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

Title	**[1.8% Sodium Hyaluronate with 2% Glycerol i.d.]**
DOC Code	C_CT_CER_005_05
Invalidation	-
Reason for modification	Deficiency letters from 20.12.2019 no. P172178-2, and 17.12.2019 no. P183244-1
Area covered	-

Appendices	Annex 01 C_CT_CER_005_05 Signature Page Medical Evaluator Annex 02 TO C_CT_CER_005_05 - IFU MASTERTEXT Annex 03 C_CT_CER_005_05 -LITERATURE SEARCH PROTOCOL C_CT_FORM_008 Annex 04 C_CT_CER_005_05 Curriculum Vitae_DOI Annex 05 C_CT_CER_005_05_PUBLISHER STATEMENTS Annex 06 C_CT_CER_005_05 LIST OF COMPLAINTS 2009-2019 Annex 07 C_CT_CER_005_05 CIR interim CPH-401-201364, CIP and ethics Annex 08 C_CT_CER_005_05 final CIR CPH-401-201364
Attachments	C_CT_CER_005_05

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Approver	Michael Henkel (Quality Compliance)	09.03.2020 16:38

Distribution List - Information groups

IG RA (for info mail), IG RA TD (for info mail)

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COMPLEMENTARY DOCUMENTS

List of documents that are not annexed to the clinical evaluation report but submitted separately with the clinical evaluation report since generated from the internal document system.

Document Number (currently valid version)	**Document title**
C_RD_BER_001	Biological Evaluation Report of [1.8% Sodium Hyaluronate with 2% Glycerol i.d.]
A_FP_SPEC_501	Specification of final product-Princess RICH
	Files on risk management
A_D_RMP_010	Risk Management Plan [1.8% Sodium Hyaluronate with 2% Glycerol i.d.]
A_RA_MRIA_PR421	Risk Assessment - Manufacturing of [1.8% Sodium Hyaluronate with 2% Glycerol i.d.]
C_RA_DRIA_403	Risk Assessment - Design of [1.8% Sodium Hyaluronate with 2% Glycerol i.d.]
C_RA_RMR_421	Risk Management Report [1.8% Sodium Hyaluronate with 2% Glycerol i.d.]
C_CT_PMCF_010	Post market clinical follow up plan – [1.8% Sodium Hyaluronate with 2% Glycerol i.d.]
C_CT _PMCFR_007	PMCF Report-[1.8% Sodium Hyaluronate with 2% Glycerol i.d.]
C_CT_CEP_007_01	Clinical evaluation plan is for the device group [1.8% Sodium Hyaluronate with 2% Glycerol i.d.]
	Files on post market surveillance
A_RA_PMSP_022	Post Market Surveillance Plan- [1.8% Sodium Hyaluronate with 2% Glycerol i.d.]
A_RA_PMSR_122	Post Market Surveillance Report - [1.8% Sodium Hyaluronate with 2% Glycerol i.d.]
C_CT_TRIR_009	Expert Review Team Meeting (11.09.2019)_Assessments of Adverse Events from the clinical study "RICH"
	Files on Princess RICH promotional, information material
36813|TFSPR_11_2019_Draft_IU	Clinical factsheet
Literature References	**Files of literature references**

Date and signatures of responsible persons of the clinical evaluation report C_CT_CER_005_05 [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] is valid from the release date.

According to the provisions of MEDDEV 2.7.1 Rev. 4 Section 6.4, the authors of this clinical evaluation report confirm that they are suitably qualified as a team to create, evaluate, review and approve appropriately and in compliance with the requirements set out in MEDDEV 2.7.1 Rev. 4.

The signature of the external evaluator Univ. Prof. Dr. Daisy Kopera, Associate Professor of Dermatology, Medical University Graz is available in Annex 01 of this clinical evaluation report.

The curriculum vitae (CV) and declaration of interest (DOI) and of the external evaluator Univ. Prof. Dr. Daisy Kopera is provided in Annex 04.

The curriculum vitae (CV) of the author, the evaluators and approver are provided in Annex 04.

All electronic signatures of the following responsible persons are on the front page, of the present CER. All contributors are employees at CROMA-PHARMA GmbH.

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This CER is valid for the medical device group [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] which consists of the following brands: Princess RICH, Esteline Vita, DERMALSTYLE light, M-HA18, Saypha RICH, Hyalax REVITALIZE SKIN, Apriline HYDRO, JALOR re-Style, ZFill refresh, Pluryal Booster, GENYAL Genyalift and Definisse hydrobooster.

Summary

[1.8% Sodium Hyaluronate with 2% Glycerol i.d.] is a viscoelastic solution used to replenish the loss of hyaluronic acid due to ageing, tomaintain hydration and to improve tone and elasticity of the skin and to act as a filler for small lines such as crow's feet, smile lines or smoke lines surrounding the mouth. It is indicated to be injected into the superficial dermal tissue .The device is intended for single-use (i.e. not reusable) and will maintain in long term contact with the body. Dermal and connective facial tissues are contacted by the device. The device is a sterile, biodegradable, viscoelastic, clear, transparent, isotonic and homogenized injectable gel implant. The implant consists of hyaluronic acid (HA) of biofermentative and not an animal origin and is formulated to a concentration of 18 mg/mL in a physiological phosphate-citrate buffer.

The device was proven in various pre-clinical tests to be non-cytotoxic, non-immunizing, and non-genotoxic. The product was well tolerated after intradermal injection. Clinical observations of test animals, overall body weight development, and histopathological examination demonstrated very good tolerability. There was no inflammation, no cell infiltration, no degeneration, fibrosis, vascularization or atypical reaction. [1.8% Sodium Hyaluronate with 2% Glycerol i.d.]was classified as a non-sensitizer. The genotoxicity testing using [1.8% Sodium Hyaluronate with 2% Glycerol i.d.]showed no mutagenic activity thus did not induce gene mutations. In conclusion, the overall results from animal experiments support the safety of the device when used as an injectable dermal implant.

This clinical evaluation report (CER) is based on a clinical investigation on [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] entitled "A prospective open-label, multicenter study evaluating Princess® RICH in correction of fine lines" (CPH-401-201364). The purpose of the study was to assess the effectiveness of Princess® RICH to correct fine lines on the face including lateral canthal lines (LCL) also called "Crow's Feet" and perioral rhytids (PR) also called "smile lines" or "smoker's lines". Furthermore, to assess the safety of Princess® RICH and to assess its ability to maintain skin hydration and improve skin tone and skin elasticity in the treatment areas.

The performance results of Princess® RICH 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 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.

These results were supported by the results seen in the subject ratings for satisfaction with IMD treatment. Subjects' treatment satisfaction was demonstrated at Week 8 with the majority of the subjects (93.1%) assessing either 'satisfied' or 'very satisfied'. The remaining subjects were 'neither satisfied nor unsatisfied' with IMD treatment. Four weeks later at Week 12, 16, 24 and 36, most of the subjects (91.1%, 73.7%, 58.3% and 71.4%, respectively) continued to be 'satisfied' or 'very satisfied'. All other subjects rated 'Neither satisfied nor unsatisfied'. 'Unsatisfied' or 'very unsatisfied' has not been rated 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 (skin elasticity) 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 skin tone was noted for LCL at Week 8 and for PR at Week 12. The greatest increase in skin elasticity was noted for both LCL and PR at Week 12 and for PR at Week 36.

The assessment of skin hydration using corneometry demonstrated based on mean corneometric values of 51.8 i.u. for LCL and 53.2 i.u. for PR at baseline only minor changes over the investigational period until Week 8. The greatest increase was noted for both LCL and PR at Week 24 (mean change from baseline 15.1 and 10.9 i.u., respectively). These results reflect that the skin hydration was maintained following treatment with Princess® RICH. At Week 36, still a considerable skin hydration (mean change from baseline 9.8 i.u.) was noted for LCL, while the skin hydration had decreased to the minimum value of -4.6 i.u. (mean change from baseline) for PR. An improvement of skin hydration was seen at Weeks 24 (LCL: 69.0 i.u. and PR: 61.4 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 (maintaining hydration, improving tone and elasticity) and an aesthetic effect lasting for a satisfactory duration.

The safety variables of this study (CPH-401-201364) demonstrated the safety and tolerability of Princess® RICH when either LCL or PR or both areas combined were treated and no new safety concerns were identified during this study. In total, 36 treatment-emergent adverse events (TEAEs) were reported in 24 subjects (41%). 2 of the TEAEs were SAEs and were considered to be unlikely or not related to IMD or procedure. The remaining TEAEs were non-serious TEAEs, mostly located at treatment area or just around treatment area. None of the TEAEs led to subject's withdrawal and the outcome of the TEAEs was 'resolved' within a few days to one week in most cases, corresponding to other HA described in literature (Abduljabbar and Basendwh, 2016). 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.

1. Scope of the clinical evaluation

The CER on the medical device group [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] and its clinical performance and safety is written in compliance with the consolidated Medical Device Directive (MDD) 93/42/EEC and MEDDEV 2.7.1 Revision 4.

The scope of the present clinical evaluation report is restricted to the pre-clinical and clinical data with the product under assessment held by the manufacturer in order to confirm whether the conclusions regarding the favorable benefit/risk ratio of the device are still valid and to address the benefit/risk ratio with regard to the use of the device for the claimed indications. The detailed relevant clinical investigation report, clinical investigation plan and the approval ofhe ethics committee and national competent authority are presented in annex 07 and annex 08.

The clinical investigation performed by the manufacturer is entitled: "A prospective open-label, multicenter study evaluating Princess® RICH in correction of fine lines" (CPH-401-201364).

1.1 Identification of devices covered by the present clinical evaluation report

This CER is valid for the medical device group [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] which consists of the following brands: Princess RICH, Esteline Vita, DERMALSTYLE light, M-HA18, Saypha RICH, Hyalax REVITALIZE SKIN, Apriline HYDRO, JALOR re-Style, ZFill refresh², Pluryal Booster, GENYAL Genyalift and Definisse hydrobooster.

1.2 Physical and chemical description

The device is a sterile, biodegradable, viscoelastic, clear, transparent, isotonic and homogenized injectable gel implant. The device consists of non-animal sodium hyaluronate, obtained from Streptococcus equi bacteria formulated to a concentration of 18 mg/mL in a physiological buffer. The hyaluronic acid used for manufacturing the medical device group [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] is of biofermentative and not of an animal origin.

Hyaluronic acid (HA) belongs to the polysaccharide family glycosaminoglycans (mucopolysaccharides). It consists of lo ng, unbranched polymer chains with repeating disaccharide units of D-glucuronic acid and N-acetyl-D-glucosamine [C14H20NaO11]n linked by alternating beta-1,4 and beta-1,3 glycosidic bonds. It occurs in a wide range of molecular weights, up to several million Dalton. In neutral aqueous media, hydrogen bonds form between water molecules and the carboxyl

and acetyl groups. HA's capacity for bonding in water is directly proportional to its molecular weight and can occur in the presence of up to 6 g/L of hyaluronic acid (Becker, Bergfeld et al., 2009), (Gooderham & Solish, 2005).

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

[1.8% Sodium Hyaluronate with 2% Glycerol i.d.] is an absorbable implant intended to be used for adult human beings. The device is a viscoelastic solution to replenish the loss of hyaluronic acid due to ageing, to maintain hydration and to improve tone and elasticity of the skin and to act as a filler for small lines such as crow's feet, smile lines or smoke lines surrounding the mouth. The device is designed to be injected into the superficial dermal tissue. The device is intended for single-use, it is sterile, non-active and without measuring function. No materials of human or animal origin are used during manufacture or as raw materials. No medicinal substances are integrated into the device. The composition and chemical, physical and microbiological parameters of [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] solution are described below according to the specification of the final product, see also (A_FP_SPEC_501) Table 1, Table 2.

Table 1 Composition of 1 mL of [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] solution

Substances	Quantity [mg/mL]	Purpose of the component
Sodium hyaluronate	17.72	Active ingredient
Citric acid monohydrate	0.11[1]	Buffer salt
Glycerol	21.16	Stabilizer
Di-sodiumhydrogen phosphate dodecahydrate	1.31	Buffer salt
Water for injection	970.76	Solvent

[1] a change in the amount of citric acid (from 0.06 to 0.11 mg/ml) was approved on 16.01.2020 (GMED Project number P601674)

Table 2 Specification of [1.8% Sodium Hyaluronate with 2% Glycerol i.d.]

Parameter	Value/Description
Appearance	Clear, viscous solution
Content Sodium hyaluronate [mg/mL]	16.6-19.4
Content glycerol [mg/mL]	19.3-22.7
Content endotoxins [EU/mL]	<0.5
Inner sterility	sterile
pH value	6.8-7.6
Osmolality [mOsmol/kg]	280-330
Extractable volume [mL]	0.9-1.1
dynamic viscosity [mPa*s] (D= 5 s-1, T=25 °C)	> 20,000
Injection force [N]	≤ 20

The device is not intended to treat any medical condition, it is for aesthetic purposes (unmet medical needs) only.

1.3 Description of innovative aspects of the device

The device under assessment has no innovative aspect.

1.4 Classification and generic group

[1.8% Sodium Hyaluronate with 2% Glycerol i.d.] is according to its field of application classified under class III medical device (MDD 93/42/EEC, Attachment IX, rule 8: Implantable devices and long-term surgically invasive devices (> 30 days)). The conformity assessment route complies with MDD 93/42/EEC Annex II.3. (Quality System) and Annex II.4. (Design Examination for Class III Medical Devices). The GMDN-Code is 59131.

All steps of the device preparation (design, manufacture, syringes filling, moist heat sterilization, labeling, packaging, final inspection and release) are done at the manufacturer's facilities, in accordance with EN ISO 13485:2016.

The sterile single-use needles (30G ½") are medical devices according to their field of application, under class IIa (MDD 93/42/EEC, Attachment IX, rule 6).

1.5 Intended purpose and indications

The intended purpose, intended application, duration of use and contact with the body, maximum number of repeat applications and precautions are described in the Instructions for Use (IFU) of the device [1.8% Sodium Hyaluronate with 2% Glycerol i.d.], see annex 02.

Description:

The device is a sterile, biodegradable, viscoelastic, clear, transparent, isotonic and homogenized injectable gel implant.

The device consists of non-animal sodium hyaluronate, obtained from Streptococcus equi bacteria.

Each box contains one prefilled syringe of 1.0 ml solution, two 30G ½" disposable sterile needles and instruction for use.

A set of two labels showing the batch number is situated at the bottom of the box.

One of these labels should be attached to the patient's file and the other should be given to the patient to ensure traceability.

Indications (unmet medical needs):

The device is a viscoelastic solution used to replenish the loss of hyaluronic acid due to ageing, to maintain hydration, to improve tone and elasticity of the skin and to act as a filler for small lines such as crow's feet, smile lines or smoke lines surrounding the mouth[2].

It is indicated to be injected into the superficial dermal tissue.

Single-use/reusable, invasive/non-invasive, implantable

The device is for single use (i.e. not reusable), it is intended to be invasive and implantable for long term contact with the body. Dermal and connective facial tissues are contacted by the device.

1.6 Contraindications

These are referred to as exclusion criteria in the IFU annex 02.

The device must not be used in:

- Patients who tend to develop hypertrophic scars, have pigment disorders or have a susceptibility to keloid formation.
- Patients with a history of autoimmune disease or who are receiving immune therapy.
- Patients who are known to be hypersensitive to hyaluronic acid.

[2] The extended indications have been approved by GMED (procedure P172178-2, the approval letter was signed on 23.01.2020 by Peter Andrawes).

- Patients who have previously received permanent fillers in the area to be treated.
- Pregnant or breastfeeding women.
- Patients under 18 years of age.
- Patients on anticoagulants or patients receiving platelet aggregation inhibitors (e.g. acetylsalicylic acid) should not be treated with the device without consulting their doctors.
- The device must not be used in areas presenting cutaneous, inflammatory and/or infectious processes (e.g. acne, herpes …).
- The device must not be used in association with laser therapy, chemical peeling or dermabrasion.

1.7 Target patient population

Target patient population is adults. Instruction for use (annex 02) in the section "exclusion criteria" specifies that patients should not be under 18 years of age.

1.8 Target user group

This device must only be administered by a doctor who is familiar with intradermal injections for aesthetic improvement.

1.9 Stability and lifetime of the product

Shelf life for [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] is set to 36 months at 2–25 °C, protected from light, heat and frost, as defined in finished product specification (see A_FP_SPEC_501). Internal stability studies have been conducted according to a stability plan. All the shelf life studies are performed in compliance with ICH guidelines.

1.10 Duration of use or contact with the body

The durability of the filling effect of [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] depends on the treatment site, skin layer and injected volume. However, a conducted clinical study (annex 08) demonstrated the effectiveness of IMD in the correction of fine lines (LCL and PR), providing rejuvenation and aesthetic effect by maintaining hydration, improving skin tone and elasticity and acting as a filler for the small lines (see study results in chapter 3.6 and annex 08). Thus, based on the duration of the effect, it can be assumed that the device may be in contact with the body for up to 16 weeks.

1.11 Maximum number of repeat application

The amount injected will depend on the skin's condition and need.

Initial treatment can be supplemented with one or two additional sessions with a three-week interval between sessions, depending on the skin's condition.

1.12 Identification of organs, tissues or body fluids contacted by the device

The device is in contact with dermal and connective facial tissues.

1.13 Precautions

The device is indicated to be injected into the superficial dermal tissue.

Precautions are referred to in the IFU (annex 02) as precautions for use and warnings.

Precautions for use:

- This device must only be administered by a doctor who is familiar with intradermal injections for aesthetic improvement.
- Sensitive skin may be pre-treated using a local anaesthetic patch or cream.
- Discard the syringe, remaining product and needle after use in a special container.

Warnings:

- Verify the integrity of the syringe and the expiry date before use.
- Do not use a syringe with an open or shifted tip cap within the protective packaging.
- Do not use any other needle or syringe than provided by the manufacturer.
- Do not manipulate/bend the needle.
- Do not re-use; quality and sterility can only be guaranteed for a syringe in its original package.
- The re-use of the device creates a potential infection risk for patients or users.
- If the 30G ½" needle is blocked, do not increase the pressure on the plunger rod but stop the injection and replace the needle.
- There are no available clinical data (efficacy, tolerance) about injecting the device into an area which has already been treated with another filling product or botulinum toxin.
- Do not inject into blood vessels, bones, tendons, ligaments, nerves or muscles.
- Do not inject the device into naevi.
- Do not use an automated injection system to inject this product.
- Patients should be advised not to apply any make up for 12 hours after the injection and to avoid prolonged exposure to sunlight and UV or using saunas or Turkish baths for one week after the injection.
- To avoid a possible risk of product mobility, the patient should be advised not to massage the treatment site for a few days following the injection.

- There are incompatibilities between sodium hyaluronate and quaternary ammonium compounds such as benzalkonium chloride solutions.
- Therefore the device should never be placed in contact with these substances or with medical-surgical instruments that have been in contact with these substances.

1.14 Methods of use and undesired effects

Methods of use:

- The device must be injected into non-inflamed, disinfected, healthy skin.
- The technique used is essential for the success of the treatment.
- Use the 30G ½" needle which is provided with the syringe and inject slowly by applying the appropriate injection technique.
- Consider that the device will attract water and will increase its volume in situ.
- Avoid injecting large volumes in the periorbital area.
- The amount injected will depend on the skin's condition and need.
- Initial treatment can be supplemented with one or two additional sessions with a three-week interval between sessions, depending on the skin's condition.
- After the injection, doctors may apply a light massage in order to distribute the product uniformly.

Undesired side effects:

Physicians must inform the patient that there are potential side effects and/or incompatibilities associated with implantation of this device, which may occur immediately or may be delayed.

The following events and reactions have been observed with the device or similar products:

- Bacterial infections
- Bleeding during and after injection
- Edema
- Erythema without swelling that resolves within one week or in extreme cases after up to 2 months
- Granuloma
- Hypersensitivity to sodium hyaluronate
- Hematoma
- Indurations or nodules at the injection site
- Inflammation that may coincide with itching and pressure sensitivity for up to a week after the injection
- Pain during injection
- Papules
- Swelling of tear troughs
- Transient pain or discoloration at the injection site.

Patients must inform their physician as soon as possible about any inflammatory reactions which persist for more than one week or any other secondary effect which develops.

The physician should treat these side effects appropriately.

Any undesirable side effects associated with the injection ofthe device must be reported to the distributor and/or to the manufacturer.

1.15 Claims on clinical performance and clinical safety

The device is a viscoelastic solution used to replenish the loss of hyaluronic acid due to aging, to maintain hydration, to improve tone and elasticity of the skin and to act as a filler for small lines such as crow's feet, smile lines or smoke lines surrounding the mouth.

The above claims were addressed in a clinical study performed by the manufacturer with the device [1.8% Sodium Hyaluronate with 2% Glycerol i.d.], see annex 07. The purpose of the study was to assess the effectiveness of Princess® RICH to correct fine lines on the face to assess the safety of Princess® RICH and to assess its ability to maintain skin hydration, improve skin tone and improve skin elasticity in the treatment areas.

The results of the study confirm that the device [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] can correct fine lines on the face and can maintain skin hydration and to improve skin tone and elasticity.

1.16 CE mark of the device and sales volumes

The present CER deals with a device CE-marked since 2009. The declaration of EU conformity was issued based on the clinical evaluation report "Safety and Efficacy of Aqueous solutions of Sodium Hyaluronate (18 mg/mL or 20 mg/mL) with 2.0% Glycerol for Intradermal Injection" evaluated and signed by the board-certified dermatologist Daisy Kopera (23.10.2008, C_CT_CER_005_01).

In the study evaluating Princess® RICH [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] (see annex 08) CPH-401-201364 "A prospective open -label, multicenter study evaluating Princess® RICH in correction of fine lines" (annex 08) the adverse events were rare and resolved completely, thus demonstrating the product's safety. In total, 36 treatment-emergent adverse events (TEAEs) were reported in 24 subjects (41%). 2 of the TEAEs were SAEs and were considered to be unlikely or not related to IMD or procedure. The remaining TEAEs were non-serious TEAEs, mostly located at the treatment area or just around the treatment area. None of the TEAEs led to the subject's withdrawal and the outcome of the TEAEs was 'resolved' within a few days to one week in most cases.

From 2009 until the end of 2019, 2.001.922 units of the product have been released with 59 complaints (affecting 390 items). This equates to a complaint ratio of 0.003% which confirms the favorable benefit/risk ratio for the device.

In the course of the post-market surveillance, complaints from CROMA and vigilance information sourced from competent authority databases for CE marked

products were checked for adverse reactions and events not yet covered by descriptions in the scientific literature. No new adverse reactions and events were found in the complaints listings (annex 06) and A_RA_PMSP_022, A_RA_PMSR_122, files on post-market surveillance Therefore, the safety profile of the device is well established and based on a sufficient number of treatments. These results confirm the favorable benefit/risk ratio for the device.

1.17 Changes since the last report

Please refer to Chapter 9.

2. Clinical background, current knowledge, state of the art

2.1 The medical field concerned and relevant medical conditions

The device is indicated for the age-related loss of hyaluronic acid in the skin. Hyaluronic acid contributes to the water retention abilities of cutaneous tissue. The hyaluronic acid content of the skin decreases with age. This causes a loss of turgor and elasticity, leading to the formation of lines and wrinkles.

The device is a viscoelastic solution used to replenish the loss of hyaluronic acid due to aging, to maintain hydration, to improve tone and elasticity of the skin and to act as a filler for small lines such as crow's feet, smile lines or smoke lines surrounding the mouth.

The device is not intended to treat any medical condition, for aesthetic purposes only (unmet medical need).

The product is designed to be injected into the superficial dermal tissue. It is totally resorbed. The device is intended for single-use, it is sterile, non-active and without measuring function. No materials of animal origin are used during manufacturing or as raw materials. No medicinal products are integrated into the device.

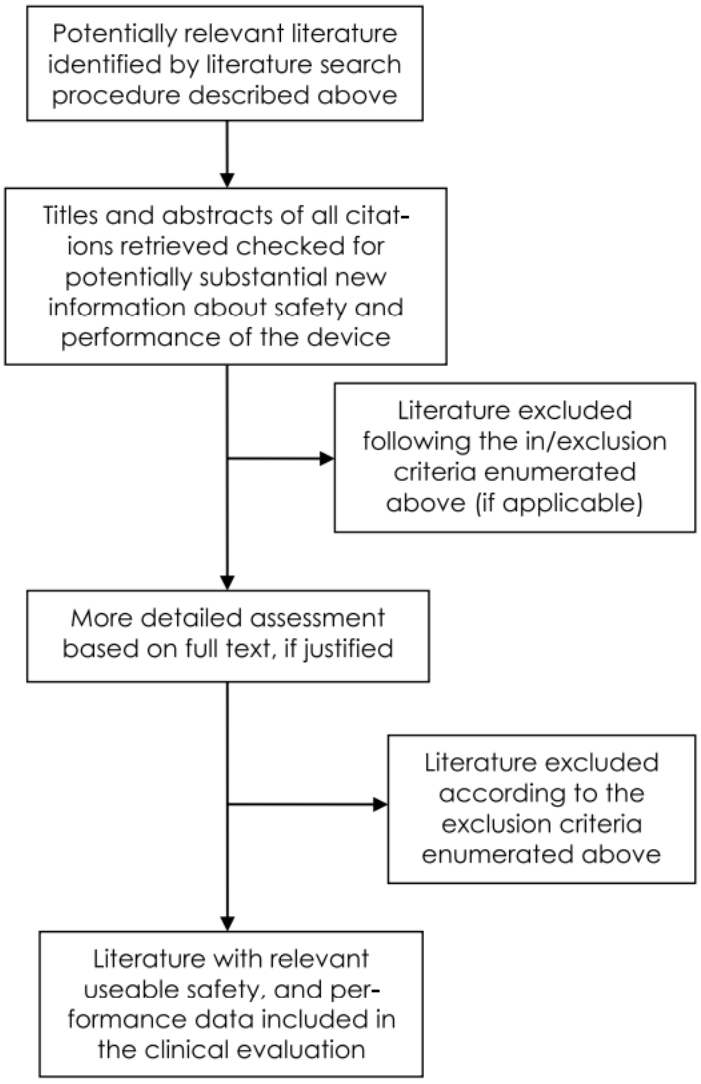
The device is an absorbable implant to be used for adult people. The product is contraindicated in pregnant or lactating women and persons under 18 years of age, see also exclusion criteria in Chapter 1.7.

2.2 Literature search strategy for the retrieval of information on current knowledge, state of the art, diagnostic option, available therapeutics and management

The objective of the literature search is to select literature reflecting the current knowledge, state of the art, diagnostic options available therapeutics and management.

The methodology for the assessment of citations is shown in the flow chart below. The methodology is further described in CROMA GmbH internal MSOP document (C_CT_MSOP_002 entitled "Literature search for post-market clinical follow-up and clinical evaluation") as well as the search protocol form C_CT_FORM_008 is a CROMA GmbH quality controlled document which is part of the EN ISO 13485:2016 certified quality management system.

Figure 1 Methodology for the assessment of citations



Literature search/retrieval for dermal aesthetic applications:

A literature search was performed on 22.10.2019 (time frame 01.01.2009 to 31.09.2019, search protocol form C_CT_FORM_008 (see annex 03).

Search Terms (number of retrieved citations in parentheses)

1. Hyaluron* Filler Filters (868)
2. Available therapeutic and dermal filler (558)
3. Available therapeutic and dermal filler Filters (98)

4. management and dermal filler (233)
5. State of the art and dermal filler (3)
6. Diagnostic options and dermal filler (19)
7. Benchmark device and dermal filler (0)
8. Princess rich (138)
9. Dermalstyle light and dermal filler (59)
10. Estelite vita (2)
11. M-HA18* (1)
12. Hyalax revitalize skin* (8)
13. Saypha RICH and dermal filler (18)
14. Hyalax REVITALIZE SKIN and dermal filler (1)
15. Apriline HYDRO and dermal filler (2)
16. JALOR re-Style and dermal filler (0)
17. ZFill refresh and dermal filler (1)
18. Pluryal Booster and dermal filler (0)
19. GENYAL Genyalift and dermal filler (0)
20. Definisse hydrobooster and dermal filler (0)
21. Hyaluron* AND Glycerol AND intradermal (2)
22. Hyaluron* AND Glycerol AND cutaneous (5)
23. Hyaluron* native AND intradermal (4)
24. Hyaluron* AND native AND cutaneous (6)
25. Hyaluron* AND Glycerol AND mesotherapy (0)
26. Hyaluron* AND native AND mesotherapy (0)
27. HA and mesotherapy (7)
28. Hyaluron and mesotherapy (0)
29. hyaluronan and meso therapy (1)
30. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 (1723)
31. #30 and improved facial hydration (4)
32. #30 and facial skin tone (17)
33. #30 and skin elasticity (52)
34. #30 and hydration (35)
35. #29 and skin tone (29)
36. HA and mesotherapy (8)
37. #31 or #32 or #33 or #34 or #35 or #36 (100)
38. #30 and small lines (10)
39. #30 and and smoker lines (0)
40. #30 and smoker lines (0)
41. #30 and smile lines (1)
42. #30 and crow's feet (9)
43. #37# or #38 or #39 or #40 or #41 or #42 (116)

Search Terms (number of retrieved citations) used for the present CER. Collection with the PubMed database retrieved 116 articles. Of the116 articles, 37 were selected for inclusion in the CER (Annnex 03).

question or alternative devices
— works dealing with "off label use" (e.g. special needles, manipulation of the product by dilution or mixture with other substances, pediatric patients)
— obvious product placement for marketing purposes without substantial clinical data.

Additional selection criteria
— systematic reviews/meta-analyses + recent articles
— including reviews
— including original study reports
— including all articles

Search performed by:	Signature:
Name/Short Name/Department/Function Robert McMahon/rmc/CT Medical Writing Manager	Robert McMahon Date 22/10/2019

The objective of the literature search strategy is to find data generated through literature searches relating tou nmet medical needs, to the description of available therapeutic/management/diagnostic options and to benchmark devices. The search results (citations and abstract) were screened for substantial new information about the safety and performance of the device.

The justification of the literature search strategy of each citation is described throughout the search protocol in annex 03, whether the citation is retrieved or not was added for purposes of quality control measures. The substantial information from the literature will support the safety and performance and the risk/benefit profile of the device under assessment. The literature search has been performed following the methodology given in MEDDEV 2.7.1 Rev. 4. The search terms were chosen so that works dealing with hyaluronic acid fillers in general, as well as with benchmark products were retrieved. Publisher statements regarding peer reviews are added in annex 05.

The following strategy for addressing the potential for duplication of data across multiple publications was adopted:

(1) Data from recognized, peer-reviewed journals were used. The potential for duplication of data across multiple publications is low with peer-reviewed journals because double publication of original data is forbidden in serious scientific periodicals and generally regarded as a violation of good scientific practice;

(2) Full-texts of all included works were retrieved and data of studies were compared;

(3) The objective of the present evaluation is to check whether there is any substantial new information concerning the risk/benefit ratio of the device published in the time frame 01.01.2009 to 31.09.2019.

None of the retrieved randomized controlled studies indicated a substantial change to the present risk/benefit ratio. Double publication of single datasets would have no impact on this result. However "multiplication" of data across publications is expected as far as reviews, systematic reviews and meta-analysis are concerned. This will not bias the outcome of the clinical evaluation because original data are not expected in reviews and meta-analysis and the source of the original data is listed in these works.

As explained above, all retrieved citations were scrutinized for new data according to the process documented in the clinical evaluation report. All relevant data were selected. There was no "selection" for or against "favorable" or "unfavorable" data. Furthermore, reviews dealing with the clinical experience with hyaluronic acid fillers were included in the evaluation. These reviews include additional independent search and evaluation processes, including an independent evaluation of clinical data.

In order to conduct a comprehensive search, all abstract of retrieved works (numbers see above) were checked for the compliance with the Inclusion/Exclusion criteria enumerated below:

Inclusion criteria:

— Works including clinical data about the safety and performance of the device and the equivalent or similar benchmark devices

— Works reflecting current state-of-the-art

— Works published in recognized scientific publications

— Works reporting the outcome of a study according to scientific principles.

Exclusion criteria[3]:

— Single case reports without substantial new safety and performance information

— Works dealing with non-equivalent/similar devices without substantial safety information

[3] Please note, that "excluded" works may be cited within this document according to the general practice of scientific documentation. These works will be also listed in the literature list, but are not included in the analysis of clinical data and may not be discussed in detail

— Unrelated works not dealing with HA fillers for facial soft tissue augmentation

— Technical descriptions dealing with injection and treatment methods

— Material related works dealing with physical and chemical properties of fillers

— Opinions and comments without substantial clinical data

— Animal studies, if unrelated to the safety of the device

— Historical and general works without actual clinical data

— Works dealing exclusively with HA fillers with additional substances other than glycerol

— Works dealing with breast and genital augmentation

— Works dealing with combination therapies not focusing on the device in question or alternative devices

— Works dealing with "off label use" (e.g. special needles, manipulation of the product by dilution or mixture with other substances, pediatric patients)

— Obvious product placement for marketing purposes without substantial clinical data.

The objective of the literature search is (1) the inclusion of substantial new data about the safety of HA dermal fillers and (2) the inclusion of substantial new data of the performance of the device, the equivalent device, and similar benchmarked devices into the clinical evaluation. Search for safety data includes necessarily the inclusion of "unfavorable data".

In order to avoid an unduly burdensome and inappropriate extent of the clinical evaluation, works without substantial new information were excluded (see exclusion criteria). The proximal reason for the exclusion of the excluded works is, that the excluded works did not meet the inclusion criteria.

2.3 Applicable standards and guidance documents

In the course of the present clinical evaluation and the particular technical and clinical properties of the medical device group [1.8% Sodium Hyaluronate with 2% Glycerol i.d.], the following standards and guidelines in Table 3 were applied.

Table 3 List of international standards complied with in full or in part

CROMA HEALTH • CARE • INNOVATION	
FORM to C_RA_MSOP_001	
List of Applied Regulatory Requirements	C_RA_FORM_092_01
	Valid from 23.09.2016
	Page 1 of 2

Technical dossier:
[1.8% Sodium Hyaluronate with 2% Glycerol i.d.]

General	
Council Directive 93/42/EEC of 14 June 1993 concerning medical devices, last amendment by Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007	
Commission communication in the framework of the implementation of the Council Directive 93/42/EEC concerning medical devices - Publication of harmonised standards under the directive	
Austrian Medical Devices Law based on MDD 93/42/EEC	
Canadian Medical Devices Regulations of May 7th 1998 (CMDCAS Supplement to ISO 13485), latest version	
Health Canada: List of applicable standards, latest version	
Taiwan – Regulations for Governing the Management of Medical Device	
MEDDEV 2.12/1 rev.8	Medical Devices – Vigilance System
EN ISO 13485:2016	Medical devices — Quality management systems — Requirements for regulatory purposes
ICH Guideline Q1A(R2)	Stability Testing of new drug substances and products
Ph. Eur.	European Pharmacopoeia
Product related	
EN ISO 14630:2012	Non-active surgical implants — General requirements
EN 20594-1:1993 / AC:1996	Conical fitting with a 6% (Luer) taper for syringes, needles and certain other medical equipment – Part 1 General requirements
EN 62366-1:2015 / AC:2015	Medical Devices – Part 1: Application of usability engineering to medical devices
EN ISO 16061:2015	Instrumentation for use in association with non-active surgical implants - General requirements
Risk Analysis	
EN ISO 14971:2012	Medical devices — Application of risk management to medical devices
Manufacturing and Sterilisation	
GMP-Guidelines	Guideline for Good Manufacturing practice for Pharmaceutical products
EN 556-1:2001 / AC:2006	Sterilization of medical devices — Requirements for medical devices to be designated 'STERILE' — Part 1: Requirements for terminally sterilized medical devices
EN ISO 11138-3:2009	Sterilization of health care products — Biological indicators — Part 3: Biological indicators for moist heat sterilization processes
EN ISO 11737-1:2006/ AC:2009	Sterilization of medical devices – Microbiological methods – Part 1: Determination of a population of microorganisms on products
EN ISO 11737-2:2009	Sterilization of medical devices – Microbiological methods – Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process
EN ISO 17665-1:2006	Sterilization of health care products — Moist heat — Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices

2.4 Current knowledge, state of the art, diagnostic option, available therapeutics, and management

Evidence that the device complies with the current state of the art results from the following:

1. Only works reflecting current state-of-the-art, published in recognized scientific publications and reporting the outcome of a study according to scientific principles were included in the analysis. The update was conducted as described above in Chapter 2.

2. Randomized clinical trials and other works, including uncontrolled clinical trials, and reviews complied with the given Inclusion/Exclusion criteria in the reporting period from 01.01.2009 to 31.09.2019 for dermal aesthetic applications. Please see annex 02 for the literature search form completed on the 22.10.2019 and the list citations collected.

A high number of papers about similar HA-fillers were published during this time. This reflects the high professional interest and the fact that hyaluronic acid fillers are considered to be superior to alternative products. The reason why more controlled studies, comparing hyaluronic acid fillers with alternative products were not retrieved for the reporting period is that other absorbable fillers were pushed from the market by hyaluronic acid fillers. Collagen fillers had a similar indication and application profile; however, they are no longer available in the EU and in the US.

3. As shown above, the included publications reach an almost unequivocally positive conclusion about the risk/benefit ratio of the device.

4. The superior safety profile of HA fillers is confirmed by multiple studies. In contrast to other devices (e.g. Collagen fillers) many complications of hyaluronic acid fillers can be easily corrected with hyaluronidase (Mckee, Remington et al., 2019). Furthermore, as expected from the fact that hyaluronic acid is a natural constituent of human tissue, immunological reactions with hyaluronic acid fillers are virtually absent.

Facial ageing involves a multitude of factors ranging from dermal thinning, to loss of dermal collagen and decreased lipid production in conjunction with a loss of hydration and elasticity causing dynamic lines formation as the result of facial muscle action. Many procedures continue to be options for the treatment of ageing , with minimally invasive aesthetic procedures gaining popularity in recent years we have seen an increase in the use of dermal fillers. This review of the current literature is a summary for understanding which dermal fillers and alternative treatments are available for improving hydration, skin tone and elasticity (Braccini & Dohan, 2010).

Due to their composition, fillers are well known and widely used in aesthetic medicine. Fillers are effective: in reducing the signs of ageing , attenuating wrinkles and skin depressions, remodeling the sides of the face, restoring shape and volume to the lips,

correcting imperfections due to acne or scarsaugmenting hydration and improving both the elasticity and tone of the skin. The filling materials that are most commonly used with respect to their degradation, filler materials may be classified as temporary (degradable), semi-permanent and permanent (not degradable).

Alternative therapeutics:

a) Botulinum toxin is a pharmaceutical blocking neurotransmission at the neuromuscular junction, thereby producing muscle paralysis/relaxation, so that the skin appears flattened. In contrast, soft tissue fillers are used for volume augmentation. Consequently, the mode of action and the clinical outcome of botulinum toxin is different from hyaluronate fillers. Both methods may be combined. However, botulinum toxin alone cannot be regarded as a therapeutic alternative to hyaluronate fillers. The application of neurotoxins is routinely performed in combination with dermal fillers (Braccini & Dohan, 2010).

b) The mode of action and the intended use of lasers in the context of facial rejuvenation is the ablation of skin layers and/or the infliction of dermal wounding, and/or the application of thermal effects. This may improve skin elasticity, homogeneity of skin color and appearance of fine lines (Langelier, Beleznay et al., 2016). However, no space-occupying effect comparable to soft tissue fillers can be achieved by laser treatment (Ricci, Navajas et al., 2015; Langelier, Beleznay et al., 2016).

c) Mesotherapy, micropeeling, and chemical peels are three very different techniques used today for the common goal of facial rejuvenation. Mesotherapy involves multiple injections of bioactive substances. The injections can be a solution such as multivitamin and a non-cross-linked HA. Microneedling utilizes controlled needle penetration of the skin to induce regeneration of the skin components. These methods aim to increase hydration (Braccini & Dohan, 2010).

A summary of the different types of fillers as well as alternative treatments is given below:

<u>Permanent or Semi-permanent Fillers</u>

Permanent fillers such as polymethymethacrylate (PMMA) behave as foreign bodies. PMMA is injected into a subdermal depth and gives the advantage of providing a long-term correction that does not require the patient to have frequent refilling. Additionally, PMMA stimulates collagen production. However, like other permanent fillers, such as those derived from silicon oil and minerals, it isnot biodegradable and may cause serious and irreversible side effects. Early generations of the product had a high incidence rate of granuloma formation but adjustments to the microsphere size have resolved this problem to an acceptable rate. This was the result of making larger PMMA microspheres (30-50 microns) in bovine collagen. Consequently, patients are required to take a skin test due to the risk of hypersensitivity reactions. PMMA is not recommended for use with the lips and around eyes (Lighthall, 2018).

Calcium hydroxyapatite: Calcium hydroxyapatite filler is well studied dermal filler that consists of a suspension of 25–45 µm large particles in a viscous carboxymethylcellulose gel. Calcium hydroxylapatite combines high elasticity and viscosity and can induce long-term collagen formation. However, calcium hydroxyapatite is a less degradable mineral substance. The gel structure dissipates in vivo and is subsequently replaced with soft tissue so that the calcium hydroxyapatite at the site of the injection is surrounded by connective tissue. This can lead to a high rate of nodularity. This is an important clinical difference to hyaluronate fillers since future changes in the fat-content or rigidity of the soft tissue have to be considered before treatment. The applicability is further limited by the lack of immediate reversibility of injected material. (Lighthall, 2018) (Emer & Sundaram, 2013).

Absorbable Fillers: All fillers that are biodegradable contain polysaccharides, components of the dermis that tend to progressively reduce the signs of the ageing process. The body can enzymatically absorb these molecules at a variable rate after filler injection. The degradationhappens under the skin aided by facial movements. Fillers based on poly Lactic acid (PLA) stimulate the production of collagen by inducing the production of a foreign body reaction thus initiating fibrosis. The product requires reconstitution with sterile water 24 hours prior to application. The product is injected in a subcutaneous orsubperiosteal plane and requires multiple treatment sessions. To minimize nodule formation patients are instructed to massage the areas to help disperse the product. Poly-L-lactic microparticles should be avoided in dynamic areas as repetitive movements lead to the product clumping together and the delayed occurrence of nodules with an often prolonged course of resolution (Lighthall, 2018).

Autologous fat: The first dermal filler for tissue augmentation was described in the late 19th century by Franz Neuber. It used autologous fat (Lipofilling) to correct facial depressions. This is a natural and non-allergenic method to fill a specific part of the body using fat cells drawn from other body sites of the same individual thereby negating autoimmune rejection. However, while the hyaluronic acid-based fillers are completely absorbable, lipofilling can be considered as nearly permanent (Bioulac, Heppt et al., 2015).

The most common absorbable fillers are based on hyaluronic acid (HA). This substance is a natural polysaccharide and is ideal for dermal fillers due to HAs chemical-physical properties, biocompatibility, biodegradability, and versatility. The substance in the body surrounds extracellular spaces, and is associated with proteins such as collagen and elastin. It is a component of the dermis, vitreous of the eye, hyaline cartilage, synovial joint fluid, and umbilical cord. Its biologic functions range from structural support to embryonic development, cellular proliferation and differentiation, cell signaling, and wound healing. These characteristics of HA along with its complete absence of immunogenicity and antigenicity and the fact thatthe body contains enzymes which can catalyze and absorb these molecules over time making it an ideal molecule for aesthetic medicine (Salwowska, Bebenek et al., 2016).

In aesthetic medicine HA is used to increase the volume and correct the borders of the lips, eye wrinkles, to remodel the shape of the face, to correct scars due to acne or trauma and to improve hydration tone and elasticity of soft tissues. The effects can last for 6-18 months, depending on the complexity of the molecule used (Mckee, Remington et al., 2019).

Several different HA fillers are available. The differences lie in the manufacturing process, allowing for tailored uses. These differences in characteristics consist of HA concentration, modulus, particle size and degree ofcross -linking, the amount of unmodified HA present and the extrusion force. To extend the duration of HAs within the dermis and obtain the particle texturing feel, HAs are crosslinked to obtain the suitable mechanical properties. Conventional cross-linking involves treating natural HA with a linking agent (often BDDE) which generates a synthetically cross-linked gel. A lower degree of cross-linking creates a softer gel, and vice versa, meaning that this range of products provides different levels of resistance to deformation. The least cross-linked product would be best for very fine lines, improving elasticity and skin tone, whereas the more cross-linked products provide volume. Furthermore, HA particle size or calibration plays are role in the characteristics of a filler and is set during manufacturing by passing the HA gel through screens of varying pore size. The smaller gel particles are less viscous and provide less lifting capacity. They are indicated for more superficial dermis such as treating for finer lines. Whereas larger gel particles have greater lifting capacity, which is required for more severe lines and deeper injections (Greene & Sidle, 2015; La Gatta, De Rosa et al., 2016) (Iannitti, Morales-Medina et al., 2016).

Hyaluronic acid in the skin can have a positive impact, as demonstrated from the work of Maytins group which made clear that HA binds to the CD44 receptoron the outer surface of dermal fibroblasts, acting to regulate fibroblast physiology, by supporting and stimulating extracellular matrix molecule production. This implies that it might be possible to modify the amount of collagen produced in the skin by upregulating or down-regulating HA synthesis (Maytin, 2016).

The two classifications of HA dermal fillers are monophasic and biphasic. Monophasic and biphasic. Monophasic HA fillers (Surgiderm 24XP, England, Juvéderm Ultra™, USA) are cross-linked with non-particulate HA gels. In contrast, biphasic fillers (Restylane®, Q-Med, Sweden) consist of gel particles of stabilized HA suspended in a non-cross linked HA (NHA). The cross-linked HA (CHA) gel particles are suspended in NHA, which acts as a lubricant, allowing the suspension to be pushed through a fine needle. They are reported to have a rapid initial degradation of NHA and slower degradation of the cross-linked gel particles, whereas monophasic gels are degraded more uniformly.

Within the context of improving hydration, skin tone and elasticity a vast array of alternative therapeutic options exist. A literature review published by (Choi, Sung et al., 2019) analysed 11 studies involving 805 patients and concluded that oral collagen supplements may improve skin elasticity, hydration and dermal collagen density.

Glycolic acid, the smallest a-hydroxy acid, is a product with exfoliating proprieties stimulating the production of new cells that give new life to the skin, eliminating wrinkles and scars. Glycolic acid peels can be effective in treating some signs of ageing. Topical glycolic acid may also be used as combined therapy with retinaldehyde in a topical cream to improve cutaneous hydration (Bergstrom, 2009).

Other topical treatments have been explored to investigate their ability to improve skin tone. Fischer et al investigated the effects of topical application of folic acid and creatine and found that treatment of aged skin counteracted the age-dependent decline in firmness by exerting sustained effects on collagen metabolism (Fischer, Achterberg et al., 2011).

Taub et al showed in a multi-center, double-blind vehicle-controlled clinical trial that an alpha defensin 5 and beta defensin 3 containing skincare regimen of 3 products globally and statistically significantly improve the visual appearance and stimulates skin rejuvenation without apparent carcinogenic risk. The mechanism of action is proposed to be that defensins activate the body's own dormant stem cells to generate healthy new epidermal cells (Taub, Bucay et al., 2018). Furthermore, the effect of a combination of recombinant epidermal growth factor (EGF) cosmetic serum and a crosslinked hyaluronic acid serum compared to a fibroblast-conditioned media serum was investigated to observe their effects on the appearance of ageing over 12 weeks in 60 females with mild to moderate photoaging. Investigator, noninvasive, and subject assessments were collected at baseline and at weeks 2, 4, 8, and 12. The blinded investigator noted a statistically significant preference for the EGF/RHA at week 2 in terms of smoothness and firmness. This improvement continued into weeks 4 and 8 with continued superior EGF/RHA results in fine lines, radiance, and overall appearance by week 12. Transepidermal water loss was reduced for the EGF/RHA over the TNS at week 12. The subjects gave high ratings to both study products. This research demonstrated the utility of recombinant growth factors when combined with hyaluronic acid hydration, in improving skin cosmetic attributes (Draelos, 2016).

Tretinoin is a form of vitamin A that is helpful in skin renewal. Topical tretinoin has been used previously to treat acne, to smooth rough facial skin, and to reduce the appearance of fine wrinkles and mottled skin discoloration. However, its irritation potential has prompted dermatologists to switch overto less irritating but comparably effective retinoids such as adapalene and to some extent retinol and retinaldehyde (Bergstrom, 2009).

Kang et al showed that adenosine-loaded dissolving microneedle patches improved skin wrinkles, dermal density, elasticity and hydration. The adenosine-loaded dissolving microneedle patches had a similar or better efficacy than the adenosine cream. Both groups showed statistically significant efficacy for almost all parameters. The dissolving microneedle patches had a long-lasting effect on the average wrinkle depth and had

an early improving effect on elasticity. Moreover, the patches demonstrated a high hydration efficacy (Kang, Tu et al., 2018).

Although the efficacy of hyaluronic acid has been shown to improve skin hydration and elasticity when applied topically (Sundaram, Cegielska et al., 2018) (Pavicic, Gauglitz et al., 2011), micropuncture (mesotherapy) treatments have proved themselves to be a reliable technique which can improve tone, elasticity and hydration ultimately rejuvenating tired skin. Mesotherapy was first conceived back in 1952 by French doctor Michel Pistor. It acts by using many small doses (in the microliter range) of substances injected intradermally over the relevant treatment area (Braccini & Dohan, 2010). For the purposes of skin rejuvenation, this technique when used with hyaluronic acid fillers has had proven success.

Benchmark HA devices used to maintain hydration, improve tone and elasticity of the skin or to act as a filler for small lines such as crow's feet, smile lines or smoke lines surrounding the mouth.

For theimprovement of small lines such as crow's feet a review from Bukari et al elucidated thorough analysis of the literature that HA-based formulations (i.e., gels, creams, intra-dermal filler injections, dermal fillers, facial fillers exhibit notable anti-wrinkle, anti-nasolabial fold, anti-ageing, space-filling, and face rejuvenating properties. This has been achieved via soft tissue augmentation, improved skin hydration, collagen and elastin stimulation, and face volume restoration. Trevidic et al performed a prospective, split-face, randomized, long term blinded objective comparison of the performance and tolerability of two new Hyaluronic acid filers ART FILLER Universal (AFU) and ART FILLER Fine lines (AFFL) with the existing HA fillers for the treatment of nasolabial folds and crow's feet. The severity of nasolabial folds and crow's feet was assessed by independent blinded evaluators using the Lemperle scale at baseline. Tolerability, Global Aesthetic Improvement Scale (GAIS), wrinkle volume, skin thickness and density were also measured at D30/D45, D90, and D180. At D30 and D180 respectively, 61 and 57 patients were assessed. Scores for nasolabial folds and crow's feet showed statistically significant improvements at D30, D90, and D180. AFU and AFFL were noninferior to JUV and FLPS, respectively. Most patients showed GAIS improvements, maintained until at least D180 and significant increases of collagen synthesis in crow's feet and nasolabial folds. Treatments were well tolerated (Trevidic, Andre et al., 2017).

In another study Beer et al studied the effects of hyaluronic acid and botulinum toxin on the periorbital, temporal, glabellar, and crow's feet areas. This study evaluate d the combination of abobotulinumtoxin A (Dysport) and hyaluronic acid 20 mg/mL (Perlane) for rejuvenating specific areas of the upper face. Subjects with mild to moderate temporal volume loss as well as glabellar and/or periorbital rhytids were enrolled in this single-center, open-label, non-randomized pilot study. Subjects were randomly assigned a number and treated with hyaluronic acid, divided between temporal and

glabellar region, and abobotulinumtoxinA in the periorbital and glabellar region. A 1-month touch-up was given if needed. Subjects were evaluated by the investigator, and each subject completed a questionnaire at baseline and at 3, 6, and 9 months after treatment. For crow's feet, median grades decreased from baseline at 1 month and at 3 months, but returned to baseline values at 6 months. For temporal assessments, the median grade decreased from baseline at 1, 3, and 6 months and returned to baseline at 9 months. Among subjects previously treated with botulinum toxin alone, 64% rated the combination treatment said "superior." Adverse effects were mild and transient. Therefore the authors concluded that the combination of abobotulinumtoxinA and hyaluronic acid appeared to rejuvenate the periorbital, temporal, glabellar, and crow's feet areas with minimal adverse effects (Beer, Julius et al., 2014).

In a review of the currents concepts in the use of small particle Hyaluronic acid (SP-HAL), Bertucci et al presented evidence that SP-HAL has demonstrated proven benefits for lip fullness, augmentation, and treatment of perioral rhytides. Although off-label in the United States, SP-HAL is also well suited for the treatment of superficial fine lines, including periorbital, forehead, marionette, and smile lines. Additionally, it was described that a novel application for SP-HAL includes use as a skin booster with intradermal micropuncture (Bertucci & Lynde, 2015).

Sundaram et al described how cohesive polydensified matrix hyaluronic acid can be used in the treatments of fine lines. The authors showed that cohesive polydensified matrix hyaluronic acid (Belotero Balance) is a notably efficacious fine line filler that can be used for the treatment of perioral lines and periocular lines withstandingmechanical stress, swelling minimally, and potentially stimulating collagenesis (Sundaram & Fagien, 2015).

Furthermore, Brandt et al assessed the safety and effectiveness of small(SGP -HA) and large (LGP-HA) gel-particle hyaluronic acid in the correction of perioral wrinkles. The primary objective of this study was to investigate the safety of SGP-HA and LGP-HA in treating facial wrinkles and folds around the mouth. Patients with a mean age of59.6 years were treated with an average of 5.58 plus minus 1.15 mL of HA for the entire perioral area. Treatment areas included NLFs, marionette lines, oral commissures and perioral rhytides. Patients experienced a total of 66 treatment-emergent AEs (TEAEs); each patient experienced at least one TEAE. The maximum intensity of all TEAEs was considered mild. Most TEAEs resolved within seven days, with an average duration of four days. No serious TEAEs occurred during the study. One hundred percent of GAIS evaluations by both investigators and patients indicated improvement, regardless of filler used or area treated. In conclusion, the authors found that both SGP-HA and LGP-HA were found to be safe and effective for the correction of perioral wrinkles and folds (Brandt, Bassichis et al., 2011).

It has been demonstrated that the efficacy and tolerance of a non-cross linked HA filler in sustainably improving the skins elastic parameters and complexion radiance. The

authors showed that intradermally microinjected HA improves suppleness of ageing skin (Baspeyras, Rouvrais et al., 2013) (Youn, Hong et al., 2018). Moreover, Tedeschi et al used with high-frequency ultrasound to determine if HA mesotherapy improves the signs of ageing and showed that significant changes in the density of the subepidermal low-echogenicity band in patients treated with HA (Lacarrubba, Tedeschi et al., 2008; Tedeschi, Lacarrubba et al., 2015).

Roh et al studied the mid-dermal injection of stabilized hyaluronic acid-based gel of nonanimal origin in a single-center, evaluator-blinded, prospective, split-face, randomized controlled trial using a stamp-type electronic multi-needle injector. Twenty-five patients were recruited. Each participant submitted to a single treatment to one side of the lower cheek. The skin hydration, melanin content, erythema, and elasticity of both cheeks were evaluated at each follow-up visit, at 1, 2, 4, 8, and 12 weeks after treatment. The authors reported significant improvements in the stratum corneum hydration after injection. Although no significant improvement was observed at 1 week after treatment, the corneometer readings for the treated side were significantly higher than those for the untreated the side after the 2-, 4-, 8-, and 12-week treatment visits. Skin elasticity was also significantly improved during the study. The treatment was well-tolerated, and no serious adverse events were reported (Roh, Kim et al., 2016). Jones et al also reported an improvement in skin hydration upon microinfections of transparent Hyaluronic acid gel for cheek rejuvenation (Jones, Vanaman Wilson et al., 2018).

Furthermore, Seok et al investigated the relationship between skin hydration and stamp type microneedle intradermal hyaluronic acid injection in middle-aged male faces and found that automatic stamp type microneedle intradermal injection of HA Elravie Balance ® improves skin hydration for rejuvenation in this patient group (Seok, Hong et al., 2016).

Lee et al conducted a study with Restylane® Vital (stabilized HA-based gel of non-animal origin for facial skin rejuvenation using a stamp-type multi-needle injector. A total of 30 female patients underwent a series of procedures including three sessions at intervals of four weeks. A total of 2 mL of Restylane Vital was injected along the whole face using an automatic injector. Improvement of skin surface roughness, elasticity, brightness, moisture, and fine wrinkles was evaluated. The majority of patients (77%) were satisfied with the therapeutic outcomes. Approximately 66% of patients responded that the effects of this procedure persisted for longer than four months, and the majority of patients (77%) wanted to undergo this procedure again and would recommend this procedure to acquaintances. Regarding the doctors' evaluation, scores for improvement of skin surface roughness, elasticity, and brightness were significantly higher than those for improvement of moisture (Lee, Han et al., 2015).

Succi et al performed a study where they treated patients with an injectable nonanimal non-crosslinked glycerol added hyaluronic acid preparation. The study found an improvement of between 25% and 50% in skin brightness, texture, and turgor was

observed in the periorbital area. Papules were present after each application, and the hematoma was the longest-lasting effect. All adverse events were reversible and well-tolerated. The authors concluded that the Injections of HA of nonanimal origin, in association with glycerol, using a micropuncture technique was well tolerated and can improve skin brightness and turgor and reduce roughness in the periorbital region (Succi, da Silva et al., 2012).

Finally, a recent publication by Kleptow aimed to study the performance and safety of a new cohesive polydensified matrix HA filler ([CPM®-HA20G, Belotero Revive,® lidocaine-free], for the treatment of early signs of facial skin ageing by use of biophysical measurements as well as subject and investigator satisfaction. Healthy female subjects with signs of facial skin ageing were enrolled in this open-label, rater-blinded, observational post-market clinical follow-up study, and received 20 micropuncture treatments of 50 µL CPM® -HA20G each into the lower cheek area at three injection visits 4 weeks apart. The authors reported a significantly increased elasticity of the skin (at weeks 9 and 12), skin firmness (up to week 24), skin tone, radiance and skin hydration (all up to 36 weeks) with little side effects. Thus confirming PM®-HA20G is considered to be an effective and safe HA injectable for skin revitalization in patients suffering from signs of skin ageing and loss of skin elasticity (Hertz-Kleptow, Hanschmann et al., 2019).

Adverse events using hyaluronic acid, diagnostic options and management of AEs

AEs following HA filler treatment are relatively uncommon when applied by an experienced physician. However, potential adverse events must be discussed with each patient. The most serious AEs associated with HA fillers involve injection into or around the facial vasculature. The most commonly reported AEs associated HA fillers include, ecchymosis, erythema, filler-associated ischemia, swelling, injection site pain, itching, infection, with the least reported being bruising, abscesses, raised bumps, allergic reactions and tissue necrosis. Embolism/retinal occlusion and recurrent herpes virus infection have also been rarely reported however it's stipulated in the IFU (annex 02) that the device must only be administered by a doctor who is familiar with intradermal injections for aesthetic improvement and must exclude patients with recurrent HSV-1 infections and to never inject blood vessels or nerves. Mainly the only proven treatment for soft tissue ischemia in cases of HA filler is the use of hyaluronidase. Although good results may be achieved, clinicians should take steps to further reduce such risks and be prepared to treat any complications that arise (Greene & Sidle, 2015), (Winslow, 2009), (Langelier, Beleznay et al., 2016), (Iannitti, Morales-Medina et al., 2016), (Seok, Hong et al., 2016), (Mckee, Remington et al., 2019), (Lighthall, 2018), (Baspeyras, Rouvrais et al., 2013), (Roh, Kim et al., 2016), (Braccini & Dohan, 2010), (Lee, Han et al., 2015), and (Hertz-Kleptow, Hanschmann et al., 2019).

Adverse events which are described in the literature, AEs from complaint listings of as well as AEs from the manufacturer's clinical study with the device are summarized in Chapter 2.5 and are included in the current IFU, annex 02. The AEs are also part of the

risk analysis (see A_D_RMP_010, A_RA_MRIA_PR421, C_RA_DRIA_403, C_RA_RMR_421), including their severity and the probability. All listed complaints were considered in the course of the post-market surveillance which is continuously performed by the manufacturer. In conclusion, the publications outlined above concerning benchmark devices confirm the safety and ability to improve skin tone, and elasticity and to maintain hydration.

Conclusion on the state of the art

In conclusion, as many authors state, chemical, physical as well as biological characterization of hyaluronic based dermal fillers are essential to choose between the numerous products available on the market. These features characterize their performance and efficacy for optimizing their application. The demand in aesthetic medicine for safe, minimally invasive, and effective soft tissue augmentation procedures has become very important subsequently the use of hyaluronic based dermal fillers. Moreover, according to the literature, most adverse reactions occurring with hyaluronic acid fillers are quite uncommon, mild and easily resolved.

Although dermal fillers have been used effectively in the periorbital area for over 20 years, the vascular infarction remains the most serious adverse event. Therefore reversible and temporary hyaluronic acid filler (such as the device under assessment) are preferred. Vascular injury is not likely to occur with [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] because it is injected superficially in the dermis. In addition, it is described in the instructions for use (see annex 02) "This device must only be administered by a doctor who is familiar with intradermal injections for aesthetic improvement." and "Do not inject the device into naevi" and "Physicians must inform the patient that there are potential side effects and/or incompatibilities associated with implantation of this device, which may occur immediately or may be delayed." and "Patients must inform their physician as soon as possible about any inflammatory reactions which persist for more than one week or any other secondary effect which develops. The physician should treat these side effects appropriately."

Proper selection and placement of product can help avoid some complications. Nevertheless, it was decided that the device should not be injected into naevi, this statement is in the section "warnings". Furthermore , it is stated in the section "Method for use" that large volumes should be avoided in the periorbital area. As optimal complication management remains difficult in the esthetic medicine, proper patient, product and injection technique selection, and good anatomy knowledge will minimize their incidence (Ricci, Navajas et al., 2015), (Winslow, 2009).

In the literature, some authors suggest combining different treatments in addition to the use of an injectable HA, for example, topical HA serum into treatment plans to protect the skin surface or skin-rejuvenating lasers and energy-based devices to

represents a patient-tailored strategy. The variety in products provespatients needs for HA if they wish for facial rejuvenation or particular medicinal indications

In summary, each type of filler discussed above may have a special niche, so that different fillers cannot be regarded as interchangeable "alternatives" to HA-based fillers. Today hyaluronate fillers are the most popular fillers because of their favorable safety profile, their reversibility and their superior performance. From the facts enumerated above, it is obvious that hyaluronic acid fillers show a superior benefit/risk ratio, if compared withother products with similar indications. Hyaluronic acid fillers, including the device in question are unquestionable "state of the art".

3. Device under evaluation

3.1 Type of evaluation

The clinical evaluation has been performed following Appendix X to the MDD and, therefore, can serve as the basis for declaration of conformity with the following essential requirements: (1) safety of the device, (2) acceptable benefit/risk profile of the device, (3) performance of the device, (4) acceptability of side-effects.

The device is intended for a well-established use. For information supplied by the manufacturer, Instructions for use please refer to annex 02 (Mastertext).

The clinical evaluation is based on:

- A clinical investigation (results are described in Chapter 3.5.1)
- Clinical data generated from risk management activities and the PMS programs

The demonstration of conformity with essential requirements, therefore, is based on a prospective open-label, multicenter study evaluating PRINCESS® RICH [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] in correction of fine lines see annex 07, clinical investigation report with accompanying clinical investigation plan, approval of ethics committee and national competent authority).

In addition to data from the conducted clinical study (annex 08 and chapter 3.6), post-market surveillance activities such as complaints (annex 06), as well as vigilance data (no new safety data were reported) confirm the favorable benefit/risk ratio for the device. The data is summarized in the post-market surveillance reports (A_RA_PMSP_022, A_RA_PMSR_122) and are part of the risk management files: (A_D_RMP_010, A_RA_MRIA_PR421, C_RA_DRIA_403, C_RA_RMR_421).

3.2 Biocompatibility results from pre-clinical data

Before placing medical devices intended for human use on the market, they must undergo a thorough and structured risk/benefit assessment. Genotoxicity, cytotoxicity, implantation test, test for reactivity, systemic toxicity of[1.8% Sodium Hyaluronate with 2% Glycerol i.d.] were evaluated *in vitro* and *in vivo* in biocompatibility studies conducted under GLP regulations, see C_RD_BER_001. Various pre-clinical studies have been conducted with the device under assessment. A short summary and conclusions of the pre-clinical safety studies is given below:

[1.8% Sodium Hyaluronate with 2% Glycerol i.d.] was tested with regard to a potential mutagenic activity using the Bacterial Reverse Mutation Assay. The results showed no mutagenic activity on the applied bacterium tester strains. The test item Princess® RICH was examined for cytotoxicity in Chinese Hamster ovary cells. The test item did not cause any significant decrease in the number of cell colonies up to, and including a very high

concentration 100,000µg/mL , therefore, is considered non-cytotoxic. The positive controls, the poly (vinyl chloride) and phenol revealed a clear cytotoxic effect and the negative reference item (poly-dimethylsiloxane) was not cytotoxic, thus validating the test.

The test item [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] was examined for cytotoxicity in cultured Chinese Hamster lung cells. [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] did not cause any significant decrease in the number of cell colonies up to, and including 100,000 µg/mL, as highest concentration in the study, and is therefore considered non-cytotoxic. The positive reference items, natural rubber latex and phenol, revealed a clear cytotoxic effect and the negative reference item (poly-dimethylsiloxane) was not cytotoxic, thus validating the test. In summary, the test item Princess® RICH proved to be non-cytotoxic in this test in Chinese Hamster lung cells.

Further another *in vitro* cytotoxicity study with Princess® RICH as a worst case, in V79 cells (Chinese Hamster lung cells) was performed in order to ensure that a change in the primary packaging in which the test item was filled, does not affect the biocompatibility of the device. [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] represents the worst case having the lowest viscosity (more product comes in contact with the tip cap). The test item did not cause any significant decrease in the number of cell colonies up to, and including a very high concentration 100,000 µg/mL, therefore, is considered as non-cytotoxic. The positive reference items natural rubber latex and phenol revealed a clear cytotoxic effect and the negative reference item (PE-tubing) was not cytotoxic, thus validating the test.

[1.8% Sodium Hyaluronate with 2% Glycerol i.d.] was well tolerated after intradermal injection in rabbits. No alterations and no tissue reactions such as hematoma, edema, encapsulation and/or other gross findings were observed, and no mortality occurred. There were no test material-related effects noted. There were no macroscopic findings noticed. There were no relevant histological findings noticed. Only in two animals at one of the test material administration site an amorphous, slightly eosinophilic material, probably residues of the test material, was found. The test material [1.8 % Sodium Hyaluronate with 2.0 % Glycerol i.d.] was well tolerated when administered intradermally and considered a nonirritant to the tissue as compared to the negative control material.

The test material [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] was administered as a single dose with multiple injections in rows longitudinal in the dorsal skin tissue of NZW rabbits. No alteration in animal observation and no other findings were observed during the test period. No erythema and eschar formation, no edema and no other adverse changes of the tissue were observed at any time point. Under the test conditions no irritation has been observed, and therefore [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] is well tolerated when administered intradermally and considered as non-irritant to the tissue.

Ten guinea pigs were subjected to sensitization procedures in two consecutive steps, i.e. an intra-dermal treatment and a topical application with [1.8% Sodium Hyaluronate with 2% Glycerol i.d.]. No signs of contact sensitization were detected in the test animals which were exposed previously to the test item. This indicates that the test item has no sensitization potential. The intensity of sensitization response : in the control and treated animals at 24 and at 48 hours no skin reactions could be observed. Princess® RICH was classified as a non-sensitizer.

Acute toxicity of the [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] was evaluated when given once intraperitoneally in a dose of 10 mL/kg to female NMRI mice. There were no mortalities at the dose of 10 mL/kg. There were no clinical findings during the entire observation period. A single treatment with Princess ® RICH did not have any negative effect on the bodyweight development. Upon the results obtained in this study, the dose of 10 mL/kg [1.8% Sodium Hyaluronate with 2% Glycerol i.d.]lies within the NOAEL (No Observed Adverse Effect Level).

In a further study the application of 10 mL/kg of Princess® RICH, intraperitoneally daily for 14 days, in male and female Wistar rats did not cause any test item related findings or the findings observed were of minor relevance. The only relevant clinical finding noted during the treatment period was hardening under the skin at the application site in nearly all female and male animals. For repeated intraperitoneal administration of 10 ml/kg Princess® RICH good local tolerability was seen.

A pyrogen test was performed with Princess® RICH acc. European Pharmacopeia, 9thedition, 2016. The purpose of this study was to evaluate if a test article extract induced a pyrogenic response following intravenous injection in rabbits. An extract was injected intravenously to three NZW rabbits. Rectal temperature was measured every 30 minutes for 3 hours after injection. The temperature rise between the highest temperature within 3 hours after injection and the initial temperature was for the three rabbits 0.08°C, 0.23°C and 0.39°C. Therefore, the sum of the response was 0.69°C which is lower than the 1.15°C required for the test. Under the conditions of the study, the product was judged non-pyrogenic.

In conclusion, the overall results from animal experiments with guinea pigs, rabbits, rats and mice showed that Princess® RICH and thus the device group [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] had no mutagenic activity, proved to be non-cytotoxic, and non-genotoxic in the various tests. The product waswell tolerated after intradermal injection. Clinical observations, overall body weight development, and histopathological examination demonstrated very good tolerability. There was no inflammation, no cell infiltration, no degeneration, fibrosis, vascularisation or atypical reaction. Princess® RICH was classified as a non-sensitizer.

3.3 Clinical data from the literature

This section is not applicable. No scientific literature is applicable.

3.4 Demonstration of equivalence

This section is not applicable. There is no equivalent product. A clinical study was performed using the device [1.8% Sodium Hyaluronate with 2% Glycerol i.d.].

3.5 Clinical data generated and held by the manufacturer

The respective clinical investigation reports, clinical investigation plans (and the approval of the ethics committee and approval of the national competent authority) can be found in annex 07 and annex 08.

The clinical study with Princess® RICH performed by CROMA described in chapter 3.6 and annex 08 confirm the above safety profile and efficacy of the device for the intended use.

In addition to the data from the dedicated clinical study, post-market surveillance activities such as complaints (annex 06), as well as vigilance data (no new safety data were reported), confirm the favorable benefit/risk ratio for the device. The data is summarized in the post-market surveillance reports (A_RA_PMSP_022_11 and A_RA_PMSR_122_04) and are part of the risk management files (A_D_RMP_010_08, A_RA_MRIA_PR421_17, C_RA_DRIA_403_09, C_RA_RMR_421_13).

3.6 Summary and appraisal of clinical data

The conducted clinical investigation (annex 08) has been defined in such a way as to confirm the manufacturer's claims for the device; and includes an adequate number of observations to guarantee the scientific validity of the conclusions.

Data obtained by the clinical investigation with [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] are comparable with literature data of benchmark or similar devices.

Commonly reported adverse events from the literature search on benchmark devices, as well as the results of the clinical study and post-marketing activities, support the acceptability of risks and undesirable effects of the medical device in question. Furthermore, the benefit/risk ratio remains positive when the risks are weighed against its benefits. The results support favorable benefit/risk profile according to current knowledge/state of the art in the medical fields concerned (unmet medical needs) and according to available alternative therapeutics. The post-market activities are described in Chapter 5 and in the PMS Plan (A_RA_PMSP_022) and in the PMCF plan (C_CT_PMCF_10).

3.6.1 A Prospective Open-label, Multicenter Study Evaluating Princess® RICH in Correction of Fine Lines (CPH-401-201364)

The present investigation was undertaken to support these claims by providing evidence of Princess® RICH performance and safety in subjects undergoing up to three treatments with the device and followed for 36 weeks.

The clinical study report, the clinical investigation plan and the approval of the ethics committee and the national competent authority can be found in annex 08.

Purpose

The purpose of the study was the following:

- To assess the effectiveness ofPrincess® RICH to correct fine lines on the face including lateral canthal lines (LCL) also called "Crow's Feet" and perioral rhytids (PR) also called "smile lines" or "smoker's lines"
- 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

Design and methodology

The study was an open-label, single treatment arm study designed in the following fashion:

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

1. Once selected, and prior to receiving any treatment, all subjects were photographed using a frontal and two lateral (left and right) views to establish a baseline for LCL and/or PR. Measurements for skin hydration, tone and elasticity were taken using the corneometer and cutometer devices to assess baseline status.

2. Subjects then received treatment of either their LCL or PR or both, based on the judgment of the treating physician, with Princess® RICH. This visit was referred to as Study Visit1.

3. At Week 3 (Visit 2) following injection, all subjects returned to the clinic and were photographed, evaluated for improvement of the severity of their LCL and/or PR using

the Global Aesthetic Improvement Scale (GAIS), and measurements for skin hydration, tone and elasticity were done using the corneometer and cutometer devices.

At this visit assessment of concomitant medication and adverse events were done. The subject then received the 2nd treatment, as per instructions for use.

4. At Week 6 (Visit 3) all subjects returned to the clinic and were photographed and evaluated for the improvement of the severity of their LCL and/or PR using the GAIS. Measurements for skin hydration, tone and elasticity were taken prior to the next injection. An assessment of the concomitant medication and adverse events was done. The subject then received the 3rd treatment, as per instructions for use.

5. At Week 8 (Visit 4, primary endpoint assessment) all subjects returned to the clinic and were photographed, as above, as well as were evaluated by the treating physician to assess the following parameters:

a. Assessment of improvement in the severity of their LCL and/or PR using GAIS.

b. Measurements for skin hydration, tone and elasticity, using the corneometer and cutometer devices.

c. Each subject was asked to grade their satisfaction with the treatment using the Subject Treatment Satisfaction Questionnaire listed in Appendix 1 of CIP, V3.0.

d. Assessment of concomitant medication and adverse events were done.

6. At Week 12 (Visit 5) all subjects returned to the clinic and were photographed, as above, as well as were evaluated by the treating physician to assess the following parameters:

a. Assessment of improvement in the severity of their LCL and/or PR using GAIS.

b. Measurements for skin hydration, tone and elasticity using the corneometer and cutometer devices.

c. Each subject was asked to grade their satisfaction with the treatment using the Subject Treatment Satisfaction Questionnaire.

d. Concomitant medication and adverse events assessment were performed.

7. At Week 16 (Visit 6) all subjects returned to the clinic and were photographed, as above, as well as evaluated by the treating physician to assess the following parameters:

a. Assessment of the improvement in the severity of their LCL and PR using GAIS.

b. Measurements for skin hydration, tone and elasticity using the corneometer and cutometer devices.

c. Each subject was asked to grade their satisfaction with the treatment using the Subject Treatment Satisfaction Questionnaire.

d. Concomitant medication and adverse events assessment were done.

8. At Weeks 24 (Visit 7) and 36 (Visit 8), subjects who consented in the participation of a follow-up period of 36 weeks returned to the clinic. Subjects were photographed, as above, and were evaluated by the treating physician to assess the following parameters:

a. Assessment of the improvement in the severity of their LCL and PR using GAIS.
b. Measurements for skin hydration, tone and elasticity using the corneometer and cutometer devices.
c. Each Subject was asked to grade their satisfaction with the treatment using the Subject Treatment Satisfaction Questionnaire.
d. Assessment of the aesthetic effect of Princess® RICH as assessed by the investigator.
e. Concomitant medication and adverse events assessment were done.

At the end of the investigation (independent of whether the subject participates in the 36-Week follow-up period), all necessary investigation closeout procedures were performed and the subjects were discharged from the investigation.

An interim analysis was performed after all subjects had completed the follow-up visit at Week 16.

End of Investigation:

The duration of the clinical investigation was planned for 52 weeks at a maximum. As it was observed by the investigator that at Week 36 (Visit 8) no aesthetic effect was any more visible in approximately 75 % of the subjects participating the follow-up period, the investigation was terminated at Week 36.

Population

100 male and female subjects aged 18 years or older were planned to be included; 102 subjects were screened and enrolled in this clinical investigation.

However, due to the outcome of the inspection and because of critical deviations, the data collected at site 03 were excluded from this clinical investigation report. Therefore, data of only 59 subjects were valid for the safety-analysis-set. Data of 58 subjects were valid for intent-to-treat-population (ITT). 47 subjects were included in the

per-protocol (PP) population (valid cases set = VCS). 12 subjects in total were excluded from PP population. The 2 subjects with premature discontinuation after Visit 4 and Visit 1 due to personal reasons.

Results

Primary performance results

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

The primary performance endpoint in this clinical investigation was:

Percentage of responders at Week 8 after initial treatment point

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

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 4):

Table 4: 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

The investigator rated 'improved' to 'very much improved' in all of the subjects of the ITT population for right andleft LCL, and PR at Week 8; 'much improved' was rated most frequently (LCL left and right: 52.0%, PR: 51.0%), followed by 'very much improved' (LCL left and right: 28.0%, PR: 37.3%), and 'improved' (LCL left and right: 20.0%, PR: 11.8%, see Table 5). Neither 'No change' nor 'worse' were rated for any treatment area in any of the subjects.

Similar results were obtained for the PP population (see Table 5).

Table 5: GAIS by the 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

Secondary performance/efficacy results

According to the study results (annex 8), at Week 12, nearly all of the subjects were still found to be responders, i.e., the proportion of responders (ITT population) was almost

the same for LCL and/or PR when compared to Week 8 (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).

At Week 12, the investigator still rated 'improved' to 'very much improved' 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%); with 'much improved' assessed mostly as for Week 8, but somewhat less subjects with 'very much improved'.

At Week 16, the investigator rated 'improved' to 'very much improved' for both right and left LCL in 62.5% of the subjects, and for PR in 80.0% of the subjects. In the other subjects 'no change' was rated for the respective areas.

At Week 24, the investigator rated 'no change' for the majority of the subjects (LCL: 71.4% both, PR: 45.5%). 'Much improved' and 'improved' were rated for both right and left LCL in 1 subject each. For PR, the investigator rated 'very much improved' and 'improved' in 1 subject each and 'much improved' for the remaining 4 subjects (36.4%).

At Week 36, the investigator rated 'no change' for 100% of the subjects for both right and left LCL and for 66.7% of the subjects for PR. 'Improved' was rated for 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.

Change in skin hydration assessed with the corneometer device from baseline at Weeks 3, 6, 8, 12, 16, 24, and 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 (mean change from baseline 15.1 and 10.9 i.u., respectively). 12 weeks later at Week 36, still considerable skin hydration (mean change from baseline 9.8 i.u.) was noted for LCL (statistically not significant), while the skin hydration had decreased to the minimum value of -4.6 i.u. (mean change from baseline) for PR. An improvement of skin hydration was seen at Weeks 24 (LCL: 69.0 i.u. and PR: 61.4 i.u.) as the corneometric values were within the values known for well-hydrated skin (range between 60 and 85 i.u.; in the eye area generally higher as perioral).

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 and 85 i.u.; in the eye area generally higher as perioral).

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

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).

Similar results were reported for the PP population.

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

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).

Similar results were reported for the PP population.

Subject satisfaction with treatment *at Weeks 8, 12, 16, 24, and 36 using one of the following categories: "Very unsatisfied", "Unsatisfied", "Neither unsatisfied nor satisfied", "Satisfied", or "Very satisfied"*

At Week 8, the majority of the subjects (93.1%) were 'satisfied' or 'very satisfied' with the IMD treatment. 'Neither satisfied nor unsatisfied' was rated by 6.9%.

Similar results were observed four weeks later at Week 12 with 91.1% of the subjects continued being 'satisfied' or 'very satisfied' with the IMD treatment. Neither satisfied nor unsatisfied' was rated by 8.9%.

After a further 4 weeks at Week 16, a decreased percentage of subjects (73.7%) were still 'satisfied' or 'very satisfied' with the IMD treatment. 'Neither satisfied nor unsatisfied' was 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%) were 'satisfied' or 'very satisfied' with the IMD treatment. 'Neither satisfied nor unsatisfied' was rated by 41.7%.

At Week 36, 'satisfied' or 'very satisfied' 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% of the subjects rated 'neither satisfied nor unsatisfied'.

'Unsatisfied' or 'very unsatisfied' has not been rated by any subject at any assessment time point.

Similar results were reported for the PP population.

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

The investigator assessed whether the aesthetic effect was still present in the subject via live-assessment of the treated areas compared to the subject's photographs obtained at the Baseline Visit. The presence of the aesthetic effect was recorded as either "Yes" or "No".

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 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.

Safety results

Injection volume

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 fewer subjects in the left and right LCL area (26 subjects each [44%]).

At Weeks 3 and 6, further IMD treatments were performed in ≥ 69% of the subjects: in about four-fifths of the subjects in the PR area, in about 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.

Adverse events (AEs)

A summary of AE characteristics can be found in Table 6.

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
A causal relationship to the investigational device and to the procedure: unlikely.

- Meniscus partial rupture left knee

Intensity: moderate
A causal relationship to the investigational device and to the procedure: not related.

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

The location of 11 TEAEs (including both SAEs) reported in 8 subjects was not related to testing 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 the 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 7) was 'general disorders and administration site conditions' noted in 17 subjects (29%) with 'injection site haematoma' reported as most frequent PT (23 TEAEs in 17 subjects [29%]). Furthermore, 'Injection site swelling' was reported once in 1 subject.

The next frequently reported SOC was 'infections and infestations' noted in 7 subjects (12%) with 'nasopharyngitis' reported as most frequent PT (in 3 subjects, 5%). 'Sinusitis' was reported in 2 subjects, and 'gastroenteritis', 'oral herpes' and 'vestibular neuronitis' in 1 subject each.

Further SOCs such as 'gastrointestinal disorders', 'immune system disorders', 'injury, poisoning and procedural complications' and 'surgical and medical procedures' were reported once with the PTs 'gastrooesophageal reflux disease', 'seasonal allergy', 'meniscus injury' and 'shoulder operation'.

The duration of the TEAEs was in most cases > 7 days (SOC 'general disorders and administration site conditions': 13 subjects; SOC 'infections and infestations': 3 subjects), followed by > 3 days and ≤ 7 days (SOC 'general disorders and administration site conditions': 4 subjects; SOC 'infections and infestations': 3 subjects). Particularly, the TEAEs with location related to testing fields especially 'injection site haematoma' (13 TEAEs) showed these longer durations.

None of the TEAEs led to the subject's withdrawal. 7 subjects took medication for the treatment of AE. None of the subjects took rescue medication.

The outcome of the TEAEs was 'resolved' in most cases. 'Ongoing' and 'resolved with sequelae' were noted for 2 TEAEs each ('ongoing': PTs: gastrooesophageal reflux disease and seasonal allergy; 'resolved with sequelae': PTs: oral herpes and shoulder operation).

Table 6: 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 the 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 the treatment area or just around the treatment area, Not related to test fields = distant from the 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

Table 7: 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

Device deficiencies

No device deficiencies were recorded during the clinical investigation.

The total amount of injected volume ranged between 0.5 and 6.0 mL (overall mean of all injections = 2.64 mL).

3.6.2 Conclusion of clinical investigation

The dedicated clinical study with [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] performed bythe manufacturer confirmed the safety profile and efficacy of the device for the intended use. Overall, the device posed a well-tolerated, safe and effective alternative to the current use of comparable dermal fillers in the treatment of LCL and PR. Princess® RICH as a non-cross-linked hyaluronic dermal injectable convinced with its performance on to maintain hydration and to improve tone and elasticity of the skin. The effects lasted for lasting for a satisfactory duration.

3.7 Analysis of clinical data

3.7.1 Clinical investigation results analysis

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 (see chapter 3.6 and annex 08). 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). Afterward, 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 treatment. Subjects' treatment satisfaction was demonstrated at Week 8 with the majority of the subjects (93.1%) assessing either 'satisfied' or 'very satisfied'. The remaining subjects were 'neither satisfied nor unsatisfied' with IMD treatment. At Weeks 12, 16, 24 and 36, most of the subjects (91.1%, 73.7%, 58.3% and 71.4%, respectively) continued to be 'satisfied' or 'very satisfied'. All other subjects rated 'Neither satisfied nor unsatisfied'. 'Unsatisfied' or 'very unsatisfied' has not been rated 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 (mean change from baseline 15.1 and 10.9 i.u., respectively). 12 weeks later at Week 36, still considerable skin hydration (mean change from baseline 9.8 i.u.) was noted for LCL, while the skin hydration had decreased to the minimum value of 4.6 i.u. (mean change from baseline) for PR. An improvement of skin hydration was seen at Weeks 24 (LCL: 69.0 i.u. and PR: 61.4 i.u.) as the corneometric values were within the values known for well-hydrated skin (range between 60 and 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 of 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.

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 to be related to study procedure (mainly 'injection site haematoma' [23 TEAEs in 17 subjects] and 'injection site 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 ('injection site haematoma').

Local injection-related side effects were expected in this clinical investigation: 30% in total, of that 25% 'injection site haematoma' which was low compared to other HA fillers. For a natural, non-cross-linked glycerol-added HA gel (Mesolis plus) 76% haematoma was seen; 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 the literature (Succi et al., 2012; Uth, Elberg and Zachariae, 2016), only 1 of the subjects (2%) in this clinical investigation presented swelling.

None of the TEAEs led to the subject's withdrawal and the outcome of the TEAEs was 'resolved' within 1 to 2 weeks in most cases, corresponding to other HA described in the literature. 'Ongoing' and 'resolved with sequelae' were noted for 2 TEAEs each ('ongoing': PTs: gastrooesophageal reflux disease and seasonal allergy; 'resolved with sequelae': PTs: oral herpes and shoulder operation).

7 subjects took medication for the treatment of AE. None of the subjects needed 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.

3.7.2 Assessment of the compliance of the requirement on safety

The demonstration of conformity with the safety requirements is based on a prospective open label, multicenter study evaluating PRINCESS® RICH [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] (annex 08). In addition to data from the conducted clinical study (annex 08 and chapter 3.6), post market surveillance activities such as complaints (annex 06), as well as vigilance data (no new safety data were reported).

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 (see 3.6.1. Clinical investigation results analysis).

In total, 36 TEAEs were reported in 24 subjects (41%). 2 of the TEAEs were SAEs, which were considered to be unlikely or not related to IMD or procedure, respectively. All other TEAEs were non-serious TEAEs, mostly located at treatment area or just around treatment area (25 TEAES in 18 subjects) and considered to be related to study procedure (mainly 'injection site haematoma' [23 TEAEs in 17 subjects] and 'injection site 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 ('injection site haematoma'). 7 subjects needed medication for the treatment of AE. None of the subjects took 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.

All information material, IFU, literature of benchmark products, clinical study report from the clinical study held by the manufacturer (adverse events found during clinical data appraisal for unmet medical needs) from PMS activities, complaint data (annex 06) from the manufacturer have been reviewed and are compliant with the requirement on safety of [1.8% Sodium Hyaluronate with 2% Glycerol i.d.].

Therefore [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] can be considered as safe when used according to the intended use.

3.7.3 Assessment of the compliance of the requirement on acceptable benefit/risk profile

The medical device group has been CE-marked since 2009. From 2009 until the end of 2019, 2.001.922 units of the product have been released with 59 complaints (affecting 390 items). This equates to a complaint ratio of 0.003% which confirms the favorable benefit/risk ratio for the device

From 2009 until end of 2019 the following AEs were observed from the complaint listings for the medical device group: inflammation, nodules and appearance of acne, erythema, swelling, pain + bleeding, granuloma, edema, papules at theinjection site, lumps, swelling, edema, induration/nodules, papules. No "unknown" (i.e. not already listed in the literature) and no serious events were recorded.

The safety profile of the device is well established and is based on a sufficient number of treatments and clinical safety data (see Chapter 3.6.1).

Data from clinical studies (annex 08 and chapter 3.6), and post-market surveillance activities such as complaints (annex 06) as well as vigilance data (no new safety data were reported), confirm the favorable benefit/risk ratio for the device. The data is summarized in the post-market surveillance reports (A_RA_PMSP202 and A_RA_PMSR_122).

All adverse events are part of the risk analysis and the Instructions for Use (see annex 02 and files on risk management: A_D_RMP_010, A_RA_MRIA_PR421, C_RA_DRIA_403, C_RA_RMR_421), which include the frequency and severity of the AEs.

With regard to adverse events that occurred in the clinical trial (chapter 3.6.2), it was concluded that based on the reported frequencies of the AE there is no change in the risk/benefits profile of the device and , therefore, IFU , as well as DRIA do not need to be revised (see A_CT_TRIR_009).

In summary, the risks associated with the use of the device, if used as claimed, are acceptable when weighed against the benefits to the patient in light of the current "state of the art". When used under the conditions and purposes intended, the above-

named medical device(s) will not compromise the clinical conditions or safety of patients, users or other persons.

It can thus be confirmed that the risk assessment of medical devices of product group [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] is appropriate and complete.

3.7.4 Assessment of the compliance of the requirement of performance

The demonstration of conformity with the performance requirements is based on a prospective open-label, multicenter study evaluating PRINCESS® RICH [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] (annex 08).

The performan 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) ce results of [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] clearly showed 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). Afterward, 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 treatment. Subjects' treatment satisfaction was demonstrated at Week 8 with the majority of the subjects (93.1%) assessing either 'satisfied' or 'very satisfied'. The remaining subjects were 'neither satisfied nor unsatisfied' with IMD treatment. At Weeks 12, 16, 24 and 36, most of the subjects (91.1%, 73.7%, 58.3% and 71.4%, respectively) continued to be 'satisfied' or 'very satisfied'. All other subjects rated 'Neither satisfied nor unsatisfied'. 'Unsatisfied' or 'very unsatisfied' has not been rated 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 (mean change from baseline 15.1 and 10.9 i.u., respectively). 12 weeks later at Week 36, still considerable skin hydration (mean change from baseline 9.8 i.u.) was noted for LCL, while the skin hydration had decreased to the minimum value of 4.6

i.u. (mean change from baseline) for PR. An improvement of skin hydration was seen at Weeks 24 (LCL: 69.0 i.u. and PR: 61.4 i.u.) as the corneometric values were within the values known for well-hydrated skin (range between 60 and 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 of the PP population showing overall similar results.

The conducted clinical investigation has confirmed the manufacturer's claims for the device; and includes an adequate number of observations to guarantee the scientific validity of the conclusions.

Data obtained by the clinical investigation with [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] are comparable with literature data of benchmark or similar devices.

Overall, [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] complies with the requirement of performance when used according to the intended use.

3.7.5 Assessment of the compliance of the requirement of acceptability of side-effects

In general, HA fillers are the most frequently used dermal fillers and are considered the most predictable, having shown to be safe andwell -tolerated, with studies from the literature reporting mild adverse events which resolve quickly (see chapter 2.4).

The adverse events retrieved from the literature search and adverse events found in during clinical investigation (annex 08) and thecomplaint listings of the manufacturer, are commonly reported after treatment with dermal fillers and are expected complications of the treatment procedure. It should be noted that the prevalence of these events tends to decrease as clinical experience accumulates. Furthermore, the possibility of rescue treatment with hyaluronidase, enables immediate correction, which is a major advantage of HA fillers compared to permanent, irreversible fillers.

In terms of risk assessment, all reported AEs, are also reported in the Instructions for Use (annex 02) and in the risk analysis (A_D_RMP_010, A_RA_MRIA_PR421, C_RA_DRIA_403 C_RA_RMR_421and A_CT_TRIR_009), which include the frequency and severity of the AEs.

In summary, the risks associated with the use of the device, if used as claimed, are acceptable when weighed against the benefits to the patientin light of the current "state of the art". When used under the conditions and purposes intended, the above

named medical device(s) will not compromise the clinical conditions or safety of patients, users or other persons.

It can thus be confirmed that the risk assessment of medical devices of product group [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] is appropriate and complete.

high number of treatments. In summary, the data outlined above indicates that [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] has low residual risk.

In relation to the conformity assessment with the requirement on performance the detailed description was provided for each indication in chapter 3.6. The device achieved the performance intended by the manufacturer as demonstrated by the conducted clinical study where it was shown that the performance results demonstrate the benefit of the non-cross-linked, glycerol-added HA product [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] in correcting fine lines in both treatment areas while also maintaining hydration and improving tone and elasticity of the skin.

The conducted clinical investigation, therefore, has confirmed the manufacturer's claims for the device; and includes an adequate number of observations to guarantee the scientific validity of the conclusions.

The results show acceptability of the benefit/risk profile according to current knowledge/state of the art in the medical fields concerned and according to available alternatives. Additionally, data has been included from published studies with benchmarked devices to provide further insight on safety and to additionally support claimed medical indications for maintaining hydration and for improving tone and elasticity of the skin.

The results of the clinical data (C_CT_CIR_013), information materials supplied by the manufacturer 36813|TFSPR_11_2019draft_IU (clinical factsheet), (IFU, annex 02), and the risk management documentation (see files on risk management: A_D_RMP_010, A_RA_MRIA_PR421, C_RA_DRIA_403 and C_RA_RMR_421) for the device under evaluation do not show any discrepancies.

As it is demonstrated in the Usability Engineering File (A_D_TRIR_278) the product has been designed and developed with the focus to produce a medical device that achieves adequate usability (including the respective packaging components, to ensure safety and maintenance of performance as required for the intended use). This assumption is confirmed by the outcomes of tests performed by the intended users.

For [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] device the correlation of any complaints with the usability of the devices is assessed within the respective PMS reports A_RA_PMSR_120, A_RA_PMSR_121 and A_RA_PMSR_122. As well, based on the clinical evaluations CIR (annex 08), there were no clinical adverse events or other occurrences, which could be attributed to a lack of device's usability. In conclusion, it is affirmed that the risk of use errors was reduced as much as possible with regard to the intended use and considering the intended user profile.

As shown in the data appraisal, the data can be regarded as suitable for a demonstration of conformity with the essential requirements covering the safety and performance of the device. The conducted clinical study demonstrated the safety

4. Conclusions

The objective of the present document is the re-evaluation of the conformity of the device with the clinical essential requirements. The following *Essential Requirements taken from MEDDEV 2.7/1 revision 4* were considered: (1) requirements on safety, (2) acceptable benefit/risk profile, (3) requirements on performance, (4) acceptability of undesirable side-effects, which coincide with the Essential Requirements set out in Annex I to MDD. The appraisal of the results for the device [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] is in compliance to the essential requirements and is confirmed by clinical data using the device [1.8% Sodium Hyaluronate with 2% Glycerol i.d.]. The clinical evaluation has been performed following Appendix X to the MDD and, therefore, can serve as the basis for the declaration of conformity with the Essential Requirements.

With regard requirements on safety and acceptable benefit/risk profile and requirement on the acceptability of undesirable side-effects, it was demonstrated that any risks which may be associated with the intended purpose are minimized and acceptable when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety. For example, the medical device group [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] was CE marked since 2009. From 2009 until the end of 2019, 2.001.922 units of the product have been released with 59 complaints (affecting 390 items). This equates to a complaint ratio of 0.003% which confirms the favorable benefit/risk ratio for the device No new adverse reactions and events were found in the complaints listings until the end of 2019.

The acceptability of undesirable side-effects is confirmed by the clinical study of the device, as well as clinical experience, during which any undesirable side-effect constitutes an acceptable risk when weighed against the performances intended.

Moreover, the IFU correctly describes the intended purpose of the device as supported by sufficient clinical evidence and contains correct information to reduce the risk of user error, information on residual risks and their management are present. A fact supported by the low number of AEs accrued during post marketing surveillance.

Furthermore, data from the conducted clinical investigation confirmed the favorable benefit/risk ratio for the device. 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. Commonly reported adverse events from post-marketing surveillance and the literature search from benchmark devices, as well as favorable results from the dedicated clinical study with the device, support the acceptability of risks and undesirable effects of the medical device in question, when weighed against its intended benefits. The safety profile of the device is well established and based on a

and performance of the device in its intended use. The favorable benefit/risk ratio, as well as the "state of the art" of the device, is confirmed by the literature published between 01.01.2009 and 31.09.2019 for dermal aesthetic purposes (unmet medical needs).

In summary, the risks associated with the use of the device, if used as claimed, are acceptable when weighed against the benefits to the patient in light of the current "*state of the art*". The conformity with the relevant essential requirements is confirmed by the clinical data.

5. Post-market surveillance

Planned post-market surveillance activities will focus on complaints and vigilance data related to the product, vigilance information sourced from competent authority database from benchmarked products, literature review, regulatory updates, release figures and post-market monitoring (PMM). With regard to the PMM a specific questionnaire is being sent to the product using a medical professional to proactively assess general satisfaction, information about safety and performance of the device [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] (See also A_RA_PMSP_022).

To evaluate the safety and performance of benchmark dermal fillers, literature search was carried out in course of the clinical evaluation. A thorough analysis of the results of the performed clinical studies using dermal filler was done. In course of this analysis no new or additional issues regarding either the saftey or the performance of the device were identified. Since neither the manufacturing nor the sterilisation process of [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] were changed since 2014, no unanswered questions regarding the safety or performance of the device are currently open which need further evaluation in course of post market surveillance/post market clinical follow up activities.

The safety profile and the performance of Princess® RICH have been demonstrated. The device [1.8% Sodium Hyaluronate with 2% Glycerol i.d.] is CE-marked since 2009 under the name Princess® RICH. From 2009 until the end of 2019 2.001.922 units of the product have been released.

Nevertheless, CROMA is currently performing a clinical study according to § 40 (2) MPG (Austrian medical device law), as described above, to assess the clinical performance and safety as well as residual risks associated with the use of medical device and ensure continuous update of the clinical evaluation by collecting and evaluating clinical data.

The clinical study was started in Q4/2018 and completed in Q4/2019 (annex 08) . The study results were evaluated in section 3.5. Study findings are analyzed by descriptive statistics and documented in the clinical investigation report (annex 08, CPH-401-201364).

In addition, the data are systematically gained from the market by post-market surveillance activities. Through the post-market surveillance activities every effort will be made to investigate if the risk/benefit ratio is still acceptable.

The PMCF and PMS activities are planned and performed accordingly (see additionally the post-market surveillance plan A_RA_PMSP_022) in order to receive proactively feedback from the market regarding the safety and performance of the device [1.8% Sodium Hyaluronate with 2% Glycerol i.d.].

These data confirm the acceptable benefit/risk ratio. Every effort will be made to investigate any residual risk or unanswered questions through the post-market surveillance activities in order to estimate the impact on the benefit/risk ratio of [1.8% Sodium Hyaluronate with 2% Glycerol i.d.]. Hence, further PMCF activities will be planned and performed accordingly (see A_RA_PMSP_022).

Results from data frompost -market surveillance activities will be actively gathered during the yearly reporting period and summarized in the annual post-market surveillance report in order to define further actions (see A_RA_PMSR_122).

The results of the clinical data (annex 08), information materials supplied by the manufacturer 36813|TFSPR_11_2019draft_IU (clinical factsheet), (IFU, annex 02), and the risk management documentation (see files on risk management: A_D_RMP_010, A_RA_MRIA_PR421, C_RA_DRIA_403 and C_RA_RMR_421) for the device under evaluation do not show any discrepancies.

6. Date of the next clinical evaluation

The present document is valid fromthe release date on and is updated on a yearly basis. The next clinical evaluation might be performed earlier than the end of the validity of the document, according to changes, risks or findings of the products or new information coming from PMS which could potentially impact the current evaluation.

7. Abbreviations

Abbreviation	Definition
AE	Adverse event
BDDE	1, 4- Butanediol diglycidyl ether
EMA	European Medicines Agency
EU	Endotoxin units
G	Gauge (specifies needle diameter)
GAIS	Global Aesthetic Improvement Scale
GCP	Good clinical practice
GMDN	Global Medical Device Nomenclature
HA	Hyaluronic Acid, Hyaluronan
ICH	International Conference on Harmonization
IFU	Instructions for use
IMD	Investigational medical device
ISO	Standard according to the International Organization for Standardization
ITT	Intent-to-treat
kDa	Kilo Daltons
LCL	Lateral Canthal Lines
MDD	Medical Device Directive (i.e. Council Directive 93/42/EEC)
MedDRA	Medical Dictionary for Regulatory Activities
NASHA	non-animal stabilized HA
NLF	Nasolabial fold
PD	Protocol deviation
PP	Per-protocol
PR	Perioral rhytids
PT	Preferred term
SA	Serious Adverse Device Event
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
VCS	Valid-cases-set

8. Qualification of the responsible evaluators

The curriculum vitae (CV) and declaration of interest (DOI) of Dr. Kopera are listed in annex 04. The curriculum vitae (CV) of the author, reviewers and approver are provided in annex 04.

9. Summary of changes

Document number incl. version number	Description of change	Valid from
C_CT_CER_005_05	Changes throughout the document due to the Deficiency letters from 20.12.2019 no. P172178-2, as well as 17.12.2019 no. P183244-1. Data from interim CIR have been replaced with data from the final CIR.	See header
C_CT_CER_005_05draft_01	Update due to the indication extencion. Changes throughout the document due to the Deficiency letters from 28.02.2019 no. P172178-1, as well as 07.01.2019 no. P183244.	02.12.2019
C_CT_CER_005_04	Update due to the renewal the following sections: summary; section 1.1, section 1.2, section 1.4, section 1.5, section 1.7, section 1.9, section 1.10, section 1.11, section 1.12, section 1.14, warnings, section 1.15, section 1.16, section 1.17, section 2.1, section 2.2, section 2.4, section 3.1, section 3.4, section 3.5 (the interim clinical study report data added), section 3.6., section 4, section 5	02.12.2019
C_CT_CER_005_03	Changes throughout the document due to the new Literature search: 3.3.1 Literature search for state of the art from 02.02.2016 to24.04.2018.	22.05.2018
C_CT_CER_005_02	➢ New creation according to MEDDEV 2.7.1 Rev. 4 ➢ Following chapters were updated: 2.7 Changes since last report 2.8 Commonly reported adverse events 3.3 Clinical background, current knowledge, state of the art; 3.3.1 Literature search for state of the art from 02.02.2016 to31.10.2017 3.3.2 Conclusion on state of the art 3.4 Applicable standards and guidance documents 4.2.3 Performance in animal models and appraisal of the pre-clinical data 5. Conclusion	23.11.2017

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

Date and signature of Medical Evaluator for C_CT_CER_005_05

[1.8% Sodium Hyaluronate with 2% Glycerol i.d.]

The benefit/risk profile, undesirable side-effects and risk mitigation measures are still

- compatible with a high level of protection of health and safety and acceptable according to current knowledge/ the state of the art;
- correctly addressed in the information materials supplied by the manufacturer of the device, the IFU;

Existing claims are still justified/new claims the manufacturer intends to use are justified.

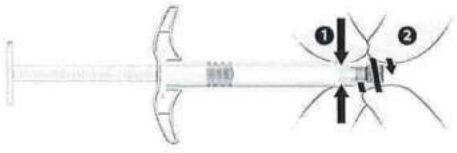
Evaluator, Medical Specialist in Dermatology

Ass. Univ. Prof. Dr. Daisy Kopera

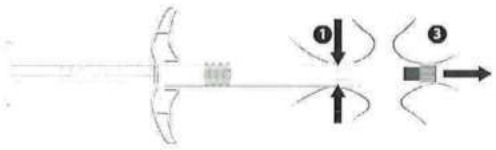
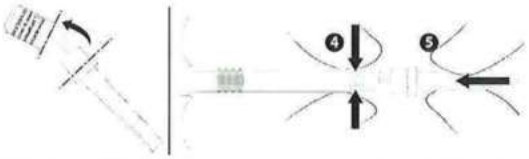
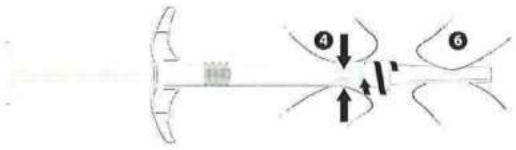
Date: 09MAR 2020 Signature: Kopera

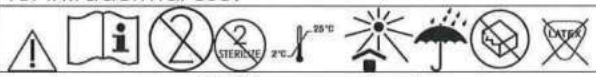
Product name: Princess® RICH		Text number: PR012
Component: IFU		Date (YYYY-MM): 2019-11
1.	**Princess® RICH**	
2.	**Instructions for use**	
3.	**Composition:**	
4.	Sodium hyaluronate 18 mg/ml.	
5.	Glycerol 20 mg/ml.	
6.	Phosphate-citrate buffer pH 6.8–7.6 q.s.	
7.	**Description:**	
8.	The device is a sterile, biodegradable, viscoelastic, clear, transparent, isotonic and homogenized injectable gel implant.	
9.	The device consists of non-animal sodium hyaluronate, obtained from *Streptococcus equi* bacteria.	
10.	Each box contains one prefilled syringe of 1.0 ml solution, two 30G ½" disposable sterile needles and an instruction for use.	
11.	A set of two labels showing the batch number is situated at the bottom of the box.	
12.	One of these labels should be attached to the patient's file and the other should be given to the patient to ensure traceability.	
13.	**Indications:**	
14.	The device is a viscoelastic solution to replenish the loss of hyaluronic acid due to ageing, to maintain hydration, to improve tone and elasticity of the skin and to act as a filler for small lines such as crow's feet, smile lines or smoke lines surrounding the mouth.	
15.	It is indicated to be injected into the superficial dermal tissue.	
16.	**Exclusion criteria:**	
17.	The device must not be used in:	
18.	- patients who tend to develop hypertrophic scars, have pigment disorders or have a susceptibility to keloid formation.	
19.	- patients with a history of autoimmune disease or who are receiving immune therapy.	
20.	- patients who are known to be hypersensitive to hyaluronic acid.	
21.	- patients who have previously received permanent fillers in the area to be treated.	
22.	- pregnant or breastfeeding women.	
23.	- patients under 18 years of age.	
24.	Patients on anticoagulants or patients receiving platelet aggregation inhibitors (e.g. acetylsalicylic acid) should not be treated with the device without consulting their doctors.	
25.	The device must not be used in areas presenting cutaneous, inflammatory and/or infectious processes (e.g. acne, herpes ...).	
26.	The device must not be used in association with laser therapy, chemical peeling or dermabrasion.	
27.	**Precautions for use:**	
28.	This device must only be administered by a doctor who is familiar with	

	intradermal injections for aesthetic improvement.
29.	Sensitive skin may be pretreated using a local anaesthetic patch or cream.
30.	Discard the syringe, remaining product and needle after use in a special container.
31.	**Undesired side effects:**
32.	Physicians must inform the patient that there are potential side effects and/or incompatibilities associated with implantation of this device, which may occur immediately or may be delayed.
33.	The following events and reactions have been observed with the device or similar products:
34.	- Bacterial infections
35.	- Bleeding during and after injection
36.	- Edema
37.	- Erythema without swelling that resolves within one week or in extreme cases after up to 2 months
38.	- Granuloma
39.	- Hypersensitivity to sodium hyaluronate
40.	- Hematoma
41.	- Indurations or nodules at the injection site
42.	- Inflammation that may coincide with itching and pressure sensitivity for up to a week after the injection
43.	- Pain during injection
44.	- Papules
45.	- Swelling of tear troughs
46.	- Transient pain or discolouration at the injection site.
47.	Patients must inform their physician as soon as possible about any inflammatory reactions which persist for more than one week or any other secondary effect which develops.
48.	The physician should treat these side effects appropriately.
49.	Any undesirable side effects associated with injection of the device must be reported to the distributor and/or to the manufacturer.
50.	**Methods of use:**
51.	The device must be injected into non-inflamed, disinfected, healthy skin.
52.	The technique used is essential for the success of the treatment.
53.	Use the 30G ½" needle which is provided with the syringe and inject slowly by applying the appropriate injection technique.
54.	Consider that the device will attract water and will increase its volume in situ.
55.	Avoid injecting large volumes in the periorbital area.
56.	The amount injected will depend on the skin's condition and need.
57.	Initial treatment can be supplemented with one or two additional sessions with a three-week interval between sessions, depending on the skin's condition.
58.	After the injection, doctors may apply a light massage in order to distribute the product uniformly.

59.	**Warnings:**
60.	Verify the integrity of the syringe and the expiry date before use.
61.	Do not use a syringe with an open or shifted tip cap within the protective packaging.
62.	Do not use any other needle or syringe than provided by the manufacturer.
63.	Do not manipulate / bend the needle.
64.	Do not re-use; quality and sterility can only be guaranteed for a syringe in its original package.
65.	The re-use of the device creates a potential infection risk for patients or users.
66.	If the 30G ½" needle is blocked, do not increase the pressure on the plunger rod but stop the injection and replace the needle.
67.	There are no available clinical data (efficacy, tolerance) about injecting the device into an area which has already been treated with another filling product or botulinum toxin.
68.	Do not inject into blood vessels, bones, tendons, ligaments, nerves or muscles.
69.	Do not inject the device into naevi.
70.	Do not use an automated injection system to inject this product.
71.	Patients should be advised not to apply any make-up for 12 hours after the injection and to avoid prolonged exposure to sunlight and UV or using saunas or Turkish baths for one week after the injection.
72.	To avoid a possible risk of product mobility, the patient should be advised not to massage the treatment site for a few days following the injection.
73.	There are incompatibilities between sodium hyaluronate and quaternary ammonium compounds such as benzalkonium chloride solutions.
74.	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.
75.	**Storage:**
76.	The device should be stored at 2 – 25 °C/ 36 – 77 °F in a dry place in the original box and protected from light, heat and frost.
77.	Handle with care.
78.	**Instructions for the correct handling of the device**
79.	Hold the Luer-Lock adapter as shown in (1).
80.	To remove the tip cap, twist (2) and pull carefully (3).
81.	

Product name: Princess® RICH	Text number: PR012
Component: IFU	Date (YYYY-MM): 2019-11

82.	
83.	Following the instruction above will prevent the formation of air bubbles.
84.	Hold the syringe as shown in (4).
85.	Open the enclosed needle case and insert the needle firmly (5) (do not use any other needle).
86.	
87.	Tightly secure the needle by twisting it clockwise (6).
88.	
89.	**Explanation of international symbols:**
90.	Caution
91.	Consult instructions for use
92.	Keep dry
93.	Temperature limitation
94.	Keep away from sunlight
95.	Do not use if package is damaged
96.	Do not re-use
97.	Do not resterilize
98.	Does not contain any latex
99.	Use by
100.	Batch number
101.	Sterilized using steam

Product name: Princess® RICH		Text number: PR006
Component: Folding Box		Date (YYYY-MM): 2019-11
1.	Princess® RICH	
2.	Hyaluronic Dermal Injectable	
3.	Princess® RICH contains 18 mg sodium hyaluronate/ml and 20 mg glycerol/ml for intradermal use.	
4.		
5.	1x Prefilled Syringe CE 0459 STERILE	
6.	CROMA GmbH	
7.	Industriezeile 6	
8.	2100 Leobendorf	
9.	Austria	
10.	www.croma.at	
11.	2 x 30G ½" Needle STERILE EO	
12.	TERUMO Europe N.V.	
13.	Interleuvenlaan 40	
14.	3001 Leuven	
15.	Belgium	
16.	CE 0197	
17.	GTIN Code Version A: 9008980000028 GTIN Code Version B: 9008980000158	
18.	<Pharma Code Version A (Region 1)> <Pharma Code Version B (Region 2)>	
19.	<Article Number Version A (Region 1)> <Article Number Version B (Region 2)>	
20.	<Revision Number Version A> <Revision Number Version B>	

Product name: Princess® RICH		Text number: PR012
Component: IFU		Date (YYYY-MM): 2019-11
102.	STERILE EO Sterilized using ethylene oxide	
103.	Prefilled Syringe Sterile syringe for single use	
104.	Needle Sterile needle for single use	
105.	Manufacturer	
106.	**Last revised**	
107.	2019-11	
108.	CROMA GmbH	
109.	Industriezeile 6	
110.	2100 Leobendorf	
111.	Austria	
112.	Tel.: +43 2262 684 68-0	
113.	Fax: +43 2262 684 68-15	
114.	www.croma.at	
115.	**CE 0459** Prefilled Syringe	
116.	TERUMO Europe N.V.	
117.	Interleuvenlaan 40	
118.	3001 Leuven	
119.	**Belgium**	
120.	**CE 0197** Needle	
121.	<Pharma Code Version A (Region 1)> <Pharma Code Version B (Region 2)>	
122.	<Article Number Version A (Region 1)> <Article Number Version B (Region 2)>	
123.	<Revision Number Version A> <Revision Number Version B>	

Project/Change control no: CC-2019-096		
Change index:		
line	change	former line
Instructions for Use		
14	"The device is a viscoelastic solution to replenish the loss of hyaluronic acid due to ageing, to maintain hydration and to improve tone and elasticity of the skin." replaced by "The device is a viscoelastic solution to replenish the loss of hyaluronic acid due to ageing, to maintain hydration, to improve tone and elasticity of the skin and to act as a filler for small lines such as crow's feet, smile lines or smoke lines surrounding the mouth."	14

Comments:
N.a.

Text created by (initial/dept.)	date	signature
her /LA	26.11.2019	
Text reviewed by (initial/dept.)		
ntr/GPM	27.11.2019	
Text released by (initial/dept.)		
fra/G	27.11.2019	
Text released by (initial/dept.)		
ike/RA	27.11.2019	

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FORM to C_CT_MSOP_002

Literature Search Protocol Form

Device name or technical file name:
[1.8% Sodium Hyaluronate with 2% Glycerol i.d.]

Purpose of the search:	**Scope of the search**
✓ clinical evaluation o post market follow-up o animal tissue (ISO 22442-3) o other (please define):	✓ Safety ✓ Performance o additional:
Time frame: 01.01.2009 to 31.09.2019	**Main database(s)** ✓ PubMed o DIMDI (Medizinische Fachliteratur) o other:

Search term(s) Search Terms (number of retrieved citations) used for the present CER.

1. Hyaluron* Filler Filters (868)
2. Available therapeutic and dermal filler (558)
3. Available therapeutic and dermal filler Filters (98)
4. management and dermal filler (233)
5. State of the art and dermal filler (3)
6. Diagnostic options and dermal filler (19)
7. Benchmark device and dermal filler (0)
8. Princess rich (138)
9. Dermalstyle light and dermal filler (59)
10. Estelite vita (2)
11. M-HA18* (1)
12. Hyalax revitalize skin* (8)
13. Saypha RICH and dermal filler (18)
14. Hyalax REVITALIZE SKIN and dermal filler (1)
15. Apriline HYDRO and dermal filler (2)
16. JALOR re-Style and dermal filler (0)
17. ZFill refresh and dermal filler (1)
18. Pluryal Booster and dermal filler (0)
19. GENYAL Genyalift and dermal filler (0)
20. Definisse hydrobooster and dermal filler (0)
21. Hyaluron* AND Glycerol AND intradermal (2)
22. Hyaluron* AND Glycerol AND cutaneous (5)
23. Hyaluron* native AND intradermal (4)
24. Hyaluron* AND native AND cutaneous (6)
25. Hyaluron* AND Glycerol AND mesotherapy (0)
26. Hyaluron* AND native AND mesotherapy (0)
27. HA and mesotherapy (7)
28. Hyaluron and mesotherapy (0)

Product name: Princess® RICH	**Text number: PR002**
Component: Primary Label	**Date** (YYYY-MM): **2011-02**
1.	Princess® RICH
2.	LOT
3.	1.0 ml
4.	STERILE
5.	CE 0459
6.	CROMA GmbH

Product name: n/a	**Text number: BIP002**
Component: Blister Paper	**Date** (YYYY-MM): **2018-06**
1.	
2.	[croma For creators of beauty.]
3.	Prefilled Syringe CROMA GmbH Industriezeile 6 2100 Leobendorf Austria
4.	Needle TERUMO Europe N.V. Interleuvenlaan 40 3001 Leuven Belgium
5.	
6.	<Revision Number>

Product name: Princess® RICH	**Text number: PR003**
Component: Secondary & Patient Label	**Date** (YYYY-MM): **2015-11**
Secondary label text	
1.	Princess® RICH
2.	1x1.0 ml
3.	LOT
Patient label text	
4.	Princess® RICH
5.	LOT
6.	CROMA GmbH

29. hyaluronan and meso therapy (1)
30. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 (1723)
31. #30 and improved facial hydration (4)
32. #30 and facial skin tone (17)
33. #30 and skin elasticity (52)
34. #30 and hydration (35)
35. #29 and skin tone (29)
36. HA and mesotherapy (8)
37. #31 or #32 or #33 or #34 or #35 or #36 (100)
38. #30 and small lines (10)
39. #30 and and smoker lines (0)
40. #30 and smoker lines (0)
41. #30 and smile lines (1)
42. #30 and crow's feet (9)
43. #37# or #38 or #39 or #40 or #41 or #42 (116)

Search Terms (number of retrieved citations) used for the present CER. Collection with the PubMed database retrieved 116 articles. Of the116 articles, 37 were selected for inclusion in the CER (Annnex 03).

Inclusion criteria:

— works including clinical data about the safety and performance of the device and the equivalent or similar benchmark devices
— works reflecting current state-of-the-art
— works published in recognized scientific publications
— works reporting the outcome of a study according to scientific principles.

Exclusion criteria :

— single case reports without substantial new safety and performance information
— works dealing with non-equivalent/similar devices without substantial safety information
— unrelated works not dealing with HA fillers for facial soft tissue augmentation
— technical descriptions dealing with injection and treatment methods
— material related works dealing with physical and chemical properties of fillers
— opinions and comments without substantial clinical data
— animal studies, if unrelated to the safety of the device
— historical and general works without actual clinical data
— works dealing exclusively with HA fillers with additional substances other than glycerol
— works dealing with breast and genital augmentation
— works dealing with combination therapies not focusing on the device in