 , 65.9
Median	56.0	54.2
Q1 , Q3	47.8 , 58.7	46.6 , 66.0
Min, max	43.3 , 74.4	29.6 , 97.1
Change from Baseline		
N	12	26
Mean ± SD	-1.4 ± 9.9	6.1 ± 12.1
95% Confidence interval for mean	-7.7 , 4.9	1.2 , 10.9
Median	-1.0	3.9
Q1 , Q3	-7.2 , 5.8	-2.3 , 12.5
Min, max	-19.5 , 13.8	-16.9 , 37.8

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

Partial exclusions from statistical analysis due to deviation from required climatic conditions: Day 0 (2 subjects), Day 0 (2 subjects), Week 3 (2 subjects), Week 6 (1 subjects), Week 12 (16 subjects), Week 16 (18 subjects), Week 24 (5 subjects)

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.8.2: Corneometer measurements [I.U.] - baseline by visit (Per-protocol population)
(Part 3 of 4)

	Skin hydration [I.U.]	
Corneometer measurements[1] (N_{PP} = 47)	**LCL**	**PR**
Baseline to Week 16		
N	15	25
Mean ± SD	55.8 ± 11.5	52.1 ± 12.3
95% Confidence interval for mean	49.4 , 62.2	47.1 , 57.2
Median	51.6	52.7
Q1 , Q3	47.1 , 64.4	45.0 , 59.3
Min, max	42.6 , 75.9	28.7 , 79.6
Week 16		
N	15	25
Mean ± SD	56.0 ± 12.4	60.1 ± 17.5
95% Confidence interval for mean	49.2 , 62.9	52.9 , 67.4
Median	58.9	55.5
Q1 , Q3	46.1 , 64.4	51.2 , 62.3
Min, max	35.1 , 80.3	30.3 , 104.5
Change from Baseline		
N	15	25
Mean ± SD	0.2 ± 10.9	8.0 ± 13.3
95% Confidence interval for mean	-5.9 , 6.3	2.5 , 13.5
Median	0.8	6.7
Q1 , Q3	-9.0 , 6.5	-2.8 , 21.3
Min, max	-16.5 , 21.7	-14.7 , 29.2
Baseline to Week 24		
N	1	3
Mean ± SD	73.8	56.5 ± 7.6
95% Confidence interval for mean	- , -	37.5 , 75.5
Median	73.8	60.3
Q1 , Q3	73.8 , 73.8	47.7 , 61.5
Min, max	73.8 , 73.8	47.7 , 61.5
Week 24		
N	1	3
Mean ± SD	69.8	61.6 ± 7.8
95% Confidence interval for mean	- , -	42.1 , 81.1
Median	69.8	66.1
Q1 , Q3	69.8 , 69.8	52.6 , 66.2
Min, max	69.8 , 69.8	52.6 , 66.2
Change from Baseline		
N	1	3
Mean ± SD	-3.9	5.1 ± 13.7
95% Confidence interval for mean	- , -	-28.9 , 39.2
Median	-3.9	5.8
Q1 , Q3	-3.9 , -3.9	-8.9 , 18.5
Min, max	-3.9 , -3.9	-8.9 , 18.5

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

Partial exclusions from statistical analysis due to deviation from required climatic conditions: Day 0 (2 subjects), Day 0 (2 subjects), Week 3 (2 subjects), Week 6 (1 subjects), Week 12 (16 subjects), Week 16 (18 subjects), Week 24 (5 subjects)

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.8.2: Corneometer measurements [I.U.] - baseline by visit (Per-protocol population)
(Part 4 of 4)

	Skin hydration [I.U.]	
Corneometer measurements[1] (N_{PP} = 47)	**LCL**	**PR**
Baseline to Week 36		
N	1	4
Mean ± SD	73.8	60.2 ± 9.8
95% Confidence interval for mean	- , -	44.7 , 75.8
Median	73.8	60.9
Q1 , Q3	73.8 , 73.8	54.0 , 66.5
Min, max	73.8 , 73.8	47.7 , 71.5
Week 36		
N	1	4
Mean ± SD	83.6	55.6 ± 4.9
95% Confidence interval for mean	- , -	47.8 , 63.4
Median	83.6	56.4
Q1 , Q3	83.6 , 83.6	51.5 , 59.7
Min, max	83.6 , 83.6	50.0 , 59.8
Change from Baseline		
N	1	4
Mean ± SD	9.8	-4.6 ± 13.3
95% Confidence interval for mean	- , -	-25.8 , 16.5
Median	9.8	-6.0
Q1 , Q3	9.8 , 9.8	-15.0 , 5.7
Min, max	9.8 , 9.8	-18.4 , 12.0

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

Partial exclusions from statistical analysis due to deviation from required climatic conditions: Day 0 (2 subjects), Day 0 (2 subjects), Week 3 (2 subjects), Week 6 (1 subjects), Week 12 (16 subjects), Week 16 (18 subjects), Week 24 (5 subjects)

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.9.1: Cutometer measurements (Intent-to-treat population)
(Part 1 of 4)

Cutometer measurements[1] (N_{ITT} = 58)	LCL, Skin tone R0 [mm]	LCL, Skin elasticity R2 [ratio]	PR, Skin tone R0 [mm]	PR, Skin elasticity R2 [ratio]
Day 0				
N	24	24	50	50
Mean ± SD	0.206 ± 0.072	0.835 ± 0.046	0.205 ± 0.090	0.887 ± 0.051
95% Confidence interval for mean	0.175 , 0.237	0.815 , 0.854	0.180 , 0.231	0.872 , 0.901
Median	0.201	0.838	0.200	0.892
Q1 , Q3	0.149 , 0.244	0.812 , 0.872	0.133 , 0.280	0.866 , 0.916
Min, max	0.087 , 0.392	0.731 , 0.909	0.040 , 0.393	0.609 , 0.955
Week 3				
N	22	24	49	50
Mean ± SD	0.161 ± 0.085	0.841 ± 0.040	0.169 ± 0.091	0.881 ± 0.041
95% Confidence interval for mean	0.123 , 0.199	0.824 , 0.858	0.143 , 0.196	0.869 , 0.893
Median	0.162	0.848	0.169	0.881
Q1 , Q3	0.107 , 0.191	0.821 , 0.875	0.077 , 0.223	0.855 , 0.910
Min, max	0.056 , 0.465	0.736 , 0.888	0.023 , 0.369	0.787 , 0.968
Change from Baseline (Day 0)				
N	21	23	48	49
Mean ± SD	-0.044 ± 0.080	0.000 ± 0.044	-0.037 ± 0.052	-0.005 ± 0.058
95% Confidence interval for mean	-0.080 , -0.007	-0.019 , 0.019	-0.052 , -0.022	-0.022 , 0.011
Median	-0.031	-0.009	-0.026	-0.020
Q1 , Q3	-0.065 , -0.009	-0.039 , 0.037	-0.065 , -0.002	-0.034 , 0.019
Min, max	-0.277 , 0.073	-0.078 , 0.067	-0.206 , 0.049	-0.139 , 0.265
Week 6				
N	24	24	49	49
Mean ± SD	0.111 ± 0.085	0.868 ± 0.042	0.145 ± 0.081	0.884 ± 0.047
95% Confidence interval for mean	0.075 , 0.146	0.850 , 0.886	0.121 , 0.168	0.870 , 0.897
Median	0.089	0.872	0.149	0.886
Q1 , Q3	0.064 , 0.141	0.845 , 0.887	0.066 , 0.199	0.865 , 0.920
Min, max	0.027 , 0.435	0.758 , 0.950	0.022 , 0.339	0.752 , 0.957
Change from Baseline (Day 0)				
N	23	23	48	48
Mean ± SD	-0.094 ± 0.070	0.035 ± 0.055	-0.063 ± 0.052	-0.004 ± 0.060
95% Confidence interval for mean	-0.124 , -0.064	0.011 , 0.059	-0.079 , -0.048	-0.021 , 0.014
Median	-0.084	0.036	-0.056	-0.002
Q1 , Q3	-0.135 , -0.046	-0.006 , 0.068	-0.101 , -0.034	-0.030 , 0.025
Min, max	-0.242 , 0.043	-0.083 , 0.154	-0.217 , 0.035	-0.138 , 0.272

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

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.9.1: Cutometer measurements (Intent-to-treat population)
(Part 2 of 4)

Cutometer measurements[1] (N_{ITT} = 58)	LCL, Skin tone R0 [mm]	LCL, Skin elasticity R2 [ratio]	PR, Skin tone R0 [mm]	PR, Skin elasticity R2 [ratio]
Day 0				
N	24	24	50	50
Mean ± SD	0.206 ± 0.072	0.835 ± 0.046	0.205 ± 0.090	0.887 ± 0.051
95% Confidence interval for mean	0.175 , 0.237	0.815 , 0.854	0.180 , 0.231	0.872 , 0.901
Median	0.201	0.838	0.200	0.892
Q1 , Q3	0.149 , 0.244	0.812 , 0.872	0.133 , 0.280	0.866 , 0.916
Min, max	0.087 , 0.392	0.731 , 0.909	0.040 , 0.393	0.609 , 0.955
Week 8				
N	24	25	51	52
Mean ± SD	0.087 ± 0.078	0.860 ± 0.047	0.116 ± 0.078	0.890 ± 0.044
95% Confidence interval for mean	0.054 , 0.120	0.841 , 0.879	0.094 , 0.138	0.877 , 0.902
Median	0.067	0.873	0.122	0.890
Q1 , Q3	0.042 , 0.105	0.822 , 0.889	0.049 , 0.157	0.865 , 0.919
Min, max	0.022 , 0.399	0.768 , 0.945	0.011 , 0.339	0.792 , 0.967
Change from Baseline (Day 0)				
N	23	23	50	50
Mean ± SD	-0.117 ± 0.072	0.023 ± 0.047	-0.088 ± 0.052	0.004 ± 0.052
95% Confidence interval for mean	-0.149 , -0.086	0.003 , 0.044	-0.103 , -0.073	-0.011 , 0.018
Median	-0.108	0.019	-0.081	0.004
Q1 , Q3	-0.173 , -0.065	-0.008 , 0.063	-0.112 , -0.049	-0.027 , 0.031
Min, max	-0.295 , 0.007	-0.064 , 0.102	-0.245 , 0.018	-0.090 , 0.246
Week 12				
N	21	21	48	48
Mean ± SD	0.118 ± 0.082	0.871 ± 0.043	0.129 ± 0.077	0.896 ± 0.059
95% Confidence interval for mean	0.081 , 0.155	0.851 , 0.891	0.106 , 0.151	0.879 , 0.913
Median	0.098	0.874	0.122	0.906
Q1 , Q3	0.059 , 0.141	0.850 , 0.898	0.087 , 0.157	0.890 , 0.921
Min, max	0.018 , 0.372	0.771 , 0.961	0.007 , 0.343	0.652 , 0.969
Change from Baseline (Day 0)				
N	20	20	47	47
Mean ± SD	-0.089 ± 0.087	0.043 ± 0.060	-0.077 ± 0.080	0.009 ± 0.073
95% Confidence interval for mean	-0.130 , -0.048	0.015 , 0.071	-0.101 , -0.053	-0.013 , 0.030
Median	-0.113	0.037	-0.085	0.014
Q1 , Q3	-0.154 , -0.017	-0.002 , 0.083	-0.134 , -0.036	-0.017 , 0.047
Min, max	-0.227 , 0.095	-0.086 , 0.147	-0.259 , 0.144	-0.232 , 0.287

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

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.9.1: Cutometer measurements (Intent-to-treat population)
(Part 3 of 4)

Cutometer measurements[1] (N_{ITT} = 58)	LCL, Skin tone R0 [mm]	LCL, Skin elasticity R2 [ratio]	PR, Skin tone R0 [mm]	PR, Skin elasticity R2 [ratio]
Day 0				
N	24	24	50	50
Mean ± SD	0.206 ± 0.072	0.835 ± 0.046	0.205 ± 0.090	0.887 ± 0.051
95% Confidence interval for mean	0.175 , 0.237	0.815 , 0.854	0.180 , 0.231	0.872 , 0.901
Median	0.201	0.838	0.200	0.892
Q1 , Q3	0.149 , 0.244	0.812 , 0.872	0.133 , 0.280	0.866 , 0.916
Min, max	0.087 , 0.392	0.731 , 0.909	0.040 , 0.393	0.609 , 0.955
Week 16				
N	24	24	50	50
Mean ± SD	0.170 ± 0.056	0.864 ± 0.049	0.124 ± 0.043	0.889 ± 0.053
95% Confidence interval for mean	0.147 , 0.194	0.843 , 0.885	0.112 , 0.137	0.874 , 0.904
Median	0.180	0.867	0.121	0.898
Q1 , Q3	0.124 , 0.205	0.829 , 0.895	0.086 , 0.155	0.864 , 0.923
Min, max	0.087 , 0.287	0.783 , 0.984	0.047 , 0.223	0.686 , 0.980
Change from Baseline (Day 0)				
N	23	23	49	49
Mean ± SD	-0.038 ± 0.074	0.028 ± 0.064	-0.083 ± 0.084	0.003 ± 0.067
95% Confidence interval for mean	-0.070 , -0.006	-0.000 , 0.055	-0.107 , -0.059	-0.016 , 0.022
Median	-0.036	0.031	-0.091	0.010
Q1 , Q3	-0.100 , 0.014	-0.023 , 0.049	-0.146 , -0.019	-0.029 , 0.040
Min, max	-0.172 , 0.094	-0.090 , 0.183	-0.259 , 0.093	-0.217 , 0.237
Week 24				
N	5	5	9	9
Mean ± SD	0.136 ± 0.041	0.806 ± 0.089	0.148 ± 0.042	0.896 ± 0.042
95% Confidence interval for mean	0.086 , 0.187	0.696 , 0.916	0.116 , 0.180	0.863 , 0.928
Median	0.147	0.825	0.146	0.881
Q1 , Q3	0.125 , 0.156	0.793 , 0.868	0.110 , 0.185	0.868 , 0.912
Min, max	0.073 , 0.181	0.661 , 0.884	0.087 , 0.203	0.850 , 0.976
Change from Baseline (Day 0)				
N	5	5	9	9
Mean ± SD	-0.062 ± 0.046	-0.020 ± 0.070	-0.012 ± 0.104	0.008 ± 0.045
95% Confidence interval for mean	-0.120 , -0.005	-0.107 , 0.067	-0.092 , 0.068	-0.026 , 0.043
Median	-0.086	0.013	-0.024	0.017
Q1 , Q3	-0.097 , -0.013	-0.026 , 0.017	-0.100 , 0.073	-0.027 , 0.046
Min, max	-0.104 , -0.012	-0.139 , 0.034	-0.156 , 0.125	-0.055 , 0.067

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

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.9.1: Cutometer measurements (Intent-to-treat population)
(Part 4 of 4)

Cutometer measurements[1] (N_{ITT} = 58)	LCL, Skin tone R0 [mm]	LCL, Skin elasticity R2 [ratio]	PR, Skin tone R0 [mm]	PR, Skin elasticity R2 [ratio]
Day 0				
N	24	24	50	50
Mean ± SD	0.206 ± 0.072	0.835 ± 0.046	0.205 ± 0.090	0.887 ± 0.051
95% Confidence interval for mean	0.175 , 0.237	0.815 , 0.854	0.180 , 0.231	0.872 , 0.901
Median	0.201	0.838	0.200	0.892
Q1 , Q3	0.149 , 0.244	0.812 , 0.872	0.133 , 0.280	0.866 , 0.916
Min, max	0.087 , 0.392	0.731 , 0.909	0.040 , 0.393	0.609 , 0.955
Week 36				
N	1	1	5	5
Mean ± SD	0.084	0.832	0.090 ± 0.024	0.916 ± 0.015
95% Confidence interval for mean	- , -	- , -	0.060 , 0.119	0.898 , 0.935
Median	0.084	0.832	0.074	0.915
Q1 , Q3	0.084 , 0.084	0.832 , 0.832	0.073 , 0.105	0.905 , 0.929
Min, max	0.084 , 0.084	0.832 , 0.832	0.072 , 0.125	0.898 , 0.933
Change from Baseline (Day 0)				
N	1	1	5	5
Mean ± SD	-0.093	0.020	-0.120 ± 0.047	0.035 ± 0.031
95% Confidence interval for mean	- , -	- , -	-0.179 , -0.061	-0.004 , 0.074
Median	-0.093	0.020	-0.108	0.026
Q1 , Q3	-0.093 , -0.093	0.020 , 0.020	-0.128 , -0.092	0.014 , 0.051
Min, max	-0.093 , -0.093	0.020 , 0.020	-0.198 , -0.076	0.003 , 0.081

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

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.9.2: Cutometer measurements - Baseline by visit (Intent-to-treat population)
(Part 1 of 4)

Cutometer measurements[1] (N_{ITT} = 58)	LCL, Skin tone R0 [mm]	LCL, Skin elasticity R2 [ratio]	PR, Skin tone R0 [mm]	PR, Skin elasticity R2 [ratio]
Baseline to Week 3				
N	21	23	48	49
Mean ± SD	0.205 ± 0.077	0.840 ± 0.047	0.208 ± 0.090	0.886 ± 0.052
95% Confidence interval for mean	0.169 , 0.240	0.819 , 0.860	0.182 , 0.235	0.871 , 0.901
Median	0.193	0.849	0.201	0.893
Q1 , Q3	0.143 , 0.246	0.813 , 0.878	0.149 , 0.280	0.864 , 0.916
Min, max	0.087 , 0.392	0.731 , 0.909	0.040 , 0.393	0.609 , 0.955
Week 3				
N	21	23	48	49
Mean ± SD	0.161 ± 0.087	0.840 ± 0.041	0.171 ± 0.091	0.881 ± 0.041
95% Confidence interval for mean	0.121 , 0.201	0.822 , 0.857	0.145 , 0.198	0.869 , 0.893
Median	0.160	0.847	0.171	0.884
Q1 , Q3	0.107 , 0.191	0.816 , 0.879	0.078 , 0.226	0.855 , 0.910
Min, max	0.056 , 0.465	0.736 , 0.888	0.023 , 0.369	0.787 , 0.968
Change from Baseline				
N	21	23	48	49
Mean ± SD	-0.044 ± 0.080	0.000 ± 0.044	-0.037 ± 0.052	-0.005 ± 0.058
95% Confidence interval for mean	-0.080 , -0.007	-0.019 , 0.019	-0.052 , -0.022	-0.022 , 0.011
Median	-0.031	-0.009	-0.026	-0.020
Q1 , Q3	-0.065 , -0.009	-0.039 , 0.037	-0.065 , -0.002	-0.034 , 0.019
Min, max	-0.277 , 0.073	-0.078 , 0.067	-0.206 , 0.049	-0.139 , 0.265
Baseline to Week 6				
N	23	23	48	48
Mean ± SD	0.206 ± 0.074	0.832 ± 0.046	0.210 ± 0.089	0.887 ± 0.052
95% Confidence interval for mean	0.174 , 0.238	0.813 , 0.852	0.184 , 0.236	0.872 , 0.902
Median	0.205	0.835	0.201	0.892
Q1 , Q3	0.143 , 0.246	0.812 , 0.867	0.163 , 0.280	0.866 , 0.917
Min, max	0.087 , 0.392	0.731 , 0.909	0.040 , 0.393	0.609 , 0.955
Week 6				
N	23	23	48	48
Mean ± SD	0.113 ± 0.086	0.867 ± 0.043	0.147 ± 0.081	0.884 ± 0.048
95% Confidence interval for mean	0.076 , 0.150	0.849 , 0.886	0.123 , 0.170	0.870 , 0.898
Median	0.091	0.872	0.149	0.886
Q1 , Q3	0.064 , 0.152	0.844 , 0.890	0.068 , 0.200	0.864 , 0.921
Min, max	0.027 , 0.435	0.758 , 0.950	0.022 , 0.339	0.752 , 0.957
Change from Baseline				
N	23	23	48	48
Mean ± SD	-0.094 ± 0.070	0.035 ± 0.055	-0.063 ± 0.052	-0.004 ± 0.060
95% Confidence interval for mean	-0.124 , -0.064	0.011 , 0.059	-0.079 , -0.048	-0.021 , 0.014
Median	-0.084	0.036	-0.056	-0.002
Q1 , Q3	-0.135 , -0.046	-0.006 , 0.068	-0.101 , -0.034	-0.030 , 0.025
Min, max	-0.242 , 0.043	-0.083 , 0.154	-0.217 , 0.035	-0.138 , 0.272

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

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.9.2: Cutometer measurements - Baseline by visit (Intent-to-treat population)
(Part 2 of 4)

Cutometer measurements[1] (N_{ITT} = 58)	LCL, Skin tone R0 [mm]	LCL, Skin elasticity R2 [ratio]	PR, Skin tone R0 [mm]	PR, Skin elasticity R2 [ratio]
Baseline to Week 8				
N	23	23	50	50
Mean ± SD	0.206 ± 0.074	0.836 ± 0.047	0.205 ± 0.090	0.887 ± 0.051
95% Confidence interval for mean	0.174 , 0.238	0.815 , 0.856	0.180 , 0.231	0.872 , 0.901
Median	0.197	0.841	0.200	0.892
Q1 , Q3	0.143 , 0.246	0.812 , 0.878	0.133 , 0.280	0.866 , 0.916
Min, max	0.087 , 0.392	0.731 , 0.909	0.040 , 0.393	0.609 , 0.955
Week 8				
N	23	23	50	50
Mean ± SD	0.088 ± 0.079	0.859 ± 0.049	0.117 ± 0.078	0.890 ± 0.045
95% Confidence interval for mean	0.054 , 0.123	0.838 , 0.880	0.095 , 0.139	0.878 , 0.903
Median	0.069	0.870	0.122	0.892
Q1 , Q3	0.038 , 0.118	0.821 , 0.902	0.051 , 0.157	0.863 , 0.920
Min, max	0.022 , 0.399	0.768 , 0.945	0.011 , 0.339	0.792 , 0.967
Change from Baseline				
N	23	23	50	50
Mean ± SD	-0.117 ± 0.072	0.023 ± 0.047	-0.088 ± 0.052	0.004 ± 0.052
95% Confidence interval for mean	-0.149 , -0.086	0.003 , 0.044	-0.103 , -0.073	-0.011 , 0.018
Median	-0.108	0.019	-0.081	0.004
Q1 , Q3	-0.173 , -0.065	-0.008 , 0.063	-0.112 , -0.049	-0.027 , 0.031
Min, max	-0.295 , 0.007	-0.064 , 0.102	-0.245 , 0.018	-0.090 , 0.246
Baseline to Week 12				
N	20	20	47	47
Mean ± SD	0.210 ± 0.079	0.829 ± 0.047	0.208 ± 0.089	0.888 ± 0.053
95% Confidence interval for mean	0.173 , 0.247	0.807 , 0.851	0.182 , 0.234	0.872 , 0.903
Median	0.218	0.827	0.201	0.895
Q1 , Q3	0.143 , 0.252	0.808 , 0.859	0.161 , 0.280	0.864 , 0.918
Min, max	0.087 , 0.392	0.731 , 0.909	0.040 , 0.393	0.609 , 0.955
Week 12				
N	20	20	47	47
Mean ± SD	0.121 ± 0.082	0.872 ± 0.044	0.131 ± 0.076	0.896 ± 0.059
95% Confidence interval for mean	0.083 , 0.160	0.852 , 0.893	0.109 , 0.154	0.879 , 0.914
Median	0.105	0.877	0.122	0.906
Q1 , Q3	0.064 , 0.143	0.852 , 0.900	0.091 , 0.158	0.892 , 0.921
Min, max	0.018 , 0.372	0.771 , 0.961	0.007 , 0.343	0.652 , 0.969
Change from Baseline				
N	20	20	47	47
Mean ± SD	-0.089 ± 0.087	0.043 ± 0.060	-0.077 ± 0.080	0.009 ± 0.073
95% Confidence interval for mean	-0.130 , -0.048	0.015 , 0.071	-0.101 , -0.053	-0.013 , 0.030
Median	-0.113	0.037	-0.085	0.014
Q1 , Q3	-0.154 , -0.017	-0.002 , 0.083	-0.134 , -0.036	-0.017 , 0.047
Min, max	-0.227 , 0.095	-0.086 , 0.147	-0.259 , 0.144	-0.232 , 0.287

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

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.9.2: Cutometer measurements - Baseline by visit (Intent-to-treat population)
(Part 4 of 4)

Cutometer measurements[1] (N_{ITT} = 58)	LCL, Skin tone R0 [mm]	LCL, Skin elasticity R2 [ratio]	PR, Skin tone R0 [mm]	PR, Skin elasticity R2 [ratio]
Baseline to Week 36				
N	1	1	5	5
Mean ± SD	0.177	0.812	0.210 ± 0.054	0.881 ± 0.022
95% Confidence interval for mean	- , -	- , -	0.143 , 0.277	0.854 , 0.908
Median	0.177	0.812	0.200	0.891
Q1 , Q3	0.177 , 0.177	0.812 , 0.812	0.180 , 0.202	0.864 , 0.895
Min, max	0.177 , 0.177	0.812 , 0.812	0.165 , 0.302	0.853 , 0.902
Week 36				
N	1	1	5	5
Mean ± SD	0.084	0.832	0.090 ± 0.024	0.916 ± 0.015
95% Confidence interval for mean	- , -	- , -	0.060 , 0.119	0.898 , 0.935
Median	0.084	0.832	0.074	0.915
Q1 , Q3	0.084 , 0.084	0.832 , 0.832	0.073 , 0.105	0.905 , 0.929
Min, max	0.084 , 0.084	0.832 , 0.832	0.072 , 0.125	0.898 , 0.933
Change from Baseline				
N	1	1	5	5
Mean ± SD	-0.093	0.020	-0.120 ± 0.047	0.035 ± 0.031
95% Confidence interval for mean	- , -	- , -	-0.179 , -0.061	-0.004 , 0.074
Median	-0.093	0.020	-0.108	0.026
Q1 , Q3	-0.093 , -0.093	0.020 , 0.020	-0.128 , -0.092	0.014 , 0.051
Min, max	-0.093 , -0.093	0.020 , 0.020	-0.198 , -0.076	0.003 , 0.081

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

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.9.2: Cutometer measurements - Baseline by visit (Intent-to-treat population)
(Part 3 of 4)

Cutometer measurements[1] (N_{ITT} = 58)	LCL, Skin tone R0 [mm]	LCL, Skin elasticity R2 [ratio]	PR, Skin tone R0 [mm]	PR, Skin elasticity R2 [ratio]
Baseline to Week 16				
N	23	23	49	49
Mean ± SD	0.206 ± 0.074	0.836 ± 0.047	0.207 ± 0.090	0.887 ± 0.052
95% Confidence interval for mean	0.174 , 0.238	0.816 , 0.856	0.182 , 0.233	0.873 , 0.902
Median	0.197	0.841	0.201	0.893
Q1 , Q3	0.143 , 0.246	0.812 , 0.878	0.161 , 0.280	0.867 , 0.916
Min, max	0.087 , 0.392	0.731 , 0.909	0.040 , 0.393	0.609 , 0.955
Week 16				
N	23	23	49	49
Mean ± SD	0.168 ± 0.056	0.863 ± 0.051	0.124 ± 0.044	0.891 ± 0.052
95% Confidence interval for mean	0.144 , 0.192	0.842 , 0.885	0.112 , 0.137	0.876 , 0.906
Median	0.175	0.866	0.120	0.900
Q1 , Q3	0.123 , 0.201	0.826 , 0.895	0.086 , 0.155	0.865 , 0.923
Min, max	0.087 , 0.287	0.783 , 0.984	0.047 , 0.223	0.686 , 0.980
Change from Baseline				
N	23	23	49	49
Mean ± SD	-0.038 ± 0.074	0.028 ± 0.064	-0.083 ± 0.084	0.003 ± 0.067
95% Confidence interval for mean	-0.070 , -0.006	-0.000 , 0.055	-0.107 , -0.059	-0.016 , 0.022
Median	-0.036	0.031	-0.091	0.010
Q1 , Q3	-0.100 , 0.014	-0.023 , 0.049	-0.146 , -0.019	-0.029 , 0.040
Min, max	-0.172 , 0.094	-0.090 , 0.183	-0.259 , 0.093	-0.217 , 0.237
Baseline to Week 24				
N	5	5	9	9
Mean ± SD	0.199 ± 0.033	0.827 ± 0.051	0.160 ± 0.075	0.888 ± 0.019
95% Confidence interval for mean	0.158 , 0.240	0.763 , 0.890	0.102 , 0.217	0.873 , 0.902
Median	0.193	0.812	0.165	0.891
Q1 , Q3	0.177 , 0.222	0.800 , 0.835	0.130 , 0.200	0.880 , 0.902
Min, max	0.160 , 0.241	0.776 , 0.909	0.046 , 0.302	0.853 , 0.909
Week 24				
N	5	5	9	9
Mean ± SD	0.136 ± 0.041	0.806 ± 0.089	0.148 ± 0.042	0.896 ± 0.042
95% Confidence interval for mean	0.086 , 0.187	0.696 , 0.916	0.116 , 0.180	0.863 , 0.928
Median	0.147	0.825	0.146	0.881
Q1 , Q3	0.125 , 0.156	0.793 , 0.868	0.110 , 0.185	0.868 , 0.912
Min, max	0.073 , 0.181	0.661 , 0.884	0.087 , 0.203	0.850 , 0.976
Change from Baseline				
N	5	5	9	9
Mean ± SD	-0.062 ± 0.046	-0.020 ± 0.070	-0.012 ± 0.104	0.008 ± 0.045
95% Confidence interval for mean	-0.120 , -0.005	-0.107 , 0.067	-0.092 , 0.068	-0.026 , 0.043
Median	-0.086	0.013	-0.024	0.017
Q1 , Q3	-0.097 , -0.013	-0.026 , 0.017	-0.100 , 0.073	-0.027 , 0.046
Min, max	-0.104 , -0.012	-0.139 , 0.034	-0.156 , 0.125	-0.055 , 0.067

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

Source: CPH-401-201364_AppA_30JAN20.rtf

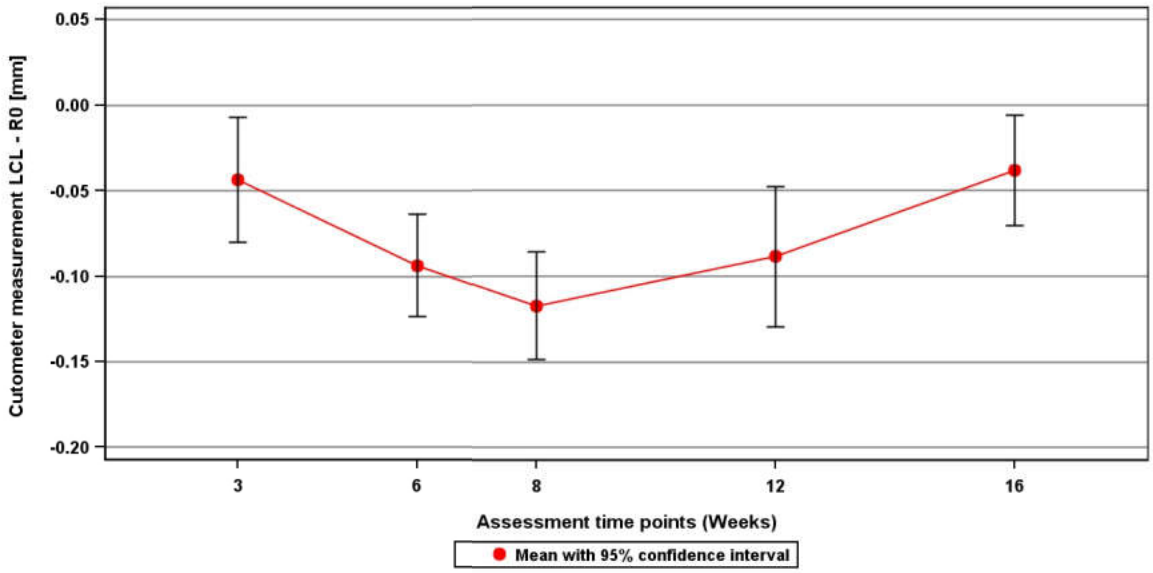
Table 2.9.3: Cutometer measurements - Statistical tests (Intent-to-treat population)
(Part 1 of 1)

Cutometer - Statistical tests	LCL, Skin tone R0 [mm]	LCL, Skin elasticity R2 [ratio]	PR, Skin tone R0 [mm]	PR, Skin elasticity R2 [ratio]
Week 3				
n	21	23	48	49
Mean change ± SD	-0.044 ± 0.080	0.000 ± 0.044	-0.037 ± 0.052	-0.005 ± 0.058
p-value of one-sample t-Test[1]	0.021	0.993	<0.001	0.530
Week 6				
n	23	23	48	48
Mean change ± SD	-0.094 ± 0.070	0.035 ± 0.055	-0.063 ± 0.052	-0.004 ± 0.060
p-value of one-sample t-Test[1]	<0.001	0.006	<0.001	0.683
Week 8				
n	23	23	50	50
Mean change ± SD	-0.117 ± 0.072	0.023 ± 0.047	-0.088 ± 0.052	0.004 ± 0.052
p-value of one-sample t-Test[1]	<0.001	0.025	<0.001	0.631
Week 12				
n	20	20	47	47
Mean change ± SD	-0.089 ± 0.087	0.043 ± 0.060	-0.077 ± 0.080	0.009 ± 0.073
p-value of one-sample t-Test[1]	<0.001	0.005	<0.001	0.424
Week 16				
n	23	23	49	49
Mean change ± SD	-0.038 ± 0.074	0.028 ± 0.064	-0.083 ± 0.084	0.003 ± 0.067
p-value of one-sample t-Test[1]	0.022	0.052	<0.001	0.737
Week 24				
n	5	5	9	9
Mean change ± SD	-0.062 ± 0.046	-0.020 ± 0.070	-0.012 ± 0.104	0.008 ± 0.045
p-value of one-sample t-Test[1]	0.039	0.555	0.743	0.602
Week 36				
n	1	1	5	5
Mean change ± SD	-0.093	0.020	-0.120 ± 0.047	0.035 ± 0.031
p-value of one-sample t-Test[1]	-	-	0.005	0.066

[1] Test for change to Baseline equal to Zero

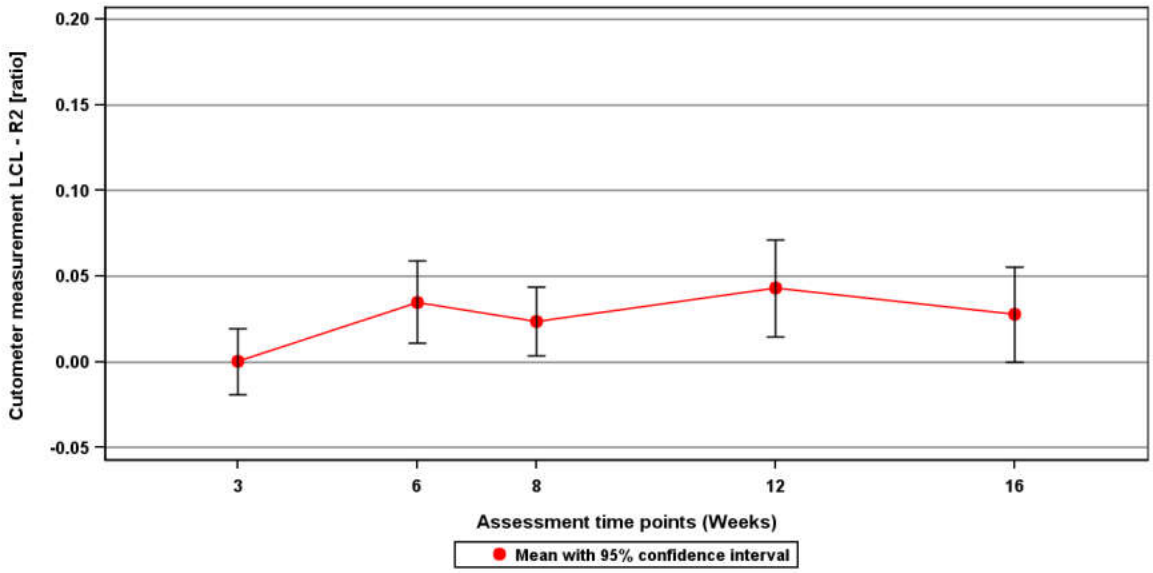
Source: CPH-401-201364_AppA_30JAN20.rtf

Figure 1: LCL Skin tone R0 [mm] - Change from Baseline (Intent-to-treat population)



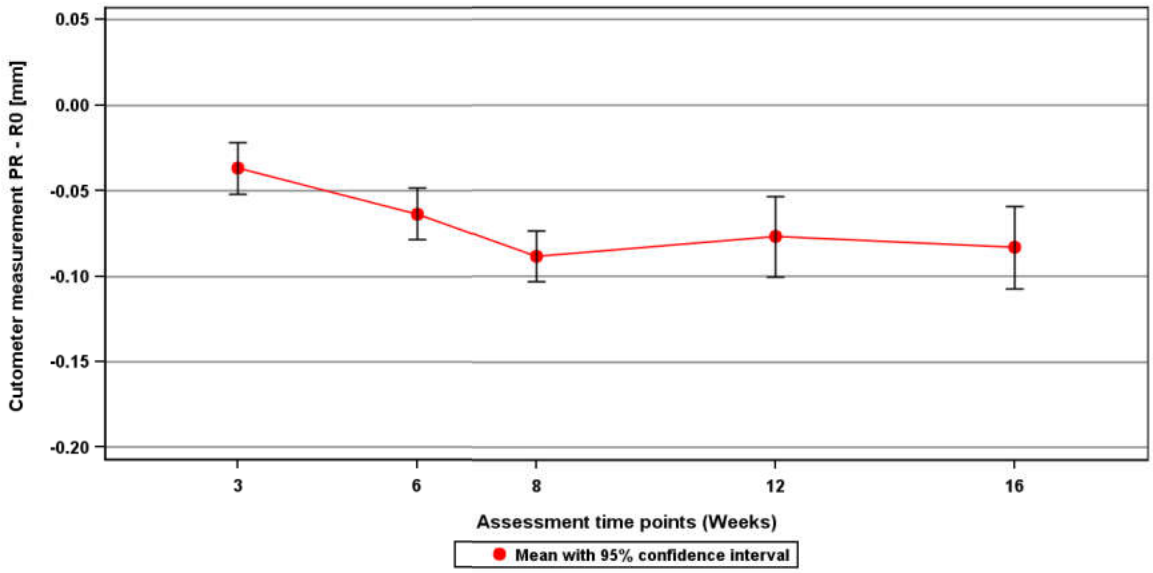
Source: CPH-401-201364_AppA_30JAN20.rtf

Figure 2: LCL Skin elasticity R2 [ratio] - Change from Baseline (Intent-to-treat population)



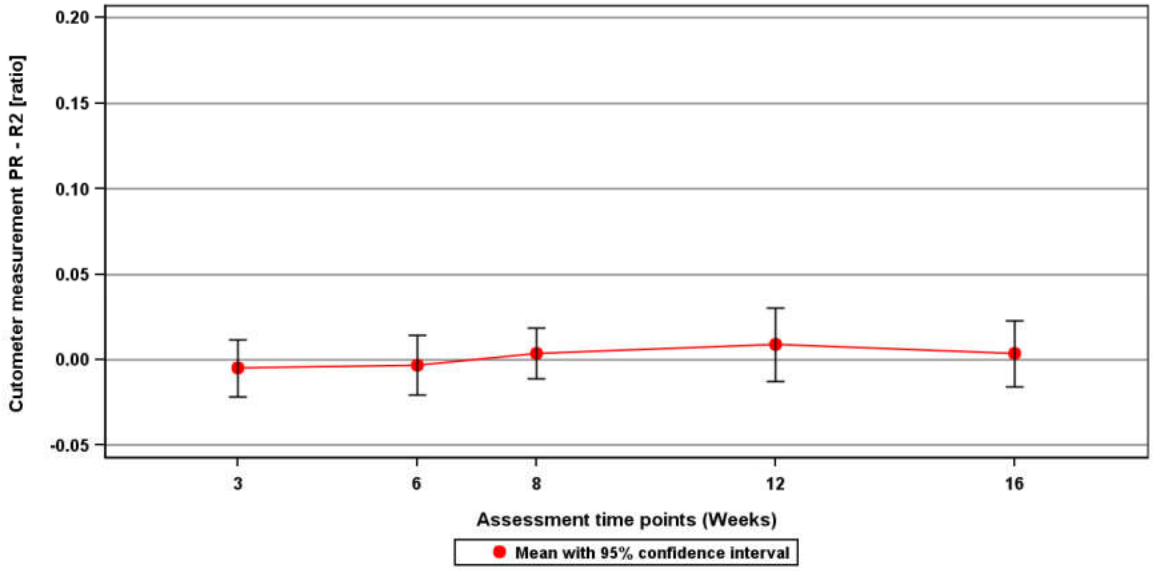
Source: CPH-401-201364_AppA_30JAN20.rtf

Figure 3: PR Skin tone R0 [mm] - Change from Baseline (Intent-to-treat population)



Source: CPH-401-201364_AppA_30JAN20.rtf

Figure 4: PR Skin elasticity R2 [ratio] - Change from Baseline (Intent-to-treat population)



Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.10.1: Cutometer measurements (Per-protocol population)
(Part 1 of 4)

Cutometer measurements[1] (N_{PP} = 47)	LCL, Skin tone R0 [mm]	LCL, Skin elasticity R2 [ratio]	PR, Skin tone R0 [mm]	PR, Skin elasticity R2 [ratio]
Day 0				
N	15	15	39	39
Mean ± SD	0.213 ± 0.074	0.831 ± 0.052	0.215 ± 0.085	0.886 ± 0.055
95% Confidence interval for mean	0.171 , 0.254	0.802 , 0.860	0.188 , 0.243	0.869 , 0.904
Median	0.213	0.835	0.217	0.893
Q1 , Q3	0.155 , 0.246	0.812 , 0.878	0.167 , 0.281	0.864 , 0.918
Min, max	0.087 , 0.392	0.731 , 0.909	0.046 , 0.393	0.609 , 0.955
Week 3				
N	15	15	40	40
Mean ± SD	0.182 ± 0.090	0.833 ± 0.032	0.174 ± 0.079	0.884 ± 0.036
95% Confidence interval for mean	0.132 , 0.232	0.815 , 0.851	0.149 , 0.199	0.873 , 0.896
Median	0.179	0.843	0.174	0.882
Q1 , Q3	0.119 , 0.215	0.807 , 0.860	0.101 , 0.222	0.858 , 0.915
Min, max	0.089 , 0.465	0.778 , 0.879	0.051 , 0.349	0.787 , 0.946
Change from Baseline (Day 0)				
N	14	14	39	39
Mean ± SD	-0.029 ± 0.058	-0.001 ± 0.044	-0.037 ± 0.055	-0.003 ± 0.063
95% Confidence interval for mean	-0.063 , 0.004	-0.026 , 0.025	-0.055 , -0.020	-0.023 , 0.018
Median	-0.032	-0.013	-0.028	-0.019
Q1 , Q3	-0.065 , 0.007	-0.038 , 0.047	-0.061 , -0.001	-0.035 , 0.024
Min, max	-0.136 , 0.073	-0.058 , 0.067	-0.206 , 0.049	-0.139 , 0.265
Week 6				
N	16	16	40	40
Mean ± SD	0.133 ± 0.095	0.874 ± 0.034	0.157 ± 0.079	0.887 ± 0.043
95% Confidence interval for mean	0.082 , 0.183	0.855 , 0.892	0.132 , 0.182	0.874 , 0.901
Median	0.106	0.872	0.160	0.887
Q1 , Q3	0.071 , 0.173	0.860 , 0.887	0.083 , 0.202	0.872 , 0.917
Min, max	0.027 , 0.435	0.803 , 0.950	0.043 , 0.339	0.759 , 0.957
Change from Baseline (Day 0)				
N	15	15	39	39
Mean ± SD	-0.075 ± 0.065	0.043 ± 0.060	-0.065 ± 0.054	0.001 ± 0.061
95% Confidence interval for mean	-0.111 , -0.039	0.009 , 0.076	-0.083 , -0.048	-0.019 , 0.021
Median	-0.082	0.044	-0.056	0.005
Q1 , Q3	-0.127 , -0.011	0.009 , 0.069	-0.105 , -0.035	-0.025 , 0.029
Min, max	-0.192 , 0.043	-0.083 , 0.154	-0.217 , 0.035	-0.109 , 0.272

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

Partial exclusions from statistical analysis due to deviation from required climatic conditions: Day 0 (2 subjects), Day 0 (2 subjects), Week 3 (2 subjects), Week 6 (1 subjects), Week 12 (16 subjects), Week 16 (18 subjects), Week 24 (5 subjects)

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.10.1: Cutometer measurements (Per-protocol population)
(Part 2 of 4)

Cutometer measurements[1] (N_{PP} = 47)	LCL, Skin tone R0 [mm]	LCL, Skin elasticity R2 [ratio]	PR, Skin tone R0 [mm]	PR, Skin elasticity R2 [ratio]
Day 0				
N	15	15	39	39
Mean ± SD	0.213 ± 0.074	0.831 ± 0.052	0.215 ± 0.085	0.886 ± 0.055
95% Confidence interval for mean	0.171 , 0.254	0.802 , 0.860	0.188 , 0.243	0.869 , 0.904
Median	0.213	0.835	0.217	0.893
Q1 , Q3	0.155 , 0.246	0.812 , 0.878	0.167 , 0.281	0.864 , 0.918
Min, max	0.087 , 0.392	0.731 , 0.909	0.046 , 0.393	0.609 , 0.955
Week 8				
N	15	16	42	43
Mean ± SD	0.110 ± 0.091	0.860 ± 0.048	0.127 ± 0.076	0.892 ± 0.043
95% Confidence interval for mean	0.060 , 0.160	0.834 , 0.885	0.104 , 0.151	0.879 , 0.905
Median	0.074	0.873	0.125	0.894
Q1 , Q3	0.061 , 0.138	0.817 , 0.891	0.051 , 0.158	0.866 , 0.920
Min, max	0.022 , 0.399	0.790 , 0.945	0.026 , 0.339	0.793 , 0.967
Change from Baseline (Day 0)				
N	14	14	41	41
Mean ± SD	-0.099 ± 0.065	0.026 ± 0.050	-0.091 ± 0.055	0.005 ± 0.055
95% Confidence interval for mean	-0.136 , -0.061	-0.003 , 0.055	-0.109 , -0.074	-0.012 , 0.022
Median	-0.098	0.028	-0.081	0.004
Q1 , Q3	-0.148 , -0.058	-0.007 , 0.065	-0.117 , -0.056	-0.027 , 0.031
Min, max	-0.225 , 0.007	-0.064 , 0.098	-0.245 , 0.018	-0.090 , 0.246
Week 12				
N	12	12	26	26
Mean ± SD	0.122 ± 0.092	0.871 ± 0.054	0.134 ± 0.092	0.898 ± 0.060
95% Confidence interval for mean	0.064 , 0.181	0.837 , 0.906	0.097 , 0.171	0.874 , 0.922
Median	0.088	0.881	0.116	0.906
Q1 , Q3	0.064 , 0.136	0.835 , 0.903	0.079 , 0.155	0.875 , 0.938
Min, max	0.054 , 0.372	0.771 , 0.961	0.015 , 0.343	0.652 , 0.969
Change from Baseline (Day 0)				
N	11	11	25	25
Mean ± SD	-0.090 ± 0.084	0.048 ± 0.072	-0.076 ± 0.082	0.016 ± 0.079
95% Confidence interval for mean	-0.146 , -0.033	-0.000 , 0.096	-0.110 , -0.042	-0.017 , 0.049
Median	-0.084	0.062	-0.068	0.014
Q1 , Q3	-0.159 , -0.015	-0.007 , 0.121	-0.113 , -0.035	-0.017 , 0.047
Min, max	-0.227 , 0.028	-0.086 , 0.147	-0.259 , 0.144	-0.193 , 0.287

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

Partial exclusions from statistical analysis due to deviation from required climatic conditions: Day 0 (2 subjects), Day 0 (2 subjects), Week 3 (2 subjects), Week 6 (1 subjects), Week 12 (16 subjects), Week 16 (18 subjects), Week 24 (5 subjects)

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.10.1: Cutometer measurements (Per-protocol population)
(Part 3 of 4)

Cutometer measurements[1] (N_{PP} = 47)	LCL, Skin tone R0 [mm]	LCL, Skin elasticity R2 [ratio]	PR, Skin tone R0 [mm]	PR, Skin elasticity R2 [ratio]
Day 0				
N	15	15	39	39
Mean ± SD	0.213 ± 0.074	0.831 ± 0.052	0.215 ± 0.085	0.886 ± 0.055
95% Confidence interval for mean	0.171 , 0.254	0.802 , 0.860	0.188 , 0.243	0.869 , 0.904
Median	0.213	0.835	0.217	0.893
Q1 , Q3	0.155 , 0.246	0.812 , 0.878	0.167 , 0.281	0.864 , 0.918
Min, max	0.087 , 0.392	0.731 , 0.909	0.046 , 0.393	0.609 , 0.955
Week 16				
N	15	15	25	25
Mean ± SD	0.195 ± 0.054	0.861 ± 0.048	0.137 ± 0.046	0.895 ± 0.049
95% Confidence interval for mean	0.165 , 0.225	0.834 , 0.888	0.118 , 0.156	0.874 , 0.915
Median	0.197	0.869	0.136	0.906
Q1 , Q3	0.161 , 0.227	0.818 , 0.895	0.096 , 0.173	0.868 , 0.930
Min, max	0.096 , 0.287	0.783 , 0.955	0.064 , 0.223	0.761 , 0.974
Change from Baseline (Day 0)				
N	14	14	24	24
Mean ± SD	-0.023 ± 0.076	0.028 ± 0.061	-0.067 ± 0.087	0.021 ± 0.066
95% Confidence interval for mean	-0.067 , 0.021	-0.007 , 0.063	-0.103 , -0.030	-0.007 , 0.049
Median	-0.013	0.027	-0.093	0.014
Q1 , Q3	-0.081 , 0.015	-0.023 , 0.060	-0.133 , 0.004	-0.026 , 0.053
Min, max	-0.172 , 0.094	-0.068 , 0.141	-0.208 , 0.093	-0.103 , 0.237
Week 24				
N	1	1	4	4
Mean ± SD	0.073	0.825	0.110 ± 0.023	0.884 ± 0.019
95% Confidence interval for mean	- , -	- , -	0.074 , 0.146	0.854 , 0.914
Median	0.073	0.825	0.106	0.878
Q1 , Q3	0.073 , 0.073	0.825 , 0.825	0.094 , 0.125	0.872 , 0.896
Min, max	0.073 , 0.073	0.825 , 0.825	0.087 , 0.141	0.868 , 0.912
Change from Baseline (Day 0)				
N	1	1	4	4
Mean ± SD	-0.104	0.013	-0.077 ± 0.039	0.007 ± 0.040
95% Confidence interval for mean	- , -	- , -	-0.140 , -0.014	-0.057 , 0.071
Median	-0.104	0.013	-0.085	-0.003
Q1 , Q3	-0.104 , -0.104	0.013 , 0.013	-0.107 , -0.047	-0.025 , 0.038
Min, max	-0.104 , -0.104	0.013 , 0.013	-0.114 , -0.024	-0.027 , 0.059

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

Partial exclusions from statistical analysis due to deviation from required climatic conditions: Day 0 (2 subjects), Day 0 (2 subjects), Week 3 (2 subjects), Week 6 (1 subjects), Week 12 (16 subjects), Week 16 (18 subjects), Week 24 (5 subjects)

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.10.1: Cutometer measurements (Per-protocol population)
(Part 4 of 4)

Cutometer measurements[1] (N_{PP} = 47)	LCL, Skin tone R0 [mm]	LCL, Skin elasticity R2 [ratio]	PR, Skin tone R0 [mm]	PR, Skin elasticity R2 [ratio]
Day 0				
N	15	15	39	39
Mean ± SD	0.213 ± 0.074	0.831 ± 0.052	0.215 ± 0.085	0.886 ± 0.055
95% Confidence interval for mean	0.171 , 0.254	0.802 , 0.860	0.188 , 0.243	0.869 , 0.904
Median	0.213	0.835	0.217	0.893
Q1 , Q3	0.155 , 0.246	0.812 , 0.878	0.167 , 0.281	0.864 , 0.918
Min, max	0.087 , 0.392	0.731 , 0.909	0.046 , 0.393	0.609 , 0.955
Week 36				
N	1	1	5	5
Mean ± SD	0.084	0.832	0.090 ± 0.024	0.916 ± 0.015
95% Confidence interval for mean	- , -	- , -	0.060 , 0.119	0.898 , 0.935
Median	0.084	0.832	0.074	0.915
Q1 , Q3	0.084 , 0.084	0.832 , 0.832	0.073 , 0.105	0.905 , 0.929
Min, max	0.084 , 0.084	0.832 , 0.832	0.072 , 0.125	0.898 , 0.933
Change from Baseline (Day 0)				
N	1	1	5	5
Mean ± SD	-0.093	0.020	-0.120 ± 0.047	0.035 ± 0.031
95% Confidence interval for mean	- , -	- , -	-0.179 , -0.061	-0.004 , 0.074
Median	-0.093	0.020	-0.108	0.026
Q1 , Q3	-0.093 , -0.093	0.020 , 0.020	-0.128 , -0.092	0.014 , 0.051
Min, max	-0.093 , -0.093	0.020 , 0.020	-0.198 , -0.076	0.003 , 0.081

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

Partial exclusions from statistical analysis due to deviation from required climatic conditions: Day 0 (2 subjects), Day 0 (2 subjects), Week 3 (2 subjects), Week 6 (1 subjects), Week 12 (16 subjects), Week 16 (18 subjects), Week 24 (5 subjects)

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.10.2: Cutometer measurements - Baseline by visit (Per-protocol population)
(Part 1 of 4)

Cutometer measurements[1] (N_{PP} = 47)	LCL, Skin tone R0 [mm]	LCL, Skin elasticity R2 [ratio]	PR, Skin tone R0 [mm]	PR, Skin elasticity R2 [ratio]
Baseline to Week 3				
N	14	14	39	39
Mean ± SD	0.212 ± 0.077	0.832 ± 0.054	0.214 ± 0.083	0.888 ± 0.055
95% Confidence interval for mean	0.168 , 0.257	0.800 , 0.863	0.187 , 0.241	0.870 , 0.906
Median	0.208	0.838	0.217	0.895
Q1 , Q3	0.155 , 0.246	0.812 , 0.878	0.167 , 0.280	0.867 , 0.918
Min, max	0.087 , 0.392	0.731 , 0.909	0.046 , 0.393	0.609 , 0.955
Week 3				
N	14	14	39	39
Mean ± SD	0.183 ± 0.094	0.831 ± 0.032	0.177 ± 0.078	0.885 ± 0.036
95% Confidence interval for mean	0.129 , 0.237	0.812 , 0.849	0.151 , 0.202	0.873 , 0.897
Median	0.180	0.839	0.176	0.885
Q1 , Q3	0.119 , 0.215	0.807 , 0.849	0.119 , 0.223	0.858 , 0.917
Min, max	0.089 , 0.465	0.778 , 0.879	0.051 , 0.349	0.787 , 0.946
Change from Baseline (Day 0)				
N	14	14	39	39
Mean ± SD	-0.029 ± 0.058	-0.001 ± 0.044	-0.037 ± 0.055	-0.003 ± 0.063
95% Confidence interval for mean	-0.063 , 0.004	-0.026 , 0.025	-0.055 , -0.020	-0.023 , 0.018
Median	-0.032	-0.013	-0.028	-0.019
Q1 , Q3	-0.065 , 0.007	-0.038 , 0.047	-0.061 , -0.001	-0.035 , 0.024
Min, max	-0.136 , 0.073	-0.058 , 0.067	-0.206 , 0.049	-0.139 , 0.265
Baseline to Week 6				
N	15	15	39	39
Mean ± SD	0.213 ± 0.074	0.831 ± 0.052	0.225 ± 0.086	0.886 ± 0.055
95% Confidence interval for mean	0.171 , 0.254	0.802 , 0.860	0.197 , 0.253	0.868 , 0.904
Median	0.213	0.835	0.225	0.893
Q1 , Q3	0.155 , 0.246	0.812 , 0.878	0.168 , 0.283	0.864 , 0.918
Min, max	0.087 , 0.392	0.731 , 0.909	0.046 , 0.393	0.609 , 0.955
Week 6				
N	15	15	39	39
Mean ± SD	0.137 ± 0.097	0.873 ± 0.035	0.160 ± 0.078	0.887 ± 0.043
95% Confidence interval for mean	0.084 , 0.191	0.854 , 0.893	0.135 , 0.185	0.873 , 0.901
Median	0.108	0.872	0.166	0.887
Q1 , Q3	0.078 , 0.178	0.857 , 0.890	0.088 , 0.205	0.872 , 0.920
Min, max	0.027 , 0.435	0.803 , 0.950	0.045 , 0.339	0.759 , 0.957
Change from Baseline (Day 0)				
N	15	15	39	39
Mean ± SD	-0.075 ± 0.065	0.043 ± 0.060	-0.065 ± 0.054	0.001 ± 0.061
95% Confidence interval for mean	-0.111 , -0.039	0.009 , 0.076	-0.083 , -0.048	-0.019 , 0.021
Median	-0.082	0.044	-0.056	0.005
Q1 , Q3	-0.127 , -0.011	0.009 , 0.069	-0.105 , -0.035	-0.025 , 0.029
Min, max	-0.192 , 0.043	-0.083 , 0.154	-0.217 , 0.035	-0.109 , 0.272

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

Partial exclusions from statistical analysis due to deviation from required climatic conditions: Day 0 (2 subjects), Day 0 (2 subjects), Week 3 (2 subjects), Week 6 (1 subjects), Week 12 (16 subjects), Week 16 (18 subjects), Week 24 (5 subjects)

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.10.2: Cutometer measurements - Baseline by visit (Per-protocol population)
(Part 2 of 4)

Cutometer measurements[1] (N_{PP} = 47)	LCL, Skin tone R0 [mm]	LCL, Skin elasticity R2 [ratio]	PR, Skin tone R0 [mm]	PR, Skin elasticity R2 [ratio]
Baseline to Week 8				
N	14	14	41	41
Mean ± SD	0.212 ± 0.077	0.832 ± 0.054	0.221 ± 0.087	0.888 ± 0.055
95% Confidence interval for mean	0.168 , 0.257	0.800 , 0.863	0.193 , 0.248	0.871 , 0.905
Median	0.208	0.838	0.222	0.895
Q1 , Q3	0.155 , 0.246	0.812 , 0.878	0.168 , 0.281	0.867 , 0.918
Min, max	0.087 , 0.392	0.731 , 0.909	0.046 , 0.393	0.609 , 0.955
Week 8				
N	14	14	41	41
Mean ± SD	0.114 ± 0.093	0.858 ± 0.051	0.129 ± 0.076	0.893 ± 0.043
95% Confidence interval for mean	0.060 , 0.168	0.828 , 0.887	0.105 , 0.153	0.880 , 0.907
Median	0.084	0.861	0.125	0.895
Q1 , Q3	0.064 , 0.138	0.814 , 0.906	0.062 , 0.158	0.866 , 0.920
Min, max	0.022 , 0.399	0.790 , 0.945	0.026 , 0.339	0.793 , 0.967
Change from Baseline (Day 0)				
N	14	14	41	41
Mean ± SD	-0.099 ± 0.065	0.026 ± 0.050	-0.091 ± 0.055	0.005 ± 0.055
95% Confidence interval for mean	-0.136 , -0.061	-0.003 , 0.055	-0.109 , -0.074	-0.012 , 0.022
Median	-0.098	0.028	-0.081	0.004
Q1 , Q3	-0.148 , -0.058	-0.007 , 0.065	-0.117 , -0.056	-0.027 , 0.031
Min, max	-0.225 , 0.007	-0.064 , 0.098	-0.245 , 0.018	-0.090 , 0.246
Baseline to Week 12				
N	11	11	25	25
Mean ± SD	0.218 ± 0.083	0.826 ± 0.058	0.215 ± 0.102	0.883 ± 0.066
95% Confidence interval for mean	0.162 , 0.274	0.787 , 0.866	0.173 , 0.257	0.856 , 0.910
Median	0.222	0.835	0.201	0.891
Q1 , Q3	0.143 , 0.246	0.776 , 0.881	0.133 , 0.295	0.864 , 0.923
Min, max	0.087 , 0.392	0.731 , 0.909	0.046 , 0.393	0.609 , 0.944
Week 12				
N	11	11	25	25
Mean ± SD	0.128 ± 0.094	0.874 ± 0.055	0.139 ± 0.091	0.899 ± 0.061
95% Confidence interval for mean	0.065 , 0.192	0.837 , 0.911	0.101 , 0.176	0.874 , 0.924
Median	0.094	0.882	0.118	0.906
Q1 , Q3	0.069 , 0.141	0.830 , 0.909	0.081 , 0.155	0.877 , 0.938
Min, max	0.054 , 0.372	0.771 , 0.961	0.015 , 0.343	0.652 , 0.969
Change from Baseline (Day 0)				
N	11	11	25	25
Mean ± SD	-0.090 ± 0.084	0.048 ± 0.072	-0.076 ± 0.082	0.016 ± 0.079
95% Confidence interval for mean	-0.146 , -0.033	-0.000 , 0.096	-0.110 , -0.042	-0.017 , 0.049
Median	-0.084	0.062	-0.068	0.014
Q1 , Q3	-0.159 , -0.015	-0.007 , 0.121	-0.113 , -0.035	-0.017 , 0.047
Min, max	-0.227 , 0.028	-0.086 , 0.147	-0.259 , 0.144	-0.193 , 0.287

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

Partial exclusions from statistical analysis due to deviation from required climatic conditions: Day 0 (2 subjects), Day 0 (2 subjects), Week 3 (2 subjects), Week 6 (1 subjects), Week 12 (16 subjects), Week 16 (18 subjects), Week 24 (5 subjects)

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.10.2: Cutometer measurements - Baseline by visit (Per-protocol population)
(Part 3 of 4)

Cutometer measurements[1] (N_{PP} = 47)	LCL, Skin tone R0 [mm]	LCL, Skin elasticity R2 [ratio]	PR, Skin tone R0 [mm]	PR, Skin elasticity R2 [ratio]
Baseline to Week 16				
N	14	14	24	24
Mean ± SD	0.215 ± 0.077	0.832 ± 0.054	0.204 ± 0.097	0.877 ± 0.064
95% Confidence interval for mean	0.171 , 0.259	0.801 , 0.863	0.163 , 0.245	0.850 , 0.904
Median	0.218	0.838	0.200	0.891
Q1 , Q3	0.155 , 0.246	0.813 , 0.878	0.107 , 0.281	0.865 , 0.914
Min, max	0.087 , 0.392	0.731 , 0.909	0.046 , 0.393	0.609 , 0.935
Week 16				
N	14	14	24	24
Mean ± SD	0.192 ± 0.055	0.860 ± 0.050	0.137 ± 0.047	0.898 ± 0.048
95% Confidence interval for mean	0.160 , 0.224	0.832 , 0.889	0.117 , 0.157	0.878 , 0.918
Median	0.196	0.869	0.136	0.908
Q1 , Q3	0.161 , 0.216	0.818 , 0.895	0.093 , 0.179	0.869 , 0.931
Min, max	0.096 , 0.287	0.783 , 0.955	0.064 , 0.223	0.761 , 0.974
Change from Baseline (Day 0)				
N	14	14	24	24
Mean ± SD	-0.023 ± 0.076	0.028 ± 0.061	-0.067 ± 0.087	0.021 ± 0.066
95% Confidence interval for mean	-0.067 , 0.021	-0.007 , 0.063	-0.103 , -0.030	-0.007 , 0.049
Median	-0.013	0.027	-0.093	0.014
Q1 , Q3	-0.081 , 0.015	-0.023 , 0.060	-0.133 , 0.004	-0.026 , 0.053
Min, max	-0.172 , 0.094	-0.068 , 0.141	-0.208 , 0.093	-0.103 , 0.237
Baseline to Week 24				
N	1	1	4	4
Mean ± SD	0.177	0.812	0.187 ± 0.017	0.878 ± 0.023
95% Confidence interval for mean	- , -	- , -	0.159 , 0.215	0.841 , 0.915
Median	0.177	0.812	0.190	0.878
Q1 , Q3	0.177 , 0.177	0.812 , 0.812	0.173 , 0.201	0.858 , 0.897
Min, max	0.177 , 0.177	0.812 , 0.812	0.165 , 0.202	0.853 , 0.902
Week 24				
N	1	1	4	4
Mean ± SD	0.073	0.825	0.110 ± 0.023	0.884 ± 0.019
95% Confidence interval for mean	- , -	- , -	0.074 , 0.146	0.854 , 0.914
Median	0.073	0.825	0.106	0.878
Q1 , Q3	0.073 , 0.073	0.825 , 0.825	0.094 , 0.125	0.872 , 0.896
Min, max	0.073 , 0.073	0.825 , 0.825	0.087 , 0.141	0.868 , 0.912
Change from Baseline (Day 0)				
N	1	1	4	4
Mean ± SD	-0.104	0.013	-0.077 ± 0.039	0.007 ± 0.040
95% Confidence interval for mean	- , -	- , -	-0.140 , -0.014	-0.057 , 0.071
Median	-0.104	0.013	-0.085	-0.003
Q1 , Q3	-0.104 , -0.104	0.013 , 0.013	-0.107 , -0.047	-0.025 , 0.038
Min, max	-0.104 , -0.104	0.013 , 0.013	-0.114 , -0.024	-0.027 , 0.059

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

Partial exclusions from statistical analysis due to deviation from required climatic conditions: Day 0 (2 subjects), Day 0 (2 subjects), Week 3 (2 subjects), Week 6 (1 subjects), Week 12 (16 subjects), Week 16 (18 subjects), Week 24 (5 subjects)

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.10.2: Cutometer measurements - Baseline by visit (Per-protocol population)
(Part 4 of 4)

Cutometer measurements[1] (N_{PP} = 47)	LCL, Skin tone R0 [mm]	LCL, Skin elasticity R2 [ratio]	PR, Skin tone R0 [mm]	PR, Skin elasticity R2 [ratio]
Baseline to Week 36				
N	1	1	5	5
Mean ± SD	0.177	0.812	0.210 ± 0.054	0.881 ± 0.022
95% Confidence interval for mean	- , -	- , -	0.143 , 0.277	0.854 , 0.908
Median	0.177	0.812	0.200	0.891
Q1 , Q3	0.177 , 0.177	0.812 , 0.812	0.180 , 0.202	0.864 , 0.895
Min, max	0.177 , 0.177	0.812 , 0.812	0.165 , 0.302	0.853 , 0.902
Week 36				
N	1	1	5	5
Mean ± SD	0.084	0.832	0.090 ± 0.024	0.916 ± 0.015
95% Confidence interval for mean	- , -	- , -	0.060 , 0.119	0.898 , 0.935
Median	0.084	0.832	0.074	0.915
Q1 , Q3	0.084 , 0.084	0.832 , 0.832	0.073 , 0.105	0.905 , 0.929
Min, max	0.084 , 0.084	0.832 , 0.832	0.072 , 0.125	0.898 , 0.933
Change from Baseline (Day 0)				
N	1	1	5	5
Mean ± SD	-0.093	0.020	-0.120 ± 0.047	0.035 ± 0.031
95% Confidence interval for mean	- , -	- , -	-0.179 , -0.061	-0.004 , 0.074
Median	-0.093	0.020	-0.108	0.026
Q1 , Q3	-0.093 , -0.093	0.020 , 0.020	-0.128 , -0.092	0.014 , 0.051
Min, max	-0.093 , -0.093	0.020 , 0.020	-0.198 , -0.076	0.003 , 0.081

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

Partial exclusions from statistical analysis due to deviation from required climatic conditions: Day 0 (2 subjects), Day 0 (2 subjects), Week 3 (2 subjects), Week 6 (1 subjects), Week 12 (16 subjects), Week 16 (18 subjects), Week 24 (5 subjects)

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.10.3: Cutometer measurements - Statistical tests (Per-protocol population)
(Part 1 of 1)

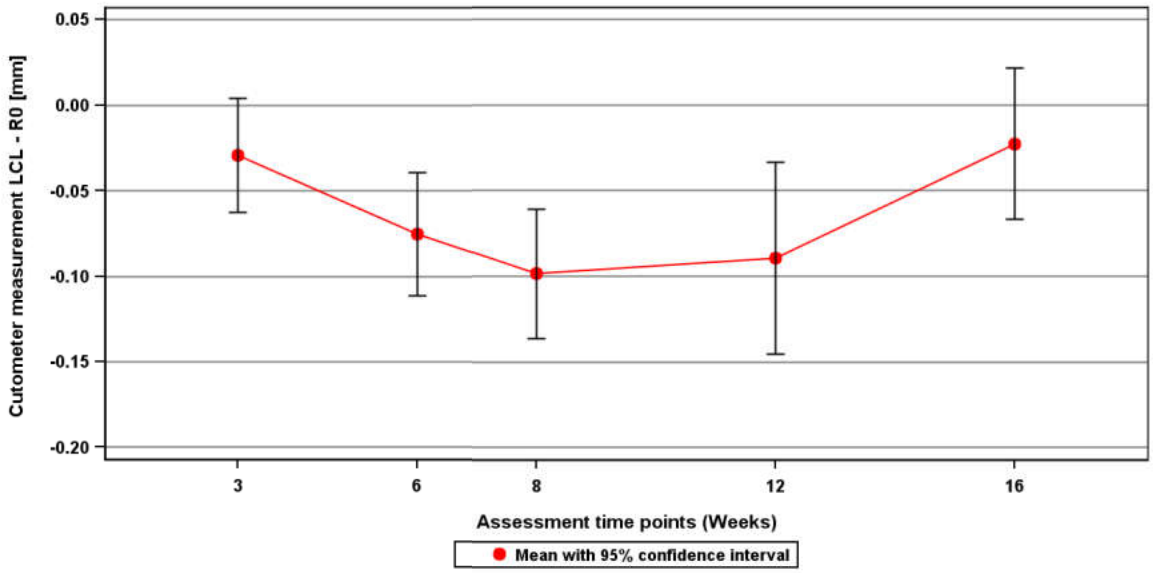
Cutometer - Statistical tests	LCL, Skin tone R0 [mm]	LCL, Skin elasticity R2 [ratio]	PR, Skin tone R0 [mm]	PR, Skin elasticity R2 [ratio]
Week 3				
n	14	14	39	39
Mean change ± SD	-0.029 ± 0.058	-0.001 ± 0.044	-0.037 ± 0.055	-0.003 ± 0.063
p-value of one-sample t-Test[1]	0.079	0.947	<0.001	0.771
Week 6				
n	15	15	39	39
Mean change ± SD	-0.075 ± 0.065	0.043 ± 0.060	-0.065 ± 0.054	0.001 ± 0.061
p-value of one-sample t-Test[1]	<0.001	0.016	<0.001	0.931
Week 8				
n	14	14	41	41
Mean change ± SD	-0.099 ± 0.065	0.026 ± 0.050	-0.091 ± 0.055	0.005 ± 0.055
p-value of one-sample t-Test[1]	<0.001	0.072	<0.001	0.543
Week 12				
n	11	11	25	25
Mean change ± SD	-0.090 ± 0.084	0.048 ± 0.072	-0.076 ± 0.082	0.016 ± 0.079
p-value of one-sample t-Test[1]	0.005	0.051	<0.001	0.316
Week 16				
n	14	14	24	24
Mean change ± SD	-0.023 ± 0.076	0.028 ± 0.061	-0.067 ± 0.087	0.021 ± 0.066
p-value of one-sample t-Test[1]	0.285	0.107	0.001	0.134
Week 24				
n	1	1	4	4
Mean change ± SD	-0.104	0.013	-0.077 ± 0.039	0.007 ± 0.040
p-value of one-sample t-Test[1]	-	-	0.030	0.762
Week 36				
n	1	1	5	5
Mean change ± SD	-0.093	0.020	-0.120 ± 0.047	0.035 ± 0.031
p-value of one-sample t-Test[1]	-	-	0.005	0.066

[1] Test for change to Baseline equal to Zero

Partial exclusions from statistical analysis due to deviation from required climatic conditions: Day 0 (2 subjects), Day 0 (2 subjects), Week 3 (2 subjects), Week 6 (1 subjects), Week 12 (16 subjects), Week 16 (18 subjects), Week 24 (5 subjects)

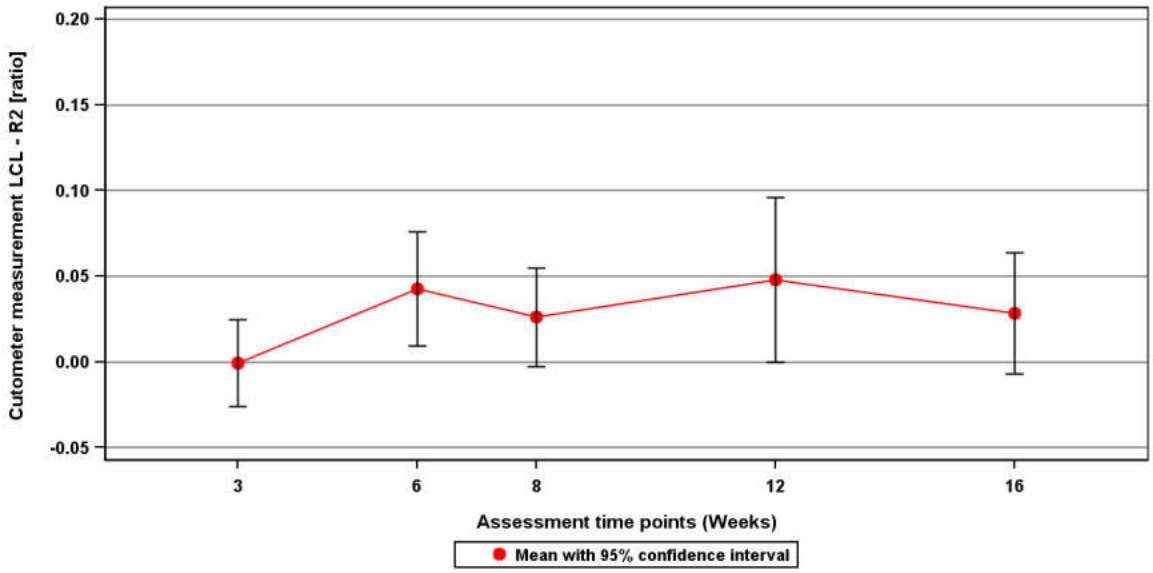
Source: CPH-401-201364_AppA_30JAN20.rtf

Figure 5: LCL Skin tone R0 [mm] - Change from Baseline (Per-protocol population)



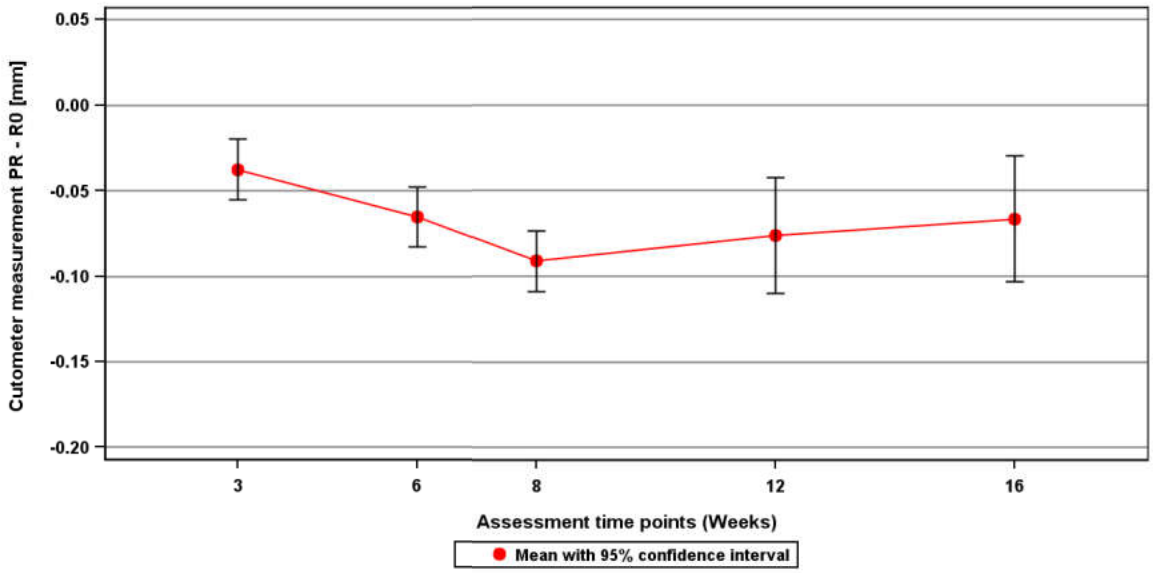
Source: CPH-401-201364_AppA_30JAN20.rtf

Figure 6: LCL Skin elasticity R2 [ratio] - Change from Baseline (Per-protocol population)



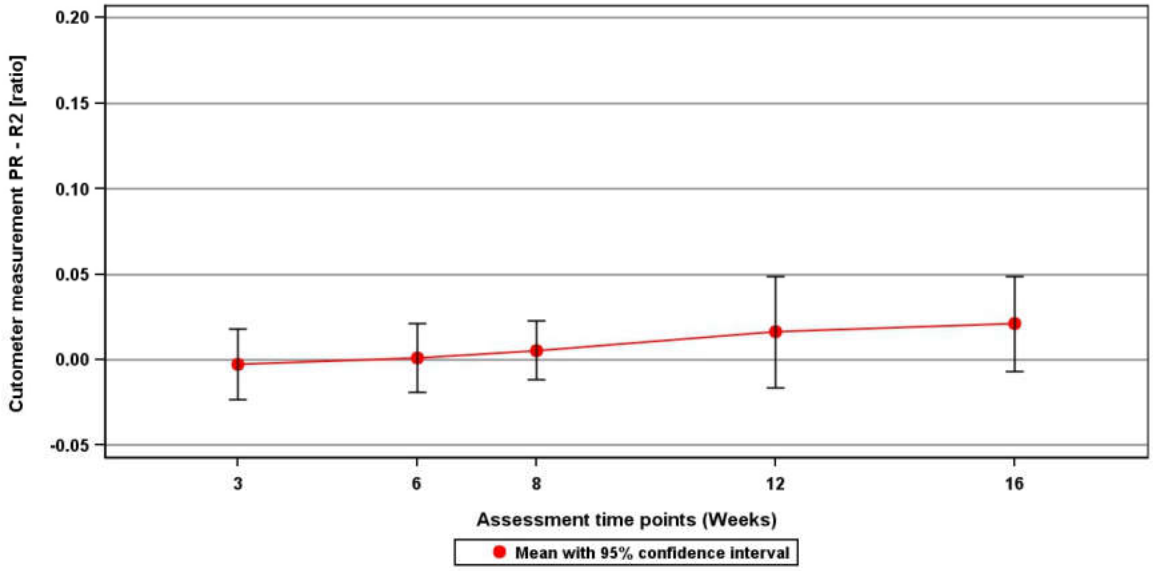
Source: CPH-401-201364_AppA_30JAN20.rtf

Figure 7: PR Skin tone R0 [mm] - Change from Baseline (Per-protocol population)



Source: CPH-401-201364_AppA_30JAN20.rtf

Figure 8: PR Skin elasticity R2 [ratio] - Change from Baseline (Per-protocol population)



Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.11: Aesthetic effect in follow up phase (Intent-to-treat population)
(Part 1 of 1)

Any aesthetic effects present?[1]	**n (%)**
N	12
Week 24	
n	12
Yes	7 (58.3%)
No	5 (41.7%)
Week 36	
n	7
Yes	2 (16.7%)
No	5 (41.7%)

[1] The follow up phase was stopped at Week 36 when the proportion of subjects with visible aesthetic effect dropped below 25% .

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 2.12: Aesthetic effect in follow up phase (Per-protocol population)
(Part 1 of 1)

Any aesthetic effects present?[1]	**n (%)**
N	11
Week 24	
n	11
Yes	7 (63.6%)
No	4 (36.4%)
Week 36	
n	7
Yes	2 (18.2%)
No	5 (45.5%)

[1] The follow up phase was stopped at Week 36 when the proportion of subjects with visible aesthetic effect dropped below 25% .

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 3.1: Injection volume (Safety analysis set)
(Part 1 of 1)

Injected volume [ml] (N_{SES} = 59)	Left LCL	Right LCL	PR	Total
Day 0				
N	26	26	52	59
Mean ± SD	0.36 ± 0.15	0.35 ± 0.15	0.98 ± 0.65	1.17 ± 0.49
Median	0.30	0.30	1.00	1.00
Min, max	0.3, 1.0	0.3, 1.0	0.2, 2.8	0.2, 2.8
Week 3				
N	21	21	35	42
Mean ± SD	0.33 ± 0.09	0.33 ± 0.10	0.79 ± 0.59	0.99 ± 0.46
Median	0.30	0.30	0.50	1.00
Min, max	0.2, 0.5	0.1, 0.5	0.2, 3.0	0.2, 3.0
Week 6				
N	19	19	32	41
Mean ± SD	0.38 ± 0.17	0.38 ± 0.17	0.95 ± 0.54	1.10 ± 0.43
Median	0.30	0.30	1.00	1.00
Min, max	0.2, 1.0	0.2, 1.0	0.4, 2.3	0.4, 2.3
Overall				
N	26	26	52	59
Mean ± SD	0.91 ± 0.27	0.90 ± 0.26	2.09 ± 1.46	2.64 ± 1.11
Median	0.90	0.90	1.80	2.60
Min, max	0.3, 1.7	0.3, 1.6	0.3, 6.0	0.5, 6.0

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 3.2: Additional anaesthetic and rescue medication (Safety analysis set)
(Part 1 of 1)

(N_{SES} = 59)	**Additional anaesthetics used**	**Rescue medication hyaluronidase**
Day 0		
N	59	59
No	28 (47.5%)	59 (100%)
Yes	31 (52.5%)	0 (0.0%)
Week 3		
N	42	42
No	23 (54.8%)	42 (100%)
Yes	19 (45.2%)	0 (0.0%)
Week 6		
N	41	41
No	19 (46.3%)	41 (100%)
Yes	22 (53.7%)	0 (0.0%)
Overall		
N	59	59
No	27 (45.8%)	59 (100%)
Yes	32 (54.2%)	0 (0.0%)

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 3.3.1: Adverse event characteristics (Safety analysis set)
(Part 1 of 1)

Adverse event characteristics (N_{SES} = 59)	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]	24 (41%)	18 (31%)	8 (14%)
Number of adverse events reported	36	25	11
Serious AEs			
No	34 (94%)	25 (100%)	9 (82%)
Yes	2 (6%)	0 (0%)	2 (18%)
Intensity			
Mild	29 (81%)	21 (84%)	8 (73%)
Moderate	6 (17%)	4 (16%)	2 (18%)
Severe	1 (3%)	0 (0%)	1 (9%)
Causal relationship to investigational device			
Definite	2 (6%)	2 (8%)	0 (0%)
Probable	1 (3%)	1 (4%)	0 (0%)
Possible	0 (0%)	0 (0%)	0 (0%)
Unlikely	2 (6%)	1 (4%)	1 (9%)
Not related	31 (86%)	21 (84%)	10 (91%)
Causal relationship to procedure			
Definite	23 (64%)	23 (92%)	0 (0%)
Probable	1 (3%)	1 (4%)	0 (0%)
Possible	0 (0%)	0 (0%)	0 (0%)
Unlikely	2 (6%)	1 (4%)	1 (9%)
Not related	10 (28%)	0 (0%)	10 (91%)
Duration[4]			
1 day	2 (6%)	0 (0%)	2 (18%)
> 1 day and 3 days	1 (3%)	0 (0%)	1 (9%)
> 3 days and 7 days	10 (28%)	6 (24%)	4 (36%)
> 7 days	21 (58%)	19 (76%)	2 (18%)
missing	2 (6%)	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: CPH-401-201364_AppA_30JAN20.rtf

Table 3.3.2: Adverse event characteristics by trial sites (Safety analysis set)
(Part 1 of 3)

Adverse event characteristics ($N_{SES(Site\ 1)}$ = 25)	All adverse events (=TEAE[1])	TEAE[1] with location related[2] to test fields	TEAE[1] with location not related[2] to test fields
Site 1 (Dermatology and venerology clinic)			
Number of subjects reporting any adverse event[3]	4 (16%)	3 (12%)	1 (4%)
Number of adverse events reported	4	3	1
Serious AEs			
No	4 (100%)	3 (100%)	1 (100%)
Yes	0 (0%)	0 (0%)	0 (0%)
Intensity			
Mild	4 (100%)	3 (100%)	1 (100%)
Moderate	0 (0%)	0 (0%)	0 (0%)
Severe	0 (0%)	0 (0%)	0 (0%)
Causal relationship to investigational device			
Definite	2 (50%)	2 (67%)	0 (0%)
Probable	0 (0%)	0 (0%)	0 (0%)
Possible	0 (0%)	0 (0%)	0 (0%)
Unlikely	1 (25%)	1 (33%)	0 (0%)
Not related	1 (25%)	0 (0%)	1 (100%)
Causal relationship to procedure			
Definite	2 (50%)	2 (67%)	0 (0%)
Probable	0 (0%)	0 (0%)	0 (0%)
Possible	0 (0%)	0 (0%)	0 (0%)
Unlikely	1 (25%)	1 (33%)	0 (0%)
Not related	1 (25%)	0 (0%)	1 (100%)
Duration[4]			
1 day	0 (0%)	0 (0%)	0 (0%)
> 1 day and 3 days	0 (0%)	0 (0%)	0 (0%)
> 3 days and 7 days	1 (25%)	0 (0%)	1 (100%)
> 7 days	3 (75%)	3 (100%)	0 (0%)
missing	0 (0%)	0 (0%)	0 (0%)

[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: CPH-401-201364_AppA_30JAN20.rtf

Table 3.3.2: Adverse event characteristics by trial sites (Safety analysis set)
(Part 2 of 3)

Adverse event characteristics ($N_{SES(Site\ 2)}$ = 34)	All adverse events (=TEAE[1])	TEAE[1] with location related[2] to test fields	TEAE[1] with location not related[2] to test fields
Site 2 (Yuvell fine aesthetics)			
Number of subjects reporting any adverse event[3]	20 (59%)	15 (44%)	7 (21%)
Number of adverse events reported	32	22	10
Serious AEs			
No	30 (94%)	22 (100%)	8 (80%)
Yes	2 (6%)	0 (0%)	2 (20%)
Intensity			
Mild	25 (78%)	18 (82%)	7 (70%)
Moderate	6 (19%)	4 (18%)	2 (20%)
Severe	1 (3%)	0 (0%)	1 (10%)
Causal relationship to investigational device			
Definite	0 (0%)	0 (0%)	0 (0%)
Probable	1 (3%)	1 (5%)	0 (0%)
Possible	0 (0%)	0 (0%)	0 (0%)
Unlikely	1 (3%)	0 (0%)	1 (10%)
Not related	30 (94%)	21 (95%)	9 (90%)
Causal relationship to procedure			
Definite	21 (66%)	21 (95%)	0 (0%)
Probable	1 (3%)	1 (5%)	0 (0%)
Possible	0 (0%)	0 (0%)	0 (0%)
Unlikely	1 (3%)	0 (0%)	1 (10%)
Not related	9 (28%)	0 (0%)	9 (90%)
Duration[4]			
1 day	2 (6%)	0 (0%)	2 (20%)
> 1 day and 3 days	1 (3%)	0 (0%)	1 (10%)
> 3 days and 7 days	9 (28%)	6 (27%)	3 (30%)
> 7 days	18 (56%)	16 (73%)	2 (20%)
missing	2 (6%)	0 (0%)	2 (20%)

[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: CPH-401-201364_AppA_30JAN20.rtf

Table 3.4: Subjects with adverse events by MedDRA class (Safety analysis set)
(Part 1 of 1)

Subjects with adverse events by MedDRA class (N_{SES} = 59)	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 (2%)	0 (0%)	1 (2%)
Gastrooesophageal reflux disease	1 (2%)	0 (0%)	1 (2%)
General disorders and administration site conditions	17 (29%)	17 (29%)	0 (0%)
Injection site haematoma	17 (29%)	17 (29%)	0 (0%)
Injection site swelling	1 (2%)	1 (2%)	0 (0%)
Immune system disorders	1 (2%)	0 (0%)	1 (2%)
Seasonal allergy	1 (2%)	0 (0%)	1 (2%)
Infections and infestations	7 (12%)	1 (2%)	6 (10%)
Gastroenteritis	1 (2%)	0 (0%)	1 (2%)
Nasopharyngitis	3 (5%)	0 (0%)	3 (5%)
Oral herpes	1 (2%)	1 (2%)	0 (0%)
Sinusitis	2 (3%)	0 (0%)	2 (3%)
Vestibular neuronitis	1 (2%)	0 (0%)	1 (2%)
Injury, poisoning and procedural complications	1 (2%)	0 (0%)	1 (2%)
Meniscus injury	1 (2%)	0 (0%)	1 (2%)
Surgical and medical procedures	1 (2%)	0 (0%)	1 (2%)
Shoulder operation	1 (2%)	0 (0%)	1 (2%)

[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: CPH-401-201364_AppA_30JAN20.rtf

Table 3.5: Subjects with adverse events by MedDRA class and seriousness (Safety analysis set)
(Part 1 of 2)

Subjects with adverse events by seriousness (N_{SES} = 59)	Seriousness	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	Not serious	1 (2%)	0 (0%)	1 (2%)
	Serious	0 (0%)	0 (0%)	0 (0%)
Gastrooesophageal reflux disease	Not serious	1 (2%)	0 (0%)	1 (2%)
	Serious	0 (0%)	0 (0%)	0 (0%)
General disorders and administration site conditions	Not serious	17 (29%)	17 (29%)	0 (0%)
	Serious	0 (0%)	0 (0%)	0 (0%)
Injection site haematoma	Not serious	17 (29%)	17 (29%)	0 (0%)
	Serious	0 (0%)	0 (0%)	0 (0%)
Injection site swelling	Not serious	1 (2%)	1 (2%)	0 (0%)
	Serious	0 (0%)	0 (0%)	0 (0%)
Immune system disorders	Not serious	1 (2%)	0 (0%)	1 (2%)
	Serious	0 (0%)	0 (0%)	0 (0%)
Seasonal allergy	Not serious	1 (2%)	0 (0%)	1 (2%)
	Serious	0 (0%)	0 (0%)	0 (0%)
Infections and infestations	Not serious	6 (10%)	1 (2%)	5 (8%)
	Serious	1 (2%)	0 (0%)	1 (2%)
Gastroenteritis	Not serious	1 (2%)	0 (0%)	1 (2%)
	Serious	0 (0%)	0 (0%)	0 (0%)
Nasopharyngitis	Not serious	3 (5%)	0 (0%)	3 (5%)
	Serious	0 (0%)	0 (0%)	0 (0%)
Oral herpes	Not serious	1 (2%)	1 (2%)	0 (0%)
	Serious	0 (0%)	0 (0%)	0 (0%)
Sinusitis	Not serious	2 (3%)	0 (0%)	2 (3%)
	Serious	0 (0%)	0 (0%)	0 (0%)
Vestibular neuronitis	Not serious	0 (0%)	0 (0%)	0 (0%)
	Serious	1 (2%)	0 (0%)	1 (2%)
Injury, poisoning and procedural complications	Not serious	0 (0%)	0 (0%)	0 (0%)
	Serious	1 (2%)	0 (0%)	1 (2%)
Meniscus injury	Not serious	0 (0%)	0 (0%)	0 (0%)
	Serious	1 (2%)	0 (0%)	1 (2%)
Surgical and medical procedures	Not serious	1 (2%)	0 (0%)	1 (2%)
	Serious	0 (0%)	0 (0%)	0 (0%)

[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 (under the greatest reported seriousness.)

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 3.5: Subjects with adverse events by MedDRA class and seriousness (Safety analysis set)
(Part 2 of 2)

Subjects with adverse events by seriousness (N_{SES} = 59)	Seriousness	All adverse events (=TEAE[1])	TEAE[1] with location related to test fields[2]	TEAE[1] with location not related to test fields[2]
Shoulder operation	Not serious	1 (2%)	0 (0%)	1 (2%)
	Serious	0 (0%)	0 (0%)	0 (0%)

[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 (under the greatest reported seriousness.)

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 3.6: Subjects with adverse events by MedDRA class and severity (Safety analysis set)
(Part 1 of 2)

Subjects with adverse events by severity (N_{SES} = 59)	Severity	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	Mild	1 (2%)	0 (0%)	1 (2%)
	Moderate	0 (0%)	0 (0%)	0 (0%)
	Severe	0 (0%)	0 (0%)	0 (0%)
Gastrooesophageal reflux disease	Mild	1 (2%)	0 (0%)	1 (2%)
	Moderate	0 (0%)	0 (0%)	0 (0%)
	Severe	0 (0%)	0 (0%)	0 (0%)
General disorders and administration site conditions	Mild	14 (24%)	14 (24%)	0 (0%)
	Moderate	3 (5%)	3 (5%)	0 (0%)
	Severe	0 (0%)	0 (0%)	0 (0%)
Injection site haematoma	Mild	14 (24%)	14 (24%)	0 (0%)
	Moderate	3 (5%)	3 (5%)	0 (0%)
	Severe	0 (0%)	0 (0%)	0 (0%)
Injection site swelling	Mild	1 (2%)	1 (2%)	0 (0%)
	Moderate	0 (0%)	0 (0%)	0 (0%)
	Severe	0 (0%)	0 (0%)	0 (0%)
Immune system disorders	Mild	1 (2%)	0 (0%)	1 (2%)
	Moderate	0 (0%)	0 (0%)	0 (0%)
	Severe	0 (0%)	0 (0%)	0 (0%)
Seasonal allergy	Mild	1 (2%)	0 (0%)	1 (2%)
	Moderate	0 (0%)	0 (0%)	0 (0%)
	Severe	0 (0%)	0 (0%)	0 (0%)
Infections and infestations	Mild	6 (10%)	1 (2%)	5 (8%)
	Moderate	0 (0%)	0 (0%)	0 (0%)
	Severe	1 (2%)	0 (0%)	1 (2%)
Gastroenteritis	Mild	1 (2%)	0 (0%)	1 (2%)
	Moderate	0 (0%)	0 (0%)	0 (0%)
	Severe	0 (0%)	0 (0%)	0 (0%)
Nasopharyngitis	Mild	3 (5%)	0 (0%)	3 (5%)
	Moderate	0 (0%)	0 (0%)	0 (0%)
	Severe	0 (0%)	0 (0%)	0 (0%)
Oral herpes	Mild	1 (2%)	1 (2%)	0 (0%)
	Moderate	0 (0%)	0 (0%)	0 (0%)
	Severe	0 (0%)	0 (0%)	0 (0%)
Sinusitis	Mild	2 (3%)	0 (0%)	2 (3%)
	Moderate	0 (0%)	0 (0%)	0 (0%)
	Severe	0 (0%)	0 (0%)	0 (0%)
Vestibular neuronitis	Mild	0 (0%)	0 (0%)	0 (0%)
	Moderate	0 (0%)	0 (0%)	0 (0%)
	Severe	1 (2%)	0 (0%)	1 (2%)

[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 (under the greatest reported severity.)

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 3.6: Subjects with adverse events by MedDRA class and severity (Safety analysis set)
(Part 2 of 2)

Subjects with adverse events by severity (N_{SES} = 59)	Severity	All adverse events (=TEAE[1])	TEAE[1] with location related to test fields[2]	TEAE[1] with location not related to test fields[2]
Injury, poisoning and procedural complications	Mild	0 (0%)	0 (0%)	0 (0%)
	Moderate	1 (2%)	0 (0%)	1 (2%)
	Severe	0 (0%)	0 (0%)	0 (0%)
Meniscus injury	Mild	0 (0%)	0 (0%)	0 (0%)
	Moderate	1 (2%)	0 (0%)	1 (2%)
	Severe	0 (0%)	0 (0%)	0 (0%)
Surgical and medical procedures	Mild	0 (0%)	0 (0%)	0 (0%)
	Moderate	1 (2%)	0 (0%)	1 (2%)
	Severe	0 (0%)	0 (0%)	0 (0%)
Shoulder operation	Mild	0 (0%)	0 (0%)	0 (0%)
	Moderate	1 (2%)	0 (0%)	1 (2%)
	Severe	0 (0%)	0 (0%)	0 (0%)

[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 (under the greatest reported severity.)

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 3.7: Subjects with adverse events by MedDRA class and duration (Safety analysis set)
(Part 1 of 3)

Subjects with adverse events by duration (N_{SES} = 59)	Duration[4]	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 day	0 (0%)	0 (0%)	0 (0%)
	> 1 day and 3 days	0 (0%)	0 (0%)	0 (0%)
	> 3 days and 7 days	0 (0%)	0 (0%)	0 (0%)
	> 7 days	0 (0%)	0 (0%)	0 (0%)
	missing	1 (2%)	0 (0%)	1 (2%)
Gastrooesophageal reflux disease	1 day	0 (0%)	0 (0%)	0 (0%)
	> 1 day and 3 days	0 (0%)	0 (0%)	0 (0%)
	> 3 days and 7 days	0 (0%)	0 (0%)	0 (0%)
	> 7 days	0 (0%)	0 (0%)	0 (0%)
	missing	1 (2%)	0 (0%)	1 (2%)
General disorders and administration site conditions	1 day	0 (0%)	0 (0%)	0 (0%)
	> 1 day and 3 days	0 (0%)	0 (0%)	0 (0%)
	> 3 days and 7 days	4 (7%)	4 (7%)	0 (0%)
	> 7 days	13 (22%)	13 (22%)	0 (0%)
	missing	0 (0%)	0 (0%)	0 (0%)
Injection site haematoma	1 day	0 (0%)	0 (0%)	0 (0%)
	> 1 day and 3 days	0 (0%)	0 (0%)	0 (0%)
	> 3 days and 7 days	4 (7%)	4 (7%)	0 (0%)
	> 7 days	13 (22%)	13 (22%)	0 (0%)
	missing	0 (0%)	0 (0%)	0 (0%)
Injection site swelling	1 day	0 (0%)	0 (0%)	0 (0%)
	> 1 day and 3 days	0 (0%)	0 (0%)	0 (0%)
	> 3 days and 7 days	1 (2%)	1 (2%)	0 (0%)
	> 7 days	0 (0%)	0 (0%)	0 (0%)
	missing	0 (0%)	0 (0%)	0 (0%)
Immune system disorders	1 day	0 (0%)	0 (0%)	0 (0%)
	> 1 day and 3 days	0 (0%)	0 (0%)	0 (0%)
	> 3 days and 7 days	0 (0%)	0 (0%)	0 (0%)
	> 7 days	0 (0%)	0 (0%)	0 (0%)
	missing	1 (2%)	0 (0%)	1 (2%)
Seasonal allergy	1 day	0 (0%)	0 (0%)	0 (0%)
	> 1 day and 3 days	0 (0%)	0 (0%)	0 (0%)
	> 3 days and 7 days	0 (0%)	0 (0%)	0 (0%)
	> 7 days	0 (0%)	0 (0%)	0 (0%)
	missing	1 (2%)	0 (0%)	1 (2%)

[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 (under the greatest reported duration.)
[4] Duration of adverse event was derived as stop date minus onset date + 1

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 3.7: Subjects with adverse events by MedDRA class and duration (Safety analysis set)
(Part 3 of 3)

Subjects with adverse events by duration (N_{SES} = 59)	Duration[4]	All adverse events (=TEAE[1])	TEAE[1] with location related to test fields[2]	TEAE[1] with location not related to test fields[2]
Meniscus injury	> 1 day and 3 days	0 (0%)	0 (0%)	0 (0%)
	> 3 days and 7 days	0 (0%)	0 (0%)	0 (0%)
	> 7 days	0 (0%)	0 (0%)	0 (0%)
	missing	0 (0%)	0 (0%)	0 (0%)
Surgical and medical procedures	1 day	1 (2%)	0 (0%)	1 (2%)
	> 1 day and 3 days	0 (0%)	0 (0%)	0 (0%)
	> 3 days and 7 days	0 (0%)	0 (0%)	0 (0%)
	> 7 days	0 (0%)	0 (0%)	0 (0%)
	missing	0 (0%)	0 (0%)	0 (0%)
Shoulder operation	1 day	1 (2%)	0 (0%)	1 (2%)
	> 1 day and 3 days	0 (0%)	0 (0%)	0 (0%)
	> 3 days and 7 days	0 (0%)	0 (0%)	0 (0%)
	> 7 days	0 (0%)	0 (0%)	0 (0%)
	missing	0 (0%)	0 (0%)	0 (0%)

[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 (under the greatest reported duration.)
[4] Duration of adverse event was derived as stop date minus onset date + 1

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 3.7: Subjects with adverse events by MedDRA class and duration (Safety analysis set)
(Part 2 of 3)

Subjects with adverse events by duration (N_{SES} = 59)	Duration[4]	All adverse events (=TEAE[1])	TEAE[1] with location related to test fields[2]	TEAE[1] with location not related to test fields[2]
Infections and infestations	1 day	0 (0%)	0 (0%)	0 (0%)
	> 1 day and 3 days	1 (2%)	0 (0%)	1 (2%)
	> 3 days and 7 days	3 (5%)	0 (0%)	3 (5%)
	> 7 days	3 (5%)	1 (2%)	2 (3%)
	missing	0 (0%)	0 (0%)	0 (0%)
Gastroenteritis	1 day	0 (0%)	0 (0%)	0 (0%)
	> 1 day and 3 days	0 (0%)	0 (0%)	0 (0%)
	> 3 days and 7 days	1 (2%)	0 (0%)	1 (2%)
	> 7 days	0 (0%)	0 (0%)	0 (0%)
	missing	0 (0%)	0 (0%)	0 (0%)
Nasopharyngitis	1 day	0 (0%)	0 (0%)	0 (0%)
	> 1 day and 3 days	1 (2%)	0 (0%)	1 (2%)
	> 3 days and 7 days	2 (3%)	0 (0%)	2 (3%)
	> 7 days	0 (0%)	0 (0%)	0 (0%)
	missing	0 (0%)	0 (0%)	0 (0%)
Oral herpes	1 day	0 (0%)	0 (0%)	0 (0%)
	> 1 day and 3 days	0 (0%)	0 (0%)	0 (0%)
	> 3 days and 7 days	0 (0%)	0 (0%)	0 (0%)
	> 7 days	1 (2%)	1 (2%)	0 (0%)
	missing	0 (0%)	0 (0%)	0 (0%)
Sinusitis	1 day	0 (0%)	0 (0%)	0 (0%)
	> 1 day and 3 days	0 (0%)	0 (0%)	0 (0%)
	> 3 days and 7 days	0 (0%)	0 (0%)	0 (0%)
	> 7 days	2 (3%)	0 (0%)	2 (3%)
	missing	0 (0%)	0 (0%)	0 (0%)
Vestibular neuronitis	1 day	0 (0%)	0 (0%)	0 (0%)
	> 1 day and 3 days	0 (0%)	0 (0%)	0 (0%)
	> 3 days and 7 days	1 (2%)	0 (0%)	1 (2%)
	> 7 days	0 (0%)	0 (0%)	0 (0%)
	missing	0 (0%)	0 (0%)	0 (0%)
Injury, poisoning and procedural complications	1 day	1 (2%)	0 (0%)	1 (2%)
	> 1 day and 3 days	0 (0%)	0 (0%)	0 (0%)
	> 3 days and 7 days	0 (0%)	0 (0%)	0 (0%)
	> 7 days	0 (0%)	0 (0%)	0 (0%)
	missing	0 (0%)	0 (0%)	0 (0%)
Meniscus injury	1 day	1 (2%)	0 (0%)	1 (2%)

[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 (under the greatest reported duration.)
[4] Duration of adverse event was derived as stop date minus onset date + 1

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 3.8: Subjects with adverse events by MedDRA class and causal relationship to the device (Safety analysis set)
(Part 1 of 3)

Subjects with adverse events by causal relationship to the device (N_{SES} = 59)	Relationship	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	Definite	0 (0%)	0 (0%)	0 (0%)
	Probable	0 (0%)	0 (0%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	0 (0%)	0 (0%)	0 (0%)
	Not related	1 (2%)	0 (0%)	1 (2%)
Gastrooesophageal reflux disease	Definite	0 (0%)	0 (0%)	0 (0%)
	Probable	0 (0%)	0 (0%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	0 (0%)	0 (0%)	0 (0%)
	Not related	1 (2%)	0 (0%)	1 (2%)
General disorders and administration site conditions	Definite	2 (3%)	2 (3%)	0 (0%)
	Probable	1 (2%)	1 (2%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	0 (0%)	0 (0%)	0 (0%)
	Not related	14 (24%)	14 (24%)	0 (0%)
Injection site haematoma	Definite	2 (3%)	2 (3%)	0 (0%)
	Probable	0 (0%)	0 (0%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	0 (0%)	0 (0%)	0 (0%)
	Not related	15 (25%)	15 (25%)	0 (0%)
Injection site swelling	Definite	0 (0%)	0 (0%)	0 (0%)
	Probable	1 (2%)	1 (2%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	0 (0%)	0 (0%)	0 (0%)
	Not related	0 (0%)	0 (0%)	0 (0%)
Immune system disorders	Definite	0 (0%)	0 (0%)	0 (0%)
	Probable	0 (0%)	0 (0%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	0 (0%)	0 (0%)	0 (0%)
	Not related	1 (2%)	0 (0%)	1 (2%)
Seasonal allergy	Definite	0 (0%)	0 (0%)	0 (0%)
	Probable	0 (0%)	0 (0%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	0 (0%)	0 (0%)	0 (0%)
	Not related	1 (2%)	0 (0%)	1 (2%)
Infections and infestations	Definite	0 (0%)	0 (0%)	0 (0%)
	Probable	0 (0%)	0 (0%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	2 (3%)	1 (2%)	1 (2%)
	Not related	5 (8%)	0 (0%)	5 (8%)

[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 (under the greatest reported causal relationship to the device.)

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 3.8: Subjects with adverse events by MedDRA class and causal relationship to the device (Safety analysis set)
(Part 2 of 3)

Subjects with adverse events by causal relationship to the device (N_{SES} = 59)	Relationship	All adverse events (=TEAE[1])	TEAE[1] with location related to test fields[2]	TEAE[1] with location not related to test fields[2]
Gastroenteritis	Definite	0 (0%)	0 (0%)	0 (0%)
	Probable	0 (0%)	0 (0%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	0 (0%)	0 (0%)	0 (0%)
	Not related	1 (2%)	0 (0%)	1 (2%)
Nasopharyngitis	Definite	0 (0%)	0 (0%)	0 (0%)
	Probable	0 (0%)	0 (0%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	0 (0%)	0 (0%)	0 (0%)
	Not related	3 (5%)	0 (0%)	3 (5%)
Oral herpes	Definite	0 (0%)	0 (0%)	0 (0%)
	Probable	0 (0%)	0 (0%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	1 (2%)	1 (2%)	0 (0%)
	Not related	0 (0%)	0 (0%)	0 (0%)
Sinusitis	Definite	0 (0%)	0 (0%)	0 (0%)
	Probable	0 (0%)	0 (0%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	0 (0%)	0 (0%)	0 (0%)
	Not related	2 (3%)	0 (0%)	2 (3%)
Vestibular neuronitis	Definite	0 (0%)	0 (0%)	0 (0%)
	Probable	0 (0%)	0 (0%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	1 (2%)	0 (0%)	1 (2%)
	Not related	0 (0%)	0 (0%)	0 (0%)
Injury, poisoning and procedural complications	Definite	0 (0%)	0 (0%)	0 (0%)
	Probable	0 (0%)	0 (0%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	0 (0%)	0 (0%)	0 (0%)
	Not related	1 (2%)	0 (0%)	1 (2%)
Meniscus injury	Definite	0 (0%)	0 (0%)	0 (0%)
	Probable	0 (0%)	0 (0%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	0 (0%)	0 (0%)	0 (0%)
	Not related	1 (2%)	0 (0%)	1 (2%)
Surgical and medical procedures	Definite	0 (0%)	0 (0%)	0 (0%)
	Probable	0 (0%)	0 (0%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	0 (0%)	0 (0%)	0 (0%)
	Not related	1 (2%)	0 (0%)	1 (2%)
Shoulder operation	Definite	0 (0%)	0 (0%)	0 (0%)

[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 (under the greatest reported causal relationship to the device.)

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 3.8: Subjects with adverse events by MedDRA class and causal relationship to the device (Safety analysis set)
(Part 3 of 3)

Subjects with adverse events by causal relationship to the device (N_{SES} = 59)	Relationship	All adverse events (=TEAE[1])	TEAE[1] with location related to test fields[2]	TEAE[1] with location not related to test fields[2]
Shoulder operation	Probable	0 (0%)	0 (0%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	0 (0%)	0 (0%)	0 (0%)
	Not related	1 (2%)	0 (0%)	1 (2%)

[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 (under the greatest reported causal relationship to the device.)

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 3.9: Subjects with adverse events by MedDRA class and causal relationship to procedure (Safety analysis set)
(Part 1 of 3)

Subjects with adverse events by causal relationship to procedure (N_{SES} = 59)	Relationship	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	Definite	0 (0%)	0 (0%)	0 (0%)
	Probable	0 (0%)	0 (0%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	0 (0%)	0 (0%)	0 (0%)
	Not related	1 (2%)	0 (0%)	1 (2%)
Gastrooesophageal reflux disease	Definite	0 (0%)	0 (0%)	0 (0%)
	Probable	0 (0%)	0 (0%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	0 (0%)	0 (0%)	0 (0%)
	Not related	1 (2%)	0 (0%)	1 (2%)
General disorders and administration site conditions	Definite	17 (29%)	17 (29%)	0 (0%)
	Probable	0 (0%)	0 (0%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	0 (0%)	0 (0%)	0 (0%)
	Not related	0 (0%)	0 (0%)	0 (0%)
Injection site haematoma	Definite	17 (29%)	17 (29%)	0 (0%)
	Probable	0 (0%)	0 (0%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	0 (0%)	0 (0%)	0 (0%)
	Not related	0 (0%)	0 (0%)	0 (0%)
Injection site swelling	Definite	0 (0%)	0 (0%)	0 (0%)
	Probable	1 (2%)	1 (2%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	0 (0%)	0 (0%)	0 (0%)
	Not related	0 (0%)	0 (0%)	0 (0%)
Immune system disorders	Definite	0 (0%)	0 (0%)	0 (0%)
	Probable	0 (0%)	0 (0%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	0 (0%)	0 (0%)	0 (0%)
	Not related	1 (2%)	0 (0%)	1 (2%)
Seasonal allergy	Definite	0 (0%)	0 (0%)	0 (0%)
	Probable	0 (0%)	0 (0%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	0 (0%)	0 (0%)	0 (0%)
	Not related	1 (2%)	0 (0%)	1 (2%)
Infections and infestations	Definite	0 (0%)	0 (0%)	0 (0%)
	Probable	0 (0%)	0 (0%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	2 (3%)	1 (2%)	1 (2%)
	Not related	5 (8%)	0 (0%)	5 (8%)

[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 (under the greatest reported causal relationship to procedure.)

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 3.9: Subjects with adverse events by MedDRA class and causal relationship to procedure (Safety analysis set)
(Part 2 of 3)

Subjects with adverse events by causal relationship to procedure (N_{SES} = 59)	Relationship	All adverse events (=TEAE[1])	TEAE[1] with location related to test fields[2]	TEAE[1] with location not related to test fields[2]
Gastroenteritis	Definite	0 (0%)	0 (0%)	0 (0%)
	Probable	0 (0%)	0 (0%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	0 (0%)	0 (0%)	0 (0%)
	Not related	1 (2%)	0 (0%)	1 (2%)
Nasopharyngitis	Definite	0 (0%)	0 (0%)	0 (0%)
	Probable	0 (0%)	0 (0%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	0 (0%)	0 (0%)	0 (0%)
	Not related	3 (5%)	0 (0%)	3 (5%)
Oral herpes	Definite	0 (0%)	0 (0%)	0 (0%)
	Probable	0 (0%)	0 (0%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	1 (2%)	1 (2%)	0 (0%)
	Not related	0 (0%)	0 (0%)	0 (0%)
Sinusitis	Definite	0 (0%)	0 (0%)	0 (0%)
	Probable	0 (0%)	0 (0%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	0 (0%)	0 (0%)	0 (0%)
	Not related	2 (3%)	0 (0%)	2 (3%)
Vestibular neuronitis	Definite	0 (0%)	0 (0%)	0 (0%)
	Probable	0 (0%)	0 (0%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	1 (2%)	0 (0%)	1 (2%)
	Not related	0 (0%)	0 (0%)	0 (0%)
Injury, poisoning and procedural complications	Definite	0 (0%)	0 (0%)	0 (0%)
	Probable	0 (0%)	0 (0%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	0 (0%)	0 (0%)	0 (0%)
	Not related	1 (2%)	0 (0%)	1 (2%)
Meniscus injury	Definite	0 (0%)	0 (0%)	0 (0%)
	Probable	0 (0%)	0 (0%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	0 (0%)	0 (0%)	0 (0%)
	Not related	1 (2%)	0 (0%)	1 (2%)
Surgical and medical procedures	Definite	0 (0%)	0 (0%)	0 (0%)
	Probable	0 (0%)	0 (0%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	0 (0%)	0 (0%)	0 (0%)
	Not related	1 (2%)	0 (0%)	1 (2%)
Shoulder operation	Definite	0 (0%)	0 (0%)	0 (0%)

[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 (under the greatest reported causal relationship to procedure.)

Source: CPH-401-201364_AppA_30JAN20.rtf

Table 3.9: Subjects with adverse events by MedDRA class and causal relationship to procedure (Safety analysis set)
(Part 3 of 3)

Subjects with adverse events by causal relationship to procedure (N_{SES} = 59)	Relationship	All adverse events (=TEAE[1])	TEAE[1] with location related to test fields[2]	TEAE[1] with location not related to test fields[2]
Shoulder operation	Probable	0 (0%)	0 (0%)	0 (0%)
	Possible	0 (0%)	0 (0%)	0 (0%)
	Unlikely	0 (0%)	0 (0%)	0 (0%)
	Not related	1 (2%)	0 (0%)	1 (2%)

[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 (under the greatest reported causal relationship to procedure.)

Source: CPH-401-201364_AppA_30JAN20.rtf

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