Utilizing a soft-tissue filler that is more fluid and less resistant to deformation may be advantageous for correction of infraorbital hollows.

OBJECTIVE:

The objective of this study was to determine the safety and efficacy of the latest hyaluronic acid filler, created with a cohesive polydensified matrix, with a low elasticity and viscosity, for infraorbital hollows correction.

METHODS AND MATERIALS:

Subjects (49) with at least a grade 2 Merz infraorbital hollow scale in the Validated Assessment Scales for the mid face (0-4) of the right and/or left side were photographed and treated at baseline, and with a touch up treatment after 2 weeks if necessary. Subjects were also photographed at 2, 6, and 10 months after baseline, with optional retreatment at 6 months. The photographs were graded by a blinded sub-investigator.

RESULTS:

Mean hollowness scores for both eyes, either individually or combined, at 2, 6, and 10 months were considerably improved compared to baseline (P<.001). No serious adverse events were reported. Of the 46 subjects completing the study, 31 (66%) did not request retreatment after 6 months. At 10 months, 27/31 (87%) still exhibited a hollowness improvement of at least 1-point from baseline.

CONCLUSION:

Belotero Balance was safe and effective for the correction of infraorbital hollows.

PMID:

25226002

[Indexed for MEDLINE]

Similar articles

Publication type, MeSH terms, Substances

•

Select item 25192332 72. **Not relevant**

Ophthalmic Plast Reconstr Surg. 2014 Nov-Dec;30(6):524-7. doi: 10.1097/IOP.0000000000000293.

Does the Tyndall effect describe the blue hue periodically observed in subdermal hyaluronic acid gel placement?

Rootman DB[1], Lin JL, Goldberg R.

Author information

1

Jules Stein Eye Institute, Division of Orbital and Oculoplastic Surgery, University of California, Los Angeles, Los Angeles, California, U.S.A.

Abstract

BACKGROUND:

The blue hue of skin overlying injected hyaluronic acid (HA) fillers in certain cases has been hypothesized in the literature as related to the Tyndall effect. This investigation aims to understand the relevant optical concepts and to discuss the plausibility of this assertion.

METHODS:

Theoretic and physical aspects of relevant optical theories including the Tyndall effect, the Raleigh criterion and the Mie Solution are discussed, with simple examples. The physical properties of the system (both HA and subcutaneous tissue) are explored. Alternate concepts of dermal hue generation are discussed.

RESULTS:

The Tyndall effect (and Rayleigh criterion) describe optical phenomenon that occur as light passes through colloidal solutions containing uniform spherical particles of sizes less than the length of a wavelength of visible light. HA fillers are complex, large, non-spherical, cross-linked hydrogels, and thus are not well characterized by these theories.Skin is a complex optical surface in which shorter wavelengths of light are selectively filtered at superficial depths. Light passing through to subdermal HA would have low blue light amplitude, minimizing what light could be preferentially scattered. Further, should blue hues be 'generated' subdermally, the same skin filters work in reverse, making the blue light poorly detectable by an external observer.

CONCLUSIONS:

The Tyndall effect is unlikely to cause dermal hue changes in HA filler instillation. Optical and perceptual processes explaining superficial vein coloration may better describe subdermal HA hue changes. Vein coloration is thought to be related to three processes: the reflective properties of the skin, the absorptive properties of blood and the perceptive properties of an observer's eyes. Subdermal HA may simulate these phenomena by a number of undetermined, yet plausible mechanisms.

PMID:

25192332

DOI:

10.1097/IOP.0000000000000293

[Indexed for MEDLINE]

MeSH terms, Substances

-

Select item 24910278 73. .Include

J Cosmet Dermatol. 2014 Jun;13(2):143-50. doi: 10.1111/jocd.12082.

Remodeling of periorbital, temporal, glabellar, and crow's feet areas with hyaluronic acid and botulinum toxin.

Beer KR[1], Julius H, Dunn M, Wilson F.

Author information

1

Kenneth R Beer MD - General, Esthetic and Surgical Dermatology, West Palm Beach, FL, USA.

Abstract

Botulinum toxins are currently used to reduce facial muscle activity, and hyaluronic acid is used to correct volume loss. This study evaluates the combination of abobotulinumtoxinA (Dysport) and hyaluronic acid 20 mg/mL (Perlane) for rejuvenating specific areas of the upper face. Subjects (n = 20) with mild to moderate temporal volume loss as well as glabellar and/or periorbital rhytids were enrolled in this single-center, open-label, nonrandomized 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 glabellar lines and 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. Similar trends were observed in subjects' perceived age, perceived social and professional limitations, and desire to alter their facial appearance. Among subjects previously treated with botulinum toxin alone, 64% rated the combination treatment said "superior." Adverse effects were mild and transient. The combination of abobotulinumtoxinA and hyaluronic acid appears to rejuvenate the periorbital, temporal, glabellar, and crow's feet areas with minimal adverse effects.

KEYWORDS:

abobotulinumtoxinA; filler; rejuvenation; upper face

PMID:

24910278

DOI:

10.1111/jocd.12082

[Indexed for MEDLINE]

Similar articles

Select item 24692598 74. **Exclude, similar papers included in CER**

Aesthet Surg J. 2014 May 1;34(4):584-600. doi: 10.1177/1090820X14525035. Epub 2014 Apr 1.

Complications of injectable fillers, part 2: vascular complications.

DeLorenzi C[1].

Author information

1 Dr DeLorenzi is a plastic surgeon in private practice in Kitchener, Ontario, Canada.

Abstract

Accidental intra-arterial filler injection may cause significant tissue injury and necrosis. Hyaluronic acid (HA) fillers, currently the most popular, are the focus of this article, which highlights complications and their symptoms, risk factors, and possible treatment strategies. Although ischemic events do happen and are therefore important to discuss, they seem to be exceptionally rare and represent a small percentage of complications in individual clinical practices. However, the true incidence of this complication is unknown because of underreporting by clinicians. Typical clinical findings include skin blanching, livedo reticularis, slow capillary refill, and dusky blue-red discoloration, followed a few days later by blister formation and finally tissue slough. Mainstays of treatment (apart from avoidance by meticulous technique) are prompt recognition, immediate treatment with hyaluronidase, topical nitropaste under occlusion, oral acetylsalicylic acid (aspirin), warm compresses, and vigorous massage. Secondary lines of treatment may involve intra-arterial hyaluronidase, hyperbaric oxygen therapy, and ancillary vasodilating agents such as prostaglandin E1. Emergency preparedness (a "filler crash cart") is emphasized, since early intervention is likely to significantly reduce morbidity. A clinical summary chart is provided, organized by complication presentation.

KEYWORDS:

Freudenthal syndrome; HA filler; Nicolau syndrome; cosmetic medicine; dermal fillers; embolia cutis medicamentosa; hyaluronic acid; hyaluronic acid complications; hyaluronidase (HYAL); intravascular injections; soft tissue filler; vascular complications

PMID:

24692598

DOI:

10.1177/1090820X14525035

[Indexed for MEDLINE]

Similar articles

OXFORD ACADEMIC

Publication types, MeSH terms, Substances

Select item 24434149 75. **Not relevant**

Biochem Biophys Res Commun. 2014 Mar 21;445(4):694-701. doi: 10.1016/j.bbrc.2013.12.070. Epub 2014 Jan 14.

In-depth proteomic analyses of ovarian cancer cell line exosomes reveals differential enrichment of functional categories compared to the NCI 60 proteome.

Sinha A[1], Ignatchenko V[2], Ignatchenko A[2], Mejia-Guerrero S[2], Kislinger T[3].

Author information

1 University of Toronto, Department of Medical Biophysics, Toronto, Ontario, Canada; Princess Margaret Cancer Center, Toronto, Ontario, Canada.

2 Princess Margaret Cancer Center, Toronto, Ontario, Canada.

3 University of Toronto, Department of Medical Biophysics, Toronto, Ontario, Canada; Princess Margaret Cancer Center, Toronto, Ontario, Canada. Electronic address: thomas.kislinger@utoronto.ca.

Abstract

Molecular communication between cancer cells and its stromal microenvironment is a key factor for cancer progression. Alongside classic secretory pathways, it has recently been proposed that small membranous vesicles are alternative mediators of intercellular communication. Exosomes carry an effector-rich proteome with the ability to modulate various functional properties of the recipient cell. In this study, exosomes isolated from four epithelial ovarian cancer cell lines (OVCAR3, OVCAR433, OVCAR5 and SKOV3) were characterized using mass spectrometry-based proteomics. Using an optimized workflow consisting of efficient exosome solubilization and the latest generation of proteomic instrumentation, we demonstrate improved detection depth. Systematic comparison of our cancer cell line exosome proteome against public data (Exocarta) and the recently published NCI 60 proteome revealed enrichment of functional categories related to signaling biology and biomarker discovery.

KEYWORDS:

Epithelial ovarian cancer; Exosomes; Mass spectrometry; Proteomics; Trifluoroethanol

PMID:

24434149

DOI:

10.1016/j.bbrc.2013.12.070

[Indexed for MEDLINE]

Similar articles

Select item 24385116 76. **Not relevant**

J Drugs Dermatol. 2014 Jan;13(1):24-31.

Recent trend in the choice of fillers and injection techniques in Asia: a questionnaire study based on expert opinion.

Lee SK, Kim HS.

Abstract

BACKGROUND:

With recognition of the value of volume enhancement in achieving a more youthful appearance, there has been concomitant explosion in the soft tissue filler market. Given the vast array of filler products and techniques currently available, choosing the right product and technique can be overwhelming to those with little experience.

OBJECTIVE:

To evaluate the recent trend in the choice of fillers and injection techniques among leading dermatologists in Asia and offer guidance to those who practice facial fillers.

METHODS:

A panel of dermatologists, who are recognized as filler experts and key speakers in Korea were asked to fill out an in-depth questionnaire on fillers in 2012. The results of the 2012 questionnaire are presented and compared with the questionnaire results of the exact same group of doctors in 2011.

RESULTS:

Those who participated in the questionnaire study practiced fillers for an average of 10.6 years with an average of 32.8 filler cases per week. Common indications for filler injection were midface augmentation and nose augmentation. Indications that most drastically increased between 2011 and 2012 were midface and forehead augmentation. For the nasolabial folds, the most preferred choice of filler product, needle, injection technique and injection depth was Radiesse®, 27G short needle, Layering technique and the Upper subcutaneous fat layer. For filler rhinoplasty, the preferred choices were Radiesse®, 27G short needle, Linear threading technique and the Mid-deep fatty layer. For dark circles, the favored choices were Esthelis Basic®, 30G short needle, Vertical technique and the SOOF (suborbicularis oculi fat) layer. For forehead augmentation, the most favored choices were Juvederm Voluma®, 23G cannula, Linear threading technique and Fanning and the Supraperiosteal layer. The physicians' satisfaction score for the nasolabial folds, filler rhinoplasty, dark circles and forehead augmentation was 71.5, 90, 84.5 and 87 respectively.

CONCLUSION:

On general, filler experts preferred fillers with relatively high visco-elasticity for the nasolabial folds, nose augmentation and forehead augmentation but chose fillers with low visco-elasticity for dark circles. Linear treading technique (with or without fanning) was universally popular but Vertical injection was considered more useful for dark circles and the nasal tip.

PMID:

24385116

[Indexed for MEDLINE]

Similar articles

MeSH terms, Substances

-

Select item 24301235 77. **.Include**

J Drugs Dermatol. 2013 Dec;12(12):1345-54.

Aesthetic applications of calcium hydroxylapatite volumizing filler: an evidence-based review and discussion of current concepts: (part 1 of 2).

Emer J, Sundaram H.

Abstract

BACKGROUND:

Calcium hydroxylapatite filler (CaHA; Radiesse) is a synthetic, non-animal derived product composed of minerals that occur naturally in bone and teeth. Following its development in the US, initial approval by the US FDA for non-aesthetic indications and CE marking in Europe, it was used off FDA-labeling for aesthetic purposes. Its use has grown further since its FDA approval in 2006 for long-lasting correction of moderate to severe wrinkles and folds. It is a popular filler for volume restoration to the face, and also to nonfacial areas such as the dorsum of the hands.

METHODS:

The first article of this two-part series provides an evidence-based review of study data pertaining to the mechanism of action and biocompatibility of CaHA filler, and its safety, efficacy and tolerability when used for aesthetic purposes. The review includes data from a number of prospective, controlled comparative studies, from several retrospective studies, and from a meta-analysis of reported complications from alloplastic filler procedures over a 20-year period. The study methodology and number of study subjects are sufficiently robust to provide a high Evidence Level for much of the data.

RESULTS:

CaHA has good safety, efficacy and tolerability profiles that are comparable to those of hyaluronic acid (HA) fillers. It provides an initial, immediate volume replacement for up to 12 months followed

by longer term correction due to biostimulation, resulting in collagenesis. Evidence Level II studies show longevity of 30 months or more after nasolabial fold implantation. Other studies demonstrate the appropriateness of CaHA filler for volume restoration to areas including the mid face, lower face and hands. CaHA is classified as an adjustable filler, whereas HA is fully reversible by hyaluronidase digestion. For this reason, and also because of CaHA's high viscosity and elasticity, evidence-based and experiential consensus suggests its avoidance in highly mobile areas (e.g. lips) or in anatomically unforgiving areas (e.g. the periocular region), where there may be increased incidence of nodules.

CONCLUSION:

CaHA filler is safe, efficacious and well-tolerated when used appropriately. It is increasingly recognized that many patients require pan-facial volume restoration, and that many can benefit from combined treatments. Therefore, CaHA and HA fillers may be considered complementary rather than competitive to each other. The second article of this series offers a discussion of product characteristics, scientific principles and injection techniques to optimize treatment with CaHA filler, including special considerations for avoidance and management of complications.

PMID:

24301235

[Indexed for MEDLINE]

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Publication types, MeSH terms, Substances

-

Select item 24295344 78. **Not relevant**

Clin Plast Surg. 2014 Jan;41(1):7-9. doi: 10.1016/j.cps.2013.09.007. Epub 2013 Oct 26.

Nonsurgical neck laxity correction.

Joseph JH[1].

Author information

1

Department of Head & Neck Surgery, University of California, Los Angeles, 757 Westwood Plaza, Los Angeles, CA 90095, USA; Clinical Testing Center of Beverly Hills, 9400 Brighton Way, Suite 203, Beverly Hills, CA 90210, USA. Electronic address: drjohnjoseph@sbcglobal.net.

KEYWORDS:

Dermal fillers; Laxity; Neck; Neuromodulators; Nonsurgical

PMID:

24295344

DOI:

10.1016/j.cps.2013.09.007

[Indexed for MEDLINE]

Similar articles

Publication type, MeSH terms

Select item 24245880 79. **Not relevant, indication nasojugal groove**

J Cosmet Laser Ther. 2014 Jan;16(1):32-6. doi: 10.3109/14764172.2013.854620. Epub 2013 Nov 19.

Rejuvenation effects of hyaluronic acid injection on groove: prospective randomized split face clinical controlled study.

Lim HK[1], Suh DH, Lee SJ, Shin MK.

Author information

1 Department of Dermatology, School of Medicine, Kyung-Hee University, Seoul , Republic of Korea.

Abstract

BACKGROUND:

Pronounced nasojugal groove (tear trough deformity) is one of the landmarks of aging. Hyaluronic acid filler can be used for attenuating the nasojugal sulcus but irregular lumpness and overcorrection are common adverse reactions.

OBJECTIVES:

We evaluated the effect of Restylane Vital® with its specialized injector on volume correction and skin tone of nasojugal groove.

SUBJECTS AND METHOD:

Ten Korean women were enrolled in this study. Subjects were randomized to be injected a stabilized hyaluronic acid-based gel of nonanimal origin (NAHSA injector, Restylane Vital®, Q-med) on one side of nasojugal groove, with the other side paired as control. The treatment was performed in one session. Outcome assessments included standardized photography, mexameter, and spectrometer for skin tone, global evaluation by blinded investigators, and patients' self-assessment. An assessment was made before treatment, immediately after treatment, and 1, 3, and 6 months after the treatment.

RESULTS:

All patients reported a high degree of satisfaction. Duration of overall effect varied among the patients. Correction of the nasojugal groove with a Restylane Vital® injector causes minimal tissue trauma and allows exact placement of hyaluronic acid. Restylane Vital® injector offers

more predictable results and a lower incidence of adverse effects than more commonly used techniques.

CONCLUSIONS:

Hyaluronic acid filler intradermal injection with special injector is a safe and effective method for correction of nasojugal groove.

PMID:

24245880

DOI:

10.3109/14764172.2013.854620

[Indexed for MEDLINE]

Similar articles

Publication type, MeSH terms, Substances

Select item 24160276 80. . **Not relevant**

Clin Dermatol. 2013 Nov-Dec;31(6):718-24. doi: 10.1016/j.clindermatol.2013.05.008.

Will nonablative rejuvenation replace ablative lasers? Facts and controversies.

Lipozenčić J[1], Mokos ZB.

Author information

1

Department of Dermatology and Venereology, University Hospital Center Zagreb, School of Medicine University of Zagreb, Zagreb, Croatia. Electronic address: jasna.lipozencic@zg.htnet.hr.

Abstract

Since the early 1980s, the field of skin rejuvenation has evolved rapidly. Traditional ablative resurfacing with carbon dioxide and Er:YAG lasers offered dramatic improvement of the skin tone and texture, but prolonged postoperative period and an increased risk for side effects and complications were unacceptable for the majority of patients. It prompted the development of nonablative lasers and non-laser systems, which stimulate dermal neocollagenesis without epidermal disruption, and therefore, produce less adverse effects with little or no healing time. Recently, fractional nonablative and ablative lasers have been introduced, employing a completely new concept of fractional photothermolysis, which ensures high efficacy and fewer risks. Ablative laser resurfacing still remains the gold standard for treating advanced and severe photoaging providing excellent results in experienced hands. Alternatively, ablative fractional resurfacing can be used, with the results, which are comparable to fully ablative lasers with better

standard of safety. Nonablative resurfacing is ideal for patients under the age of 50 years with minimal facial sagging, and for those who are unwilling to undergo expensive and demanding ablative procedures. It can be concluded that the key of therapeutic success is in proper patient selection, setting appropriate expectations and combining different rejuvenation technologies with other therapeutic modalities, such as botulinum toxin and fillers.

PMID:

24160276

DOI:

10.1016/j.clindermatol.2013.05.008

[Indexed for MEDLINE]

Similar articles

ELSEVIER FULL-TEXT ARTICLE

MeSH terms

Select item 24114294 81. **Not relevant**

Aesthetic Plast Surg. 2013 Dec;37(6):1073-89. doi: 10.1007/s00266-013-0219-9. Epub 2013 Oct 11.

Single treatment of grades II and III cellulite using a minimally invasive 1,440-nm pulsed Nd:YAG laser and side-firing fiber: an institutional review board-approved study with a 24-month follow-up period.

Sasaki GH[1].

Author information

1

Loma Linda University School of Medicine, Loma Linda, CA, USA, ghsasakimd@drsasaki.com.

Abstract

BACKGROUND:

Cellulite represents one of the common topographic alterations to the skin surface and one of the structural changes to the subdermal fat and septal band of the posterolateral thighs. Currently, no treatment exists to address this entity with a multifactorial genesis that produces long-term beneficial outcomes. This clinical study evaluated the safety and efficacy of the 1,440-nm laser and the duration of the clinical benefits during 2 years.

METHODS:

Initially, 25 healthy women with thigh cellulite were enrolled in this prospective institutional review board (IRB)-approved study. For grade II cellulite, the laser fiber delivered up to 1,000 J of energy

to the undersurface of the entire involved skin. For grade III cellulite, the laser fiber distributed 1,300 to 1,500 J of energy to melt the subdermal fat, subcise the taut septal bands, and heat the reticular dermis. Baseline and posttreatment analyses included standardized high-resolution photography, skin elasticity measurements, ultrasound scanning for dermal thickness, histology, investigator global assessment scores, and recording of adverse events.

RESULTS:

Of the 24 subjects who underwent treatment, only 20 were available for the 6-month follow-up assessment. Objective measurements at 2 years demonstrated an increase over the baseline mean skin elasticity (34 %) and mean dermal thickness (11 %), as well as an increase in the average percentage of dermal thickening determined by ultrasound imaging. Independent investigator global assessments were rated higher for grade II subjects than for grade III subjects throughout the 2-year follow-up period. Mild adverse events disappeared by the third month.

CONCLUSIONS:

This IRB-conducted clinical trial, as part of a multicenter study for Food and Drug Administration approval, demonstrated the safety and efficacy of a single minimally invasive treatment for grades II and III thigh cellulite during a 2-year follow-up period.

LEVEL OF EVIDENCE II:

This journal requires that authors assign a level of evidence to each article. For a full description of these Evidence-Based Medicine ratings, please refer to the Table of Contents or the online Instructions to Authors www.springer.com/00266 .

PMID:

24114294

DOI:

10.1007/s00266-013-0219-9

[Indexed for MEDLINE]

Similar articles

Publication type, MeSH terms

-

Select item 24077010 82. **Not relevant, indication, nasolabial folds**

Plast Reconstr Surg. 2013 Oct;132(4 Suppl 2):41S-47S. doi: 10.1097/PRS.0b013e318299ff53.

A multicenter study of the safety and effectiveness of hyaluronic acid with a cohesive polydensified matrix for treatment of nasolabial folds in subjects with Fitzpatrick skin types IV, V, and VI.

Downie JB[1], Grimes PE, Callender VD.

Author information

1

Montclair, N.J.; Los Angeles, Calif.; Washington, D.C.; and Glenn Dale, Md. From private practice; the Vitiligo and Pigmentation Institute of Southern California; the Department Dermatology, University of California, Los Angeles; Howard University School of Medicine; and the Callender Skin and Laser Center.

Abstract

BACKGROUND:

Although the use of the hyaluronic acid with cohesive polydensified matrix hyaluronic acid has been well explored in subjects with lighter skin (i.e., Fitzpatrick skin types I, II, and III), further exploration in subjects with Fitzpatrick skin types IV, V, and IV is warranted. The primary purpose of the study was to assess the safety of a cohesive polydensified matrix hyaluronic acid in the correction of nasolabial folds in subjects with Fitzpatrick skin types IV, V and VI, especially assessment of hyperpigmentation, hypopigmentation, and scarring. Effectiveness was also assessed.

METHODS:

A total of 93 subjects were enrolled in this 24-week investigation at three sites in the United States. All were injected bilaterally for nasolabial fold correction with cohesive polydensified matrix hyaluronic acid. Assessments included the recording of adverse events; injected volumes; wrinkle severity ratings; and global aesthetic improvement by evaluating investigators, treating investigators, and study subjects.

RESULTS:

Injection of cohesive polydensified matrix hyaluronic acid for the treatment of nasolabial folds in subjects with Fitzpatrick skin types IV, V, and VI showed no evidence of an association with hypopigmentation, hyperpigmentation, or scarring. Adverse events reported were typical of dermal filler injections with respect to type, rate, duration, and severity.

CONCLUSION:

Cohesive polydensified matrix hyaluronic acid is a safe and well-tolerated dermal filler for subjects with Fitzpatrick skin types IV, V, and VI.

PMID:

24077010

DOI:

10.1097/PRS.0b013e318299ff53

[Indexed for MEDLINE]

Similar articles

Publication type, MeSH terms, Substance

Select item 23893239 83. **Not relevant-non clinical**

Oncogene. 2014 Jun 26;33(26):3364-73. doi: 10.1038/onc.2013.303. Epub 2013 Jul 29.

Dual role of sphingosine kinase-1 in promoting the differentiation of dermal fibroblasts and the dissemination of melanoma cells.

Albinet V[1], Bats ML[1], Huwiler A[2], Rochaix P[3], Chevreau C[4], Ségui B[1], Levade T[5], Andrieu-Abadie N[1].

Author information

1 1] Inserm UMR1037, Equipe Labellisée Ligue Contre le Cancer 2013, Centre de Recherches en Cancérologie de Toulouse, Toulouse, France [2] Université Toulouse III Paul-Sabatier, Toulouse, France.

2 Institute of Pharmacology, University of Bern, Bern, Switzerland.

3 Service d'anatomie et cytologie pathologiques, Toulouse, France.

4 Département d'oncologie médicale, Institut Claudius Regaud, Toulouse, France.

5 1] Inserm UMR1037, Equipe Labellisée Ligue Contre le Cancer 2013, Centre de Recherches en Cancérologie de Toulouse, Toulouse, France [2] Université Toulouse III Paul-Sabatier, Toulouse, France [3] Laboratoire de Biochimie Métabolique, CHU, Toulouse, France.

Abstract

Despite progress in the understanding of the biology and genetics of melanoma, no effective treatment against this cancer is available. The adjacent microenvironment has an important role in melanoma progression. Defining the molecular signals that control the bidirectional dialog between malignant cells and the surrounding stroma is crucial for efficient targeted therapy. Our study aimed at defining the role of sphingosine-1-phosphate (S1P) in melanoma-stroma interactions. Transcriptomic analysis of human melanoma cell lines showed increased expression of sphingosine kinase-1 (SPHK1), the enzyme that produces S1P, as compared with normal melanocytes. Such an increase was also observed by immunohistochemistry in melanoma specimens as compared with nevi, and occurred downstream of ERK activation because of BRAF or NRAS mutations. Importantly, migration of melanoma cells was not affected by changes in SPHK1 activity in tumor cells, but was stimulated by comparable modifications of S1P-metabolizing enzymes in cocultured dermal fibroblasts. Reciprocally, incubation of fibroblasts with the conditioned medium from SPHK1-expressing melanoma cells resulted in their differentiation to myofibroblasts, increased production of matrix metalloproteinases and enhanced SPHK1 expression and activity. In vivo tumorigenesis experiments showed that the lack of S1P in the microenvironment prevented the development of orthotopically injected melanoma cells. Finally, local tumor growth and dissemination were enhanced more efficiently by coinjection of wild-type skin fibroblasts than by fibroblasts from Sphk1(-/-) mice. This report is the first to document that SPHK1/S1P modulates the communication between melanoma cells and dermal fibroblasts. Altogether, our findings highlight SPHK1 as a potential therapeutic target in melanoma progression.

Comment in

- Sphingosine kinase 1 enables communication between melanoma cells and fibroblasts that provides a new link to metastasis. [Oncogene. 2014]

PMID:

23893239

DOI:

10.1038/onc.2013.303

[Indexed for MEDLINE]

Similar articles

Publication type, MeSH terms, Substances

Select item 23715889 84. **.Include**

Arch Dermatol Res. 2013 Oct;305(8):673-82. doi: 10.1007/s00403-013-1360-7. Epub 2013 May 29.

Clinical and biometrological efficacy of a hyaluronic acid-based mesotherapy product: a randomised controlled study.

Baspeyras M[1], Rouvrais C, Liégard L, Delalleau A, Letellier S, Bacle I, Courrech L, Murat P, Mengeaud V, Schmitt AM.

Author information

1 Dermatologist, Bordeaux, France.

Abstract

Data demonstrating the efficacy of hyaluronic acid (HA)-based mesotherapy for skin rejuvenation are scarce. The aim of the study is to assess the efficacy of non-reticulated HA-based mesotherapy on skin elasticity and complexion radiance. 55 women with cutaneous ageing signs included in the Full Analysis Set (FAS) population blindly received intradermal micro-injections (50 × 0.02 mL) of non-cross-linked HA filler with mannitol (Glytone 1, HA concentration: 14 mg/g) in one cheek and saline physiological solution in the other according to hemifacial randomisation in 3 monthly sessions. Elasticity (E1 and E2 stiffness parameters) and dermis thickness were measured by cutometry and 20 MHz echography, before (D0) treatment and 1 (1M) and 3 months (3M) after the last injection. A trained panel blindly scored skin complexion radiance from standardised and calibrated photographs, using 100 mm analogue scales. In the FAS population, only HA filler significantly decreased E1 at 1M (-10.9 %, p = 0.026) and 3M (-10.5 %, p = 0.035) compared with D0; its effect versus the control tended to be more persistent, with a difference between treatments at 3M close to significance (p = 0.063). E2 also decreased at 1M (-8.2 %, p = 0.027 in the per protocol population, n = 53) and 3M after HA-treatment only.

Dermis thickness significantly increased after HA-treatment at 1M (+3.4 %, p = 0.028) and 3M (+4 %, p = 0.008), and after control-treatment at 1M only (+2.5 %, p = 0.015). The HA filler significantly improved complexion radiance at 3M compared with the control (p = 0.012) and for 51 % of subjects, their skin status. Non-reticulated HA-based mesotherapy significantly and sustainably improves skin elasticity and complexion radiance.

PMID:

23715889

PMCID:

PMC3778226

DOI:

10.1007/s00403-013-1360-7

[Indexed for MEDLINE]

Select item 23507088 85. **Not relevant-indication treatment of osteoarthritis**

Acta Biomater. 2013 Jul;9(7):7081-92. doi: 10.1016/j.actbio.2013.03.005. Epub 2013 Mar 15.

Applications and emerging trends of hyaluronic acid in tissue engineering, as a dermal filler and in osteoarthritis treatment.

Fakhari A[1], Berkland C.

Author information

1 Bioengineering Graduate Program, University of Kansas, Lawrence, KS 66045, USA.

Abstract

Hyaluronic acid (HA) is a naturally occurring biodegradable polymer with a variety of applications in medicine, including scaffolding for tissue engineering, dermatological fillers and viscosupplementation for osteoarthritis treatment. HA is available in most connective tissues in body fluids such as synovial fluid and the vitreous humor of the eye. HA is responsible for several structural properties of tissues as a component of extracellular matrix and is involved in cellular signaling. Degradation of HA is a stepwise process that can occur via enzymatic or non-enzymatic reactions. A reduction in HA mass or molecular weight via degradation or slowing of synthesis affects physical and chemical properties such as tissue volume, viscosity and elasticity.

This review addresses the distribution, turnover and tissue-specific properties of HA. This information is used as the context for considering recent products and strategies for modifying the viscoelastic properties of HA in tissue engineering, as a dermal filler and in osteoarthritis treatment.

PMID:

23507088

PMCID:

PMC3669638

DOI:

10.1016/j.actbio.2013.03.005

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Select item 23441646 86. **Not relevant-non-clinical**

Skin Res Technol. 2013 Aug;19(3):299-307. doi: 10.1111/srt.12042. Epub 2013 Feb 26.

Does skin hydration influence keratinocyte biology? In vivo evaluation of microscopic skin changes induced by moisturizers by means of reflectance confocal microscopy.

Manfredini M, Mazzaglia G, Ciardo S, Simonazzi S, Farnetani F, Longo C, Pellacani G.

Author information

1

Department of Dermatology, University of Modena and Reggio Emilia, Italy.

Erratum in

- Skin Res Technol. 2014 Aug;20(3):388. Marco, Manfredini [corrected to Manfredini, Marco]; Giovanna, Mazzaglia [corrected to Mazzaglia, Giovanna]; Silvana, Ciardo [corrected to Ciardo, Silvana]; Silvia, Simonazzi [corrected to Simonazzi, Silvia]; Francesca, Farnetani [corrected to Farnetani, Fr.

Abstract

BACKGROUND:

Skin hydration is defined as the water content of the epidermis and the dermis. In vivo reflectance confocal microscopy offers the opportunity to determine in vivo the kinetics of the skin after the application of topical products.

OBJECTIVE:

To define confocal features associated with dry skin and assess the microscopic effects of different moisturizers.

METHODS:

Ten healthy volunteers were enrolled for the study. Two different formulations were tested: petrolatum and a commercially available emulsion. Measurements were performed from baseline to 3 h after removal of the occlusion at regular time points. Nine confocal features were assessed: furrows' size, overall interkeratinocyte reflectance, furrows' morphology, scales, skin surface irregularity, non-rimmed dermal papillae, exocytosis, dermal inflammation and collagen type. Furrows' size and interkeratinocyte reflectance were also quantitated using a digital analysis. Stratum corneum capacitance was recorded.

RESULTS:

At baseline, RCM showed the presence of micro-scales and high skin surface irregularity score. After the application of topical products, the scale score decreased significantly; Furrow's size and Digital Furrow's Size had a marked and directly correlated decrement. Furrow's morphology and Epidermal Irregularity scores decreased from baseline to 30 min, the latter reaching a plateau in product application areas. Interestingly, interkeratinocyte reflectance progressively increased with the application of the topical products, while remained stable in the control area, confirmed by Digital Interkeratinocytes reflectance quantitation.

CONCLUSION:

RCM revealed that the changes involve the skin surface by reducing the micro-scales and epidermal irregularity. Even more interestingly, RCM showed that higher interkeratinocytes' brightness is seen for moisturizer, but not for the control area. This RCM finding could be linked to keratinocyte membrane protein exposure and/or substance release in the interkeratinocytic space. To sum up, RCM represents a useful imaging tool to analyze the morphologic changes at different time points following the application of topical products.

KEYWORDS:

in vivo confocal microscopy; skin hydration

PMID:

23441646

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10.1111/srt.12042

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Select item 23377386 87. **Not relevant**

J Drugs Dermatol. 2013 Feb;12(2):154-7.

Periocular hyperpigmentation: a review of etiology and current treatment options.

Alsaad SM[1], Mikhail M.

Author information

1

Department of Dermatology, King Saud University, Riyadh, Saudi Arabia.
salmanalsaad@gmail.com

Abstract

BACKGROUND:

Periocular "dark circles" fall among the most difficult chief complaints to address. In most cases, we have little information regarding etiology and no gold-standard treatment option. The extent of the problem is reflected in the sheer number of products on the market advertised to either lighten or cover the pigmentation.

OBJECTIVE/METHODS:

To present dermatologists with a complete review of the literature with regard to anatomy, definition, etiology, and treatment of periocular hyperpigmentation.

CONCLUSIONS:

Our understanding of the causes and treatment of periocular hyperpigmentation continues to advance. Nevertheless, we are in need of additional controlled clinical trials and novel therapeutic options. Individual patients will likely benefit most from a combination of approaches. Although more randomized clinical studies are necessary, Pfaffia paniculata/Ptychopetalum olacoides B⁄Lilium candidum L.-associated compound cream seems to be a promising option, with 90% improvement. For patients with increased melanin deposition, quality-switched ruby laser therapy could offer a better treatment option. In the hands of experienced professionals, a surgical option might be suitable, either by autologous fat transplantation or hyaluronic acid filler.

PMID:

23377386

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Select item 23252753 88. **Not relevant-non clinical paper**

Clin Exp Dermatol. 2013 Jan;38(1):57-65. doi: 10.1111/j.1365-2230.2012.04405.x.

Automicroneedle therapy system combined with topical tretinoin shows better regenerative effects compared with each individual treatment.

Kim JH[1], Park HY, Jung M, Choi EH.
Author information
1
Department of Dermatology, Yonsei University Wonju College of Medicine, Korea.

Abstract

BACKGROUND:

Regenerative therapy is a relatively new dermatological field. However, the currently available topical agents are unsuitable for transdermal drug delivery because of their high molecular weight and low liposolubility. Therefore, a more effective transdermal drug delivery system is needed in order to achieve better therapeutic effects with these agents. A recently introduced microneedle therapy system (MTS), which is a mechanical method for making minute holes in the skin, improves transdermal delivery. A recently developed refinement of this technique, the automicroneedle therapy system (AMTS), has several advantages over the traditional MTS, as it can achieve consistent results because of its automatic punching method.

AIM:

To evaluate the cutaneous effects of an AMTS in combination with topical tretinoin.

METHODS:

Twelve hairless mice were divided into two groups, and the dorsal skin of each mouse was marked down the centre. The first group was treated with the AMTS plus 0.025% tretinoin on one side of the back, and with 0.025% tretinoin only on the other side. The other group was treated with the AMTS and vehicle on one side, while the other side was left untreated. The effects on cutaneous regeneration and the treatment side-effects were evaluated by functional assessment including transepidermal water loss and skin hydration, and by histopathology including epidermal and dermal thickness, and density of collagen fibres. Western blotting and real-time reverse transcriptase PCR were also performed to determine protein and mRNA expression of procollagen type 1 and matrix metalloproteinase-13.

RESULTS:

Compared with the individual treatments (the AMTS alone or tretinoin alone) the combination of tretinoin plus the AMTS produced greater dermal regeneration as a result of increased

proliferation of collagen fibres. This combination therapy did not result in treatment-related adverse effects.

CONCLUSIONS:

An AMTS combined with topical tretinoin is a safe and effective method for skin regeneration, which works by increasing collagen production, and might be a new therapeutic option for regenerative therapy.

PMID:

23252753

DOI:

10.1111/j.1365-2230.2012.04405.x

[Indexed for MEDLINE]

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Select item 23164066 89. **Not relevant**

Dermatol Surg. 2013 Feb;39(2):205-31. doi: 10.1111/dsu.12036. Epub 2012 Nov 16.

Systematic review of clinical trials of small- and large-gel-particle hyaluronic acid injectable fillers for aesthetic soft tissue augmentation.

Cohen JL[1], Dayan SH, Brandt FS, Nelson DB, Axford-Gatley RA, Theisen MJ, Narins RS.

Author information

1 AboutSkin Dermatology and DermSurgery, Englewood, Colorado 80113, USA. jcohenderm@yahoo.com

Abstract

BACKGROUND:

Hyaluronic acid (HA) is the most frequently injected filler for soft tissue augmentation in the United States.

OBJECTIVE:

To systematically review published evidence for aesthetic use of small- and large-gel-particle HA.

METHODS AND MATERIALS:

Clinical data on anatomic area, level of evidence, patient population, trial design, endpoints, efficacy, and safety were extracted from PubMed.

RESULTS:

Fifty-three primary clinical reports were analyzed. The highest-quality efficacy evidence was for the nasolabial folds (NLFs), with 10 randomized, blind, split-face, comparative trials. Several randomized, blind trials supported treatment of the glabella, lips, and hands. Lower-level evidence (from studies with nonrandomized, open-label, or retrospective designs) was recorded for the nasojugal folds (tear troughs), upper eyelids, nose, infraorbital hollows, oral commissures, marionette lines, perioral rhytides, temples, and cheeks. Common adverse events (AEs) across anatomic areas were pain, bruising, swelling, and redness. Serious AEs were uncommon (8 events in 8 patients of 4,605 total patients) and were considered to be unrelated (7 events) or probably unrelated (1 event) to treatment.

CONCLUSION:

The efficacy and safety of small- and large-gel-particle HA are well established for NLFs; evidence for the glabella, lips, and hands is more limited. Preliminary reports in other anatomic regions suggest efficacy without major complications.

PMID:

23164066

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10.1111/dsu.12036

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Select item 23135085 90. **Not relevant**

J Drugs Dermatol. 2012 Nov;11(11):1336-41.

The optimal filler: immediate and long-term results with emulsified silicone (1,000 centistokes) with cross-linked hyaluronic acid.

Fulton J[1], Caperton C.

Author information

1

Department of Dermatology, University of Miami, FL, USA.

Abstract

BACKGROUND:

Silicone is one of the oldest and longest lasting of the dermal fillers. Microdroplet silicone injections have proven to be safe and effective. This paper describes how to obtain microdroplet silicone (1,000 centistokes) in a consistent manner, including a discussion of its efficacy and safety.

METHODS AND MATERIALS:

A simple, permanent method of tissue augmentation is described. U.S. Food and Drug Administration- approved liquid silicone (Silikon®) is emulsified with cross-linked hyaluronic acid through a Luer-Lok to Luer-Lok connector between two 3-cc syringes. This stable emulsion is injected through a 27G needle or through a 25G or 27G microcannula into the middermis, subcutaneous tissue, or periosteum.

RESULTS:

The results of 95 cases are described. The emulsion is most beneficial for distensible acne valleys, nasolabial folds, glabellar frown lines, augmentation of the vermilion border of the lips, and projection of the nose, cheekbones, and chin. Exterior nasal deviations and soft tissue defects are also improved. Complications are minimal and include temporary bruising, erythema, and mild edema. Any temporary small nodules are easily leveled with massage. Occasionally, it takes a repeat session at 1 month to completely elevate depressions. The resulting elevations remain stable during the 2-year follow-up period. No silicone granulomas have developed.

CONCLUSIONS:

This methodology has replaced many indications for temporary, semipermanent, or permanent fillers.

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Select item 22939964 91. **Not relevant**

Int J Pharm. 2012 Nov 1;437(1-2):277-87. doi: 10.1016/j.ijpharm.2012.08.015. Epub 2012 Aug 19.

Preparation and evaluation of antifungal efficacy of griseofulvin loaded deformable membrane vesicles in optimized guinea pig model of Microsporum canis--dermatophytosis.

Aggarwal N[1], Goindi S.

Author information

1

University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, India.

Abstract

The present study is aimed at the encapsulation of griseofulvin in the deformable membrane vesicles (DMVs) for dermal delivery. Presently, griseofulvin is available only in conventional oral dosage forms that suffer from the issues of poor and highly variable bioavailability, numerous systemic side effects and long duration of treatment. Multi-lamellar drug-loaded DMVs of griseofulvin (Indian Patent Application 208/DEL/2009) were prepared by thin-film hydration method and were optimized for type and concentration of edge activator (EA). The optimized formulation was evaluated for vesicular shape, size, drug entrapment efficiency, drug content, pH, stability, spreadability, ex vivo skin permeation, dermatokinetics, skin sensitivity, in vitro antifungal assay and in vivo antifungal activity against Microsporum canis using guinea pig model for dermatophytosis. The optimized DMVs illustrated remarkably higher drug permeation and skin retention when compared with liposomes. A complete clinical and mycological cure was observed in animals treated with topical griseofulvin formulation in 10 days. The formulation was observed to be non-sensitizing, histopathologically safe, and stable at 5±3 °C, 25±2 °C and 40±2 °C for a period of six months. The results indicated that the topical formulation of DMVs of griseofulvin could be utilized as an alternative to reduce the encumbrance of conventional oral formulations.

PMID:

22939964

DOI:

10.1016/j.ijpharm.2012.08.015

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Select item 22907426 92. **Not relevant**

Lasers Med Sci. 2013 May;28(3):957-64. doi: 10.1007/s10103-012-1178-0. Epub 2012 Aug 21.

Clinical and histologic effects from CO2 laser treatment of keloids.

Nicoletti G[1], De Francesco F, Mele CM, Cataldo C, Grella R, Brongo S, Accardo M, Ferraro GA, D'Andrea F.

Author information

1

Department of Orthopedic, Traumatologic, Rehabilitative and Plastic-Reconstructive Sciences, Second University of Naples, Naples, Italy.

Abstract

Keloids and hypertrophic scars are abnormal responses to wound healing. In general, keloids exhibit a proliferative growth beyond the margins of the scar and remain persistent; while hypertrophic scars are contained to the original wound and may regress over time. In particular, keloid formation is one of the most challenging clinical problems, with increasing frequency in surgical practice. Many treatments are available such as intralesional corticosteroids, topical applications, cryotherapy, surgical excision, radiation therapy, silicone gel sheeting, pressure therapy, and laser therapy. There are no set guidelines for the treatment of keloids and the most common treatments are individualized and depended on the distribution, size, thickness, and consistency of lesions. The authors have evaluated carbon dioxide laser successfully in the treatment of keloids and the aim of this study was to determine the immediate and long-term histologic and clinical effects of keloids after carbon dioxide laser. Fifty consecutive patients (40 females, 10 males, ages 18-60 years, mean age 40 years) with moderate to severe keloids were evaluated. All the patients received regional treatments (deltoid, elbow, chin, and ear) in an outpatient setting with a high-energy pulsed CO2 laser. Significant immediate and prolonged clinical improvement in skin tone, texture, and appearance of carbon dioxide laser was examined in all patients. Dermal remodeling was observed also on histologic examination of biopsied tissue after treatment. Carbon dioxide laser appears to be effective and well tolerated for the treatment of keloids, avoiding the adverse effects and lengthy recovery time.

PMID:

22907426

DOI:

10.1007/s10103-012-1178-0

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Select item 22871878 93. **Not relevant**

Curr Opin Ophthalmol. 2012 Sep;23(5):443-9. doi: 10.1097/ICU.0b013e3283560ab5.

Volumetric considerations for lower eyelid and midface rejuvenation.

Montes JR[1].

Author information

1

Ophthalmology Department, University of Puerto Rico, School of Medicine, San Juan, Puerto Rico, USA. jrmontespr@aol.com

Abstract

PURPOSE OF REVIEW:

With the accepted understanding of volume loss as one of the main factors in facial aging, oculofacial surgeons are embracing the concept of 'removing' less and 'filling' more. The purpose of this review is to present an update of the different alternatives and techniques for lower eyelid and midface restoration/rejuvenation using filler agents.

RECENT FINDINGS:

When a filler agent is chosen, the aim is to provide some lift, support and sculpting to the treated area. Nonpermanent or semi-permanent fillers are most widely accepted by physicians mainly because there is a lower possibility of complications. The involutional changes in the facial structures are a continuous process; this requires reassessment and variation in techniques in addition to choosing different products at different ages. Safety, support capability, ease of injection and cost are the factors to consider when choosing an injectable implant. But, physicochemical structure or rheological properties, such as viscosity and elasticity, enable the clinician to objectively select the most appropriate injectable implant depending on the specific anatomical area. An injectable with low viscosity may be ideal for lip enhancement wherein softness is required, whereas a higher viscosity filler or a harder filler may be better indicated for structure and support in the midface.

SUMMARY:

Given the wide variety of filler materials available, clinicians and surgeons must be able to select products based on safety, lifting or sculpting capability and rheological properties, such as viscosity and elasticity. These factors provide an objective parameter of how the filler agent will perform in a specific area.

PMID:

22871878

DOI:

10.1097/ICU.0b013e3283560ab5

[Indexed for MEDLINE]

- Select item 22723229 94. **Not relevant**

Facial Plast Surg. 2012 Jun;28(3):288-93. doi: 10.1055/s-0032-1312695. Epub 2012 Jun 21.

Facial filler and neurotoxin complications.

Nettar K[1], Maas C.
Author information
1
Maas Clinic for Aesthetic and Facial Plastic Surgery, University of California-San Francisco, CA, USA. Drnettar@maasclinic.com

Abstract

Botulinum neuromodulators and injectable dermal fillers have become part of the armamentarium in the treatment of facial aging. Their successful use requires a fundamental knowledge of anatomy and physiology and a sound understanding of their risks and complications. Although neuromodulators and fillers continue to demonstrate a strong record of safety, several notable risks exist.

Thieme Medical Publishers 333 Seventh Avenue, New York, NY 10001, USA.

PMID:

22723229

DOI:

10.1055/s-0032-1312695

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Select item 22694593 95. **Not relevant**

J Ocul Pharmacol Ther. 2012 Oct;28(5):484-96. Epub 2012 Jun 13.

Development and evaluation of novel surfactant-based elastic vesicular system for ocular delivery of fluconazole.

Kaur IP[1], Rana C, Singh M, Bhushan S, Singh H, Kakkar S.
Author information
1
University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, India. indupalkaur@yahoo.com

Abstract

PURPOSE:

Fluconazole is a bis-triazole antifungal agent with a low molecular weight (306 Da). It is hydrophilic in nature and has low protein binding. It is available as eye drops for the treatment of ocular mycoses, the second most common cause of blindness in developing countries. However, its administration often results in poor patient compliance and limited use due to its short half-life (15-30 min) and a low log P (0.25). Therefore, fluconazole was incorporated into a novel sorbitan

(spans) based elastic (spanlastic) vesicular system with intent to achieve a prolonged and better effect. Spanlastics are to niosomes what Transfersomes(®) are to liposomes.

METHODS:

Developed spanlastics consisted of spans and an edge activator prepared by the ether injection method. Developed vesicles were characterized for size, shape, and the number of vesicles/ml by optical microscopy. Entrapment efficiency was determined by the dialysis method, and the ex vivo corneal permeability study was performed using porcine cornea. A 3-tier safety of the novel formulation was established by the Ames test, the 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay, and in rabbits according to the OECD guidelines 404 and 405.

RESULTS:

Spanlastics were smaller in size (3 times) and showed a better permeation in comparison to a corresponding niosomal formulation. The system showed an increase (3-fold) in the apparent permeability coefficient compared to the marketed formulation Zocon(®) (0.3% w/v solution of fluconazole) due to its elastic nature. The developed system was found to be stable for 2 months under refrigerated conditions and under extreme storage conditions. Safety was established in terms of genotoxicity (Ames test), cytotoxicity (MTT assay; mouse peritoneal macrophages), acute dermal/eye irritation/corrosion, and chronic eye irritation/corrosion tests (OECD guidelines).

CONCLUSION:

The developed system is novel and provides an effective and safe formulation of fluconazole.

PMID:

22694593

DOI:

10.1089/iop.2011.0176

[Indexed for MEDLINE]

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MeSH terms, Substances

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Select item 22672272 96. .Include

J Cosmet Dermatol. 2012 Jun;11(2):87-92. doi: 10.1111/j.1473-2165.2012.00608.x.

Hyaluronic acid plus mannitol treatment for improved skin hydration and elasticity.

Taieb M[1], Gay C, Sebban S, Secnazi P.

Author information

1

11 Avenue d'Eylau, Paris, France. marynataieb@hotmail.com

Abstract

BACKGROUND:

Mesotherapy treatment of aging skin aims to replace depleting levels of minerals, vitamins, amino acids, and hyaluronic acid (HA).

AIM:

To investigate the efficacy of 13.5 mg/g uncross-linked HA+0.9% mannitol (HA+mannitol) on skin hydration and elasticity.

PATIENTS/METHODS:

Four centers enrolled 34 women: Subgroup 1 comprised 27 subjects injected using a "depot" technique; Subgroup 2 comprised seven subjects injected using a "picotage" technique.

RESULTS:

A notable difference was seen between the two subgroups in outcome and subject satisfaction. In Subgroup 1, a significant improvement was seen in hydration, anisotropy, and skin roughness, but Subgroup 2 showed no significant improvements. Most physicians assessed HA+mannitol as "easy/very easy" to inject. Physician esthetic assessment in Subgroup 1 was "improved/very improved" for >90% of subjects at Day 60, and >80% according to subject assessment. 95% of subjects were delighted with treatment, and 85% would undergo repeat treatment and would recommend treatment to a friend. However, results for Subgroup 2 indicated 86% of subjects were unhappy with treatment and 83% would refuse to undergo repeat treatment.

CONCLUSIONS:

HA+mannitol is effective for skin hydration, anisotropy, and roughness when treated using a depot technique.

PMID:

22672272

DOI:

10.1111/j.1473-2165.2012.00608.x

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Select item 22092545 97.**Include**

Dermatol Surg. 2012 Feb;38(2):192-8. doi: 10.1111/j.1524-4725.2011.02182.x. Epub 2011 Oct 14.

Rejuvenation of periorbital area: treatment with an injectable nonanimal non-crosslinked glycerol added hyaluronic acid preparation.

Succi IB[1], da Silva RT, Orofino-Costa R.

Author information

1 Dermatology Department, Hospital Universitário Pedro Ernesto, Rio de Janeiro, Brazil.

Abstract

BACKGROUND:

Therapeutic approaches to aging of the periorbital region are unique because of the delicacy of the anatomical structures and the possibility of adverse events. The synthesis of hyaluronic acid (HA) and other components responsible for skin hydration and elasticity diminish with age.

OBJECTIVE:

To evaluate the efficacy and safety of an injectable product containing non-crosslinked HA of nonanimal origin in association with glycerol to treat aging of the periorbital region.

MATERIALS AND METHODS:

A pilot study in which 20 women were administered three monthly superficial intradermal injections of non-crosslinked HA of nonanimal origin containing glycerol in the periorbital area. The clinical results consisted of the evaluation of three researchers and an independent evaluator and the degree of posttreatment patient satisfaction.

RESULTS:

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 hematoma was the longest lasting effect. All adverse events were reversible and well tolerated.

CONCLUSION:

Injections of HA of nonanimal origin, in association with glycerol, using a micropuncture technique are well tolerated and can improve skin brightness and turgor and reduce roughness in the periorbital region.

PMID:

22092545

DOI:

10.1111/j.1524-4725.2011.02182.x

[Indexed for MEDLINE]

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MeSH terms, Substances

Select item 22065390 98.**Not relevant exclude**

J Appl Biomater Biomech. 2011 May-Aug;9(2):127-36. doi: 10.5301/JABB.2011.8566.

Rheological properties of cross-linked hyaluronic acid dermal fillers.

Santoro S[1], Russo L, Argenzio V, Borzacchiello A.

Author information

1 Division of General Surgery, University of Naples SUN, Naples, Italy.

Abstract

AIM:

Ha based dermal fillers in recent years aroused big interest in the area of cosmetic surgery for the rejuvenation of the dermis. There is not a ideal dermal filler (DF) for all applications and in commerce there are many types of DF that differ for their chemical-physical properties. So the aim of this paper is to correlate the rheological and physical properties of different DF to their clinical effectiveness.

MATERIALS AND METHODS:

In this frame the samples have been subjected to oscillation dynamic rheological and steady shear measurements.

RESULTS:

Our results demonstrate that the viscoelastic properties of different DF varie strongly also considering fillers of the same family. Furthermore it was found that the materials physical properties influence significantly the performance of dermal filler. In particular the clinical data appear to correlate with the concentration of the polymer and with the product between the concentration and the percent elasticity, so these should be crucial parameters for the clinical performance of DF.

CONCLUSION:

So rheological data can be a tool to have an indication on the efficacy and longevity of DF but it has to be considered that production technology, in-vivo-conditions, injector skills and experience influence them also significantly.

PMID: 22065390

DOI:

10.5301/JABB.2011.8566

[Indexed for MEDLINE]

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MeSH terms, Substance

Select item 22052267 99. .Include

J Drugs Dermatol. 2011 Sep;10(9):990-1000.

Efficacy of cream-based novel formulations of hyaluronic acid of different molecular weights in anti-wrinkle treatment.

Pavicic T[1], Gauglitz GG, Lersch P, Schwach-Abdellaoui K, Malle B, Korting HC, Farwick M.

Author information

1

Department of Dermatology and Allergology, Ludwig Maximilians University, Munich, Germany. tatjana.pavicic@med.uni-muenchen.de

Abstract

BACKGROUND:

Due to its strong water-binding potential, hyaluronic acid (HA) is a well-known active ingredient for cosmetic applications. Native HA is proposed to help the skin to retain and maintain elasticity, turgor and moisture.

OBJECTIVE:

To observe the efficacy of topical application of 0.1% hyaluronan formulations of different molecular weights (MW) (50, 130, 300, 800 and 2000 kDa, respectively) in the periocular area as anti-wrinkle treatment.

MATERIAL AND METHODS:

Seventy-six female subjects between 30 and 60 years of age with clinical signs of periocular wrinkles applied one of the formulations twice-daily to the area of interest in a randomized fashion for 60 days. Around the other eye, a vehicle control cream was applied. Measurements of skin hydration and skin elasticity were performed before treatment, 30 and 60 days thereafter. At similar time points negative replicas were taken and evaluated by semi-automated morphometry.

RESULTS:

All HA-based creams utilized in this study demonstrated a significant improvement in skin hydration and overall elasticity values (R2) when compared to placebo. Measurements of wrinkle depth using mean roughness (Ra) and maximum roughness (Rz) values revealed

significant improvement in the 130 and the 50 kDa HA group after 60 days of treatment compared to placebo-treated area.

CONCLUSION:

Topical application of all 0.1% HA formulations used in this study led to significant improvement in skin hydration and elasticity. Application of low-molecular-weight (LMW) HA was associated with significant reduction of wrinkle depth, which may be due to better penetration abilities of LMW HA.

PMID:

22052267

[Indexed for MEDLINE]

Similar articles

Publication types, MeSH terms, Substance

Select item 22052266 100. **.Include**

J Drugs Dermatol. 2011 Sep;10(9):982-7.

Safety and effectiveness of small and large gel-particle hyaluronic acid in the correction of perioral wrinkles.

Brandt F[1], Bassichis B, Bassichis M, O'Connell C, Lin X.

Author information

1

Dermatology Research Institute, Coral Gables, FL, USA.

Abstract

BACKGROUND:

FDA-approved for the correction of moderate-to-severe facial wrinkles and folds, small gel-particle hyaluronic acid (SGP-HA, Restylane, Medicis Aesthetics, Inc., Scottsdale, AZ) and large gel-particle hyaluronic acid (LGP-HA, Perlane, Medicis Aesthetics, Inc., Scottsdale, AZ) were studied to evaluate their safety for the correction of oral commissures, marionette lines, upper perioral rhytides and nasolabial folds (NLFs).

OBJECTIVES:

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; the secondary objective was to evaluate the effectiveness of these products.

METHODS:

This open-label, 4-week study at two US centers evaluated SGP-HA and LGP-HA in patients who intended to undergo intradermal injection for correction of of perioral wrinkles and folds. At screening, a 5-grade Wrinkle Severity Rating Scale (WSRS) was used to evaluate the baseline appearance of bilateral NLFs, and a 6-grade Wrinkle Severity (WS) scale was used to evaluate

the appearance of bilateral oral commissures, marionette lines and upper perioral rhytides. To qualify, each patient must have had moderate-to-severe wrinkles at one pair of marionette lines and upper perioral rhytides. Each wrinkle was treated to optimal correction with either SGP-HA or LGP-HA at the discretion of the treating investigator. All reported local and systemic adverse events (AEs) were recorded. At two weeks after treatment or touch-up, the treating investigator and the patient assessed appearance using the Global Aesthetic Improvement Scale (GAIS).

RESULTS:

Twenty patients with a mean age of 59.6 years (range 49 to 65 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. Eighteen of 20 patients received both SGP-HA and LGP-HA. Product was injected into the mid or deep dermis using primarily linear threading and multiple punctate pools. Patients experienced a total of 66 treatment-emergent AEs (TEAEs); each patient experienced at least one TEAE. The reported events in decreasing order of occurrence were bruising, tenderness, swelling, redness, headache and discomfort. Bruising was more common in the NLFs and marionette lines than in the oral commissures and perioral rhytides. Tenderness occurred more often in the perioral rhytides than in the other areas. 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.

CONCLUSION:

Both SGP-HA and LGP-HA were found to be safe and effective for the correction of perioral wrinkles and folds, with few differences among treatment areas Both investigator and patient GAIS evaluations indicated aesthetic improvement after SGP-HA and LGP-HA treatment in the perioral area.

PMID:

22052266

[Indexed for MEDLINE]

Similar articles

Publication types, MeSH terms, Substance

-

Select item 22052265 101. **Not relevant exclude**

J Drugs Dermatol. 2011 Sep;10(9):974-80.

Rheological evaluation of the physical properties of hyaluronic acid dermal fillers.

Stocks D[1], Sundaram H, Michaels J, Durrani MJ, Wortzman MS, Nelson DB.

Author information

1 Intertek MSG, Redcar, United Kingdom.

Abstract

BACKGROUND:

Hyaluronic acid (HA) gels are commonly injected into the skin to lift rhytides and to improve facial appearance. The different processes used in their manufacture and formulation yield products with unique physical characteristics that play an important role in predicting their clinical performance.

OBJECTIVE:

The following rheologic evaluation was performed to objectively measure the physical characteristics of HA dermal filler products derived from similar bacterial sources and containing the same butanediol diglycidyl ether cross-linker, but formulated using different manufacturing techniques. The objective of this study was to evaluate the physical characteristics of two distinct families of HA products, thereby providing clinicians with a greater understanding of these products' attributes and the ability to optimize their use in the treatment of patients seeking facial rejuvenation.

MATERIALS AND METHODS:

The physical properties of commercially-available dermal fillers containing HA were evaluated using rheologic testing methods under clinically-relevant conditions. Additionally, light microscopy was used to assess the particulate nature of each product.

RESULTS:

The gels tested demonstrated a broad range of elasticity, firmness and viscosity. Light microscopy confirmed the particulate nature of each product and revealed HA particles of varying size and distribution.

CONCLUSION:

This rheologic evaluation demonstrates that differences exist among the HA products tested including gel elasticity, viscosity, and the range and distribution of gel particle sizes. Understanding the distinct physical characteristics of different HA dermal fillers and how these characteristics may predict their clinical behavior can assist clinicians in achieving the desired results in patients seeking facial rejuvenation.

Comment in

- The new face of fillers: why evidence and experience both count. [J Drugs Dermatol. 2011]
- Commentary: rheological evaluation of the physical properties of hyaluronic acid dermal fillers. [J Drugs Dermatol. 2011]

PMID:

22052265

[Indexed for MEDLINE]

Similar articles

Publication type, MeSH terms, Substances

Select item 21447385 102. **Not relevant exclude-non-clinical**

Biochim Biophys Acta. 2011 Jul;1812(7):752-9. doi: 10.1016/j.bbadis.2011.03.012. Epub 2011 Apr 3.

Systemic administration of high-molecular weight hyaluronan stimulates wound healing in genetically diabetic mice.

Galeano M[1], Polito F, Bitto A, Irrera N, Campo GM, Avenoso A, Calò M, Lo Cascio P, Minutoli L, Barone M, Squadrito F, Altavilla D.

Author information

1 Department of Clinical and Experimental Medicine and Pharmacology, Section of Pharmacology, School of Medicine, University of Messina, Italy.

Abstract

Hyaluronic acid (HA), an essential component of the extracellular matrix, is an efficient space filler that maintains hydration, serves as a substrate for assembly of proteoglycans and is involved in wound healing. Although numerous pieces of evidence demonstrate beneficial effects in promoting wound healing in diabetes, a systemic approach has never been tested. We used an incisional wound healing model in genetically diabetic mice to test the effects of systemic injection of HA. Diabetic (n=56) and normoglycemic (n=56) mice were subjected to incision and randomized (8 groups of 7 animals each) to receive HA at different doses, 7.5, 15 and 30mg/kg/i.p., or vehicle (0.9% NaCl solution) for 12days. At the end of the experiment animals were sacrificed and skin wounds were excised for histological, biochemical and molecular analysis. Histology revealed that the most effective dose to improve wound repair and angiogenesis in diabetic mice was 30mg/kg. Furthermore HA injection (30mg/kg) improved the altered healing pattern in diabetic animals, increased skin remodeling proteins TGF-β and transglutaminase-II and restored the altered expression of cyclin B1/Cdc2 complex. Evaluation of skin from diabetic animals injected with HA revealed also an increase in HA content, suggesting that systemic injection may be able to restore the reduced intracellular HA pool of diabetic mice. Finally HA markedly improved skin mechanical properties. These promising results, if confirmed in a clinical setting, may improve the care and management of diabetic patients.

PMID:

21447385

DOI:

10.1016/j.bbadis.2011.03.012

[Indexed for MEDLINE]

Free full text

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MeSH terms, Substance

•

Select item 21332911 103. .Include

J Cosmet Dermatol. 2011 Mar;10(1):15-23. doi: 10.1111/j.1473-2165.2010.00543.x.

Folic acid and creatine improve the firmness of human skin in vivo.

Fischer F[1], Achterberg V, März A, Puschmann S, Rahn CD, Lutz V, Krüger A, Schwengler H, Jaspers S, Koop U, Blatt T, Wenck H, Gallinat S.

Author information

1 Research & Development, Skin Research, Beiersdorf AG, Hamburg, Germany.

Abstract

BACKGROUND:

The decrease in firmness is a hallmark of skin aging. Accelerated by chronic sun exposure, fundamental changes occur within the dermal extracellular matrix over the years, mainly impairing the collagenous network.

AIMS:

Based on the qualitative and quantitative assessment of skin firmness, in vitro and in vivo studies were carried out to elucidate the effects of topical folic acid and creatine to counteract this age-dependent reduction in the amount of collagen.

PATIENTS/METHODS:

Topical application of a commercially available formulation containing folic acid and creatine was performed to study effects on skin firmness in vivo using cutometric analysis. Imaging and quantification of collagen density were carried out using multiphoton laser scanning microscopy (MPLSM). To investigate the effects of these compounds on collagen gene expression, procollagen synthesis, and collagen fibril organization, complementary in vitro studies on cultured fibroblast-populated collagen gels were carried out.

RESULTS:

The underlying structural changes in the collagen network of young and aged sun-exposed facial skin in vivo were visualized by MPLSM. Topical application of a folic acid- and

creatine-containing formulation significantly improved firmness of mature skin in vivo. Treatment of fibroblast-populated dermal equivalents with folic acid and creatine increased collagen gene expression and procollagen levels and improved collagen fiber density, suggesting that the in vivo effects are based on the overall improvement of the collagen metabolism.

CONCLUSIONS:

Employing MPLSM, dermal changes occurring in photo-aged human skin were visualized in an unprecedented manner and correlated to a loss of firmness. Treatment of aged skin with a topical formulation containing folic acid and creatine counteracted this age-dependent decline by exerting sustained effects on collagen metabolism. Our results support previous findings on the efficacy of these actives.

PMID:

21332911

DOI:

10.1111/j.1473-2165.2010.00543.x

[Indexed for MEDLINE]

Similar articles

MeSH terms, Substances

Select item 21284223 104. .Include

Rev Laryngol Otol Rhinol (Bord). 2010;131(2):89-95.

[Advantages of combined therapies in cosmetic medicine for the treatment of face aging: botulinum toxin, fillers and mesotherapy].

[Article in French]

Braccini F[1], Dohan Ehrenfest DM.

Author information

1

Institut Azuréen d'ORL et de Chirurgie de la Face, 25 Avenue Jean Médecin, F-06000 Nice, France. contact@braccini.net

Abstract

Non surgical cosmetic medicine procedures for the face are developing considerably, as they deliver good results using simple, non invasive, atraumatic and reproducible techniques. Aesthetic mesotherapy, also known as anti-aging mesotherapy, uses intra-dermal injections of a nutritive and moisturizing solution to improve brightness, skin hydration and tonus, and also smooth out superficial wrinkles. Subcutaneous filler injections enable to fill wrinkles and folds; by

using high density products it is also able to provide genuine facial volumetric reconstruction. Finally, botulinum toxin acts by reducing certain muscle contractions to smooth out expression lines and folds induced by facial dynamics. In this article, we explore the concept of combined therapy and describe our experience associating anti-aging mesotherapy (NCTF-135HA, Filorga, Paris, France), hyaluronic acid based fillers (X-HA3 and X-HA-Volume, Filorga, Paris, France) and botulinum toxin (Vistabel, Allergan, Irvine CA, USA). A therapy combining anti-aging mesotherapy, botulinum toxin and filler injections, offers full treatment of the 3 biological levels of the covering tissues. This non-invasive therapeutic strategy brings patient satisfaction through a global approach to facial aging.

PMID:

21284223

[Indexed for MEDLINE]

Similar articles

MeSH terms, Substances

Select item 20969663 105. **Not relevant**

Dermatol Surg. 2010 Nov;36 Suppl 3:1859-65. doi: 10.1111/j.1524-4725.2010.01743.x.

Comparison of the rheological properties of viscosity and elasticity in two categories of soft tissue fillers: calcium hydroxylapatite and hyaluronic acid.

Sundaram H[1], Voigts B, Beer K, Meland M.

Author information

1 Research and Development, BioForm Medical, Inc, San Mateo, California, USA.

Abstract

BACKGROUND:

Two types of soft tissue filler that are in common use are those formulated primarily with calcium hydroxylapatite (CaHA) and those with cross-linked hyaluronic acid (cross-linked HA).

OBJECTIVE:

To provide physicians with a scientific rationale for determining which soft tissue fillers are most appropriate for volume replacement.

MATERIALS:

Six cross-linked HA soft tissue fillers (Restylane and Perlane from Medicis, Scottsdale, AZ; Restylane SubQ from Q-Med, Uppsala, Sweden; and Juvéderm Ultra, Juvéderm Ultra Plus, and Juvéderm Voluma from Allergan, Pringy, France) and a soft tissue filler consisting of CaHA microspheres in a carrier gel containing carboxymethyl cellulose (Radiesse, BioForm Medical, Inc., San Mateo, CA). METHODS The viscosity and elasticity of each filler gel were quantified

according to deformation oscillation measurements conducted using a Thermo Haake RS600 Rheometer (Newington, NH) using a plate and plate geometry with a 1.2-mm gap. All measurements were performed using a 35-mm titanium sensor at 30°C. Oscillation measurements were taken at 5 pascal tau (τ) over a frequency range of 0.1 to 10 Hz (interpolated at 0.7 Hz). Researchers chose the 0.7-Hz frequency because it elicited the most reproducible results and was considered physiologically relevant for stresses that are common to the skin. RESULTS The rheological measurements in this study support the concept that soft tissue fillers that are currently used can be divided into three groups. CONCLUSION Rheological evaluation enables the clinician to objectively classify soft tissue fillers, to select specific filler products based on scientific principles, and to reliably predict how these products will perform--lifting, supporting, and sculpting--after they are appropriately injected.

PMID:

20969663

DOI:

10.1111/j.1524-4725.2010.01743.x

[Indexed for MEDLINE]

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Wolters Kluwer

Publication type, MeSH terms, Substances

Select item 20517106 106. **Not relevant**

Plast Reconstr Surg. 2010 Jun;125(6):1805-13. doi: 10.1097/PRS.0b013e3181d0ac75.

Characterization of physical properties and histologic evaluation of injectable Dermicol-p35 porcine-collagen dermal filler.

Lorenc ZP[1], Nir E, Azachi M.

Author information

1 Lorenc Aesthetic Plastic Surgery and ColBar LifeScience Ltd., New York, NY 10028, USA. lorenc@lorenc.com

Abstract

BACKGROUND:

Injectable dermal fillers have become important alternatives to traditional surgical procedures for the correction of facial wrinkles and restoration of facial volume. The physical properties of a dermal filler/volumizing agent, and the host tissue response to the agent, influence its clinical performance and patient outcomes.

METHODS:

In this study, several key physical properties of the new porcine collagen dermal filler Dermicol-P35 27G were measured and compared with those of commercially available hyaluronic acid-based dermal fillers. Furthermore, the in vivo properties of implanted Dermicol-P35 27G were evaluated by histologic and histopathologic methods.

RESULTS:

This study found that Dermicol-P35 27G provides a lower extrusion force profile and yield point compared with the hyaluronic acid-based dermal fillers tested. At 2 years, staining of punch biopsy specimens with hematoxylin and eosin and Herovici stains revealed no inflammatory cells and no evidence of other adverse events in any of the samples containing Dermicol-P35 27G. Within-implant colonization by fibroblasts depositing new collagen and the formation of elastin within the implanted collagen material (as shown by Luna staining) suggest that Dermicol-P35 27G is a bioactive implant.

CONCLUSIONS:

Compared with several hyaluronic acid-based dermal fillers, Dermicol-P35 exhibited lower extrusion force, higher viscosity under low shear rate, and a higher modulus of elasticity. Results of histologic evaluation indicated that Dermicol-P35 27G did not elicit an inflammatory response and was well integrated within the host tissue. Together, these results suggest that Dermicol-P35 27G offers several advantages that may result in improved clinical experiences for both patients and clinicians.

PMID:

20517106

DOI:

10.1097/PRS.0b013e3181d0ac75

[Indexed for MEDLINE]

Similar articles

Publication types, MeSH terms, Substances

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Select item 20419876 107. **Not relevant**

Wound Repair Regen. 2010 Mar-Apr;18(2):235-44.

Occlusion regulates epidermal cytokine production and inhibits scar formation.

Gallant-Behm CL[1], Mustoe TA.

Author information

1 Division of Plastic and Reconstructive Surgery, Northwestern University, Chicago, IL 60611, USA.

Abstract

Hypertrophic scars are a major clinical problem, yet there are few therapeutics available to prevent or treat scar formation. One of the oldest known and most effective treatments is occlusion with silicone gel. However, little is known about its mode of action. It is hypothesized that occlusion increases the hydration state of the epidermis, and that this affects the epidermal and dermal cell behavior. This study investigated this possibility. Using the rabbit hypertrophic scar model, we determined that occlusion increased the hydration state of the epidermis in a dose-dependent manner, and significantly reduced the scar hypertrophy. Quantitative reverse transcription-polymerase chain reaction and immunohistochemistry showed that occlusion altered keratinocyte behavior, including keratin expression. Furthermore, occlusion significantly decreased the epidermal expression of the profibrotic cytokine interleukin-1beta and increased the epidermal expression of the antifibrotic cytokine tumor necrosis factor alpha. These alterations in the epidermal gene expression resulted in concomitant changes in the expression of the transforming growth factor-beta family members by cells in the dermis, resulting in a decrease in profibrotic signaling within the dermis. In summary, the results of this study indicate that occlusive therapy was able to decrease dermal fibrosis by hydrating the epidermis and altering the pro- and antifibrotic signals produced following injury.

PMID: 20419876

PMCID: PMC2860621

[Indexed for MEDLINE]

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Publication type, MeSH terms, Substances, Grant support

Select item 20398812 108. **Not relevant**

J Am Acad Dermatol. 2010 May;62(5):824-30. doi: 10.1016/j.jaad.2009.08.016.

Assessment of recovery time for the collagen products Dermicol-P35 27G and 30G.

Solish NJ[1].

Author information

1

Division of Dermatology, University of Toronto, Women's College Hospital, 76 Grenville St, Toronto, ON M5S 1B2, Canada. n.solish@utoronto.ca

Abstract

BACKGROUND:

Dermicol-P35 27G and 30G are purified advanced collagen dermal fillers that are effective and well tolerated for cosmetic procedures.

OBJECTIVE:

The primary objectives of this study were to: (1) document recovery time and return to daily activities after treatment with Dermicol-P35 27G, 30G, or both; and (2) assess the immediate adverse effects of these products and monitor their time to resolution.

METHODS:

In all, 30 patients were treated with Dermicol-P35 27G, 30G, or both in nasolabial folds, lips, corners of the mouth, vermillion border, marionette lines, or a combination of these and monitored for 7 days. Comfort with resuming daily routine, adverse events, and satisfaction with results were documented by patients in diaries. The clinician assessed aesthetic improvement and rated satisfaction with results.

RESULTS:

The majority of patients (63.4%) were very comfortable or comfortable returning to their daily routine immediately postprocedure. Most patients (86.7%) participated in normal work or social events within 2 days of treatment. Adverse events were mild to moderate and were resolved or tolerable by day 7. The clinician assessed that most patients had between 50% and 100% improvement over baseline for all procedures at all time points. Clinician and patients were very satisfied or satisfied with aesthetic results at days 2 and 7 postprocedure.

LIMITATIONS:

The limitations of this study were the small number of patients, the assessment of short-term results, and the lack of touch-up injections.

CONCLUSIONS:

Treatment with Dermicol-P35 27G, 30G, or both allowed for rapid return to daily activities and produced only transient and tolerable adverse events.

TRIAL REGISTRATION:

ClinicalTrials.gov NCT00911872.

PMID:

20398812

DOI:

10.1016/j.jaad.2009.08.016

[Indexed for MEDLINE]

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ELSEVIER FULL-TEXT ARTICLE

Publication types, MeSH terms, Substances, Secondary source ID

Select item 19864070 109. **Not relevant**

Burns. 2010 Feb;36(1):23-8. doi: 10.1016/j.burns.2009.07.011. Epub 2009 Oct 27.

An objective long-term evaluation of Integra (a dermal skin substitute) and split thickness skin grafts, in acute burns and reconstructive surgery.

Nguyen DQ[1], Potokar TS, Price P.

Author information

1

Welsh Center for Burns and Plastic Surgery, Morriston Hospital, Swansea SA6 6NL, United Kingdom. dainguyen@doctors.org.uk

Abstract

INTRODUCTION:

The field of wound healing and tissue repair has advanced rapidly in the last decade, with this there is an increasing emphasis on the importance of the functional and cosmetic outcomes following injury. Integra artificial skin is the most widely used synthetic skin substitute and is reported to have better outcomes in relation to the appearance and elasticity when compared to split thickness skin grafting (SSG). A review of the literature reveals very few trials that are based on an objective evaluation of Integra treated scars as compared to SSGs. This research aimed to provide objective data on the long-term outcome of Integra.

METHOD:

All adult patients from the Welsh Burns Centre who had been successfully treated with Integra+/-SSG were invited to attend a clinic for a follow up provided they had been healed for greater than one year. The hypothesis that Integra scars are more pliable than skin grafts was tested objectively using the Cutometer, a suction device which measures skin elasticity.

RESULTS:

Of the 13 patients eligible, six were available for assessment. The results of this study suggest that Integra treated sites correlate well with normal skin as measured by the Cutometer. This was statistically significant for the parameters Ur/Ue (elastic function) and Ur/Uf (gross elasticity). On the other hand there was no correlation seen between the patients SSG sites and the patient's normal skin.

CONCLUSION:

With advances in medicine we are increasingly able to modulate wound healing and the resultant scars. In order to assess new and often costly treatments the need for objective scar measurement tools have become apparent. Integra has been advocated to improve scarring from injury. However, there have been few studies to evaluate the long-term outcome of Integra as compared to traditional methods such as SSG. In the past scar evaluation has been based on subjective scores by patients and clinicians. Now the mechanical properties of the skin can be evaluated using simple bioengineering methods such as the Cutometer Suction Device. Using this device our study has objectively demonstrated that the elastic properties of areas treated with Integra is comparable to normal skin.

PMID:

19864070

DOI:

10.1016/j.burns.2009.07.011

[Indexed for MEDLINE]

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ELSEVIER FULL-TEXT ARTICLE

Publication type, MeSH terms, Substances

•

Select item 19735512 110. **Not relevant**

J Cosmet Dermatol. 2009 Sep;8(3):162-8. doi: 10.1111/j.1473-2165.2009.00457.x.

Safety and effectiveness of hyaluronic acid fillers in skin of color.

Grimes PE[1], Thomas JA, Murphy DK.

Author information

1

Vitiligo and Pigmentation Institute of Southern California, Los Angeles, CA, USA. pegrimesmd@earthlink.net

Abstract

OBJECTIVES:

To assess the safety and effectiveness of hyaluronic acid (HA) fillers in skin of color.

METHODS:

Two prospective studies followed up subjects with Fitzpatrick skin phototypes of IV, V, or VI for 24 weeks after dermal filler injections. In a double-blind, randomized study, subjects were injected with one of three high concentration (24 mg/mL) HA fillers (Juvéderm Ultra, Ultra Plus, and 30) in one nasolabial fold and Zyplast collagen in the other. In an open-label, randomized study,

subjects received one of three low concentration (5.5 mg/mL) HA fillers (Hylaform, Hylaform Plus, and Captique) in both nasolabial folds.

RESULTS:

A total of 160 subjects (a subset of 439 study subjects) were randomized and treated with one of the three high concentration fillers, and 119 subjects were randomized and treated with one of the three low concentration fillers. For subjects treated with the high concentration fillers there were no occurrences of hypersensitivity or hypertrophic scarring, and no increased incidence of hyperpigmentation or hypopigmentation in non-Caucasian vs. Caucasian subjects. For subjects treated with the low concentration fillers there were no occurrences of keloid formation, hypertrophic scarring, hypopigmentation, hypersensitivity, and three instances of mild hyperpigmentation. For all of the fillers the majority of subjects maintained >/=1 point improvement in nasolabial fold severity scores through 24 weeks.

CONCLUSIONS:

All of the HA fillers were well tolerated in individuals with skin of color and demonstrated effectiveness throughout the 24 week period. Furthermore, the fillers provided smooth, natural-looking wrinkle correction in darker skin types.

PMID:

19735512

DOI:

10.1111/j.1473-2165.2009.00457.x

[Indexed for MEDLINE]

Similar articles

Publication type, MeSH terms, Substances

•

Select item 19708876 111. **Not relevant**

Dermatol Surg. 2009 Oct;35 Suppl 2:1641-5. doi: 10.1111/j.1524-4725.2009.01311.x. Epub 2009 Aug 25.

Six-month safety results of calcium hydroxylapatite for treatment of nasolabial folds in Fitzpatrick skin types IV to VI.

Marmur ES[1], Taylor SC, Grimes PE, Boyd CM, Porter JP, Yoo JY.

Author information

1

Division of Dermatologic and Cosmetic Surgery, Department of Dermatology, Mount Sinai Medical Center, New York, New York 10029-6574, USA. Ellen.Marmur@MountSinai.org

Abstract

BACKGROUND:

Recently, the cosmetic market has seen an increase in the options for treatment for people with dark skin.

OBJECTIVES:

This study evaluates the use of calcium hydroxylapatite (CaHA), a dermal filler indicated for the correction of moderate to severe facial wrinkles and folds, including the nasolabial folds (NLFs) in individuals with dark skin.

METHODS:

This open-label, nonrandomized, prospective, five-center trial enrolled 100 patients aged 18 and older with Fitzpatrick skin types IV to VI. CaHA was injected subdermally with a 25- to 27-gauge needle. Participants received a range of 0.6 to 2.8 mL of CaHA and returned at 3 and 6 months to be assessed for keloid formation, hypertrophic scarring, and hyper- or hypopigmentation. If necessary, each subject was offered a touch-up at the conclusion of the 6-month visit.

RESULTS:

No reports of keloid formation, hypertrophic scarring, hypo- or hyperpigmentation, or other clinically significant adverse events were recorded.

CONCLUSIONS:

People with dark skin injected subdermally with CaHA do not show signs of keloid formation, hypertrophic scarring, or hyper- or hypopigmentation. Because of this safety feature, as well as other characteristics of the product already shown in clinical literature, CaHA is an attractive dermal filler in this population.

PMID:

19708876

DOI:

10.1111/j.1524-4725.2009.01311.x

[Indexed for MEDLINE]

Publication types, MeSH terms, Substances

-

Select item 19588645 112. **.Include**

J Drugs Dermatol. 2009 Jul;8(7):674-7.

Beyond tretinoin: cosmeceuticals for aging skin.

Bergstrom KG[1].

Author information
1
Manhattan Dermatology, New York, NY 10016, USA.

Abstract

In contrast to youthful skin, mature skin undergoes well-established clinical and microscopic changes, particularly after menopause. In particular, dermal thinning, loss of dermal collagen and decreased lipid production are complicated by the effects of life-long sun exposure. These changes manifest as wrinkling, loss of elasticity, dryness and textural changes that characterize mature skin. To effectively combat these age- and sun-related changes, a multifaceted approach is required. Any treatment for mature skin must address the many causes of skin changes, that is, collagen production, lipid balance and epidermal texture. Several currently available compounds have scientifically-established effects on skin, and are anticipated to be even more effective in combination. Women worldwide struggle with coming to terms with their aging skin, and seek ways to preserve its youthful appearance. While dermatologists' offices may offer tretinoin cream (Renova and related products), laser resurfacing approaches, volume fillers and Botox, demand also exists for topical products that preserve and improve skin tone. With the push toward "natural," "organic" and "herbal" products, public and private research has never generated more evidence for complementary therapy. During skin aging, and particularly menopause, characteristic changes occur. Topical compounds can target many aspects of the aging process. The following is a review of topical compounds that may help with particular parts of this process. How can different problems be approached? In addition to prescription approaches and physical modalities, several topical compounds, many available over the counter, show evidence for helping aged and photo-damaged skin. Clinical data exist for many of these compounds, and is divided by mechanism of action.

PMID:

19588645

[Indexed for MEDLINE]

Similar articles

MeSH terms, Substances

Select item 19415583 113. **Not relevant**

Facial Plast Surg. 2009 May;25(2):135-42. doi: 10.1055/s-0029-1220655. Epub 2009 May 4.

Choosing injectable implants according to treatment area: the European experience.

Bergeret-Galley C[1].
Author information
1
Cabinet Medical Marignan, Paris, France. cbg@wanadoo.fr

Abstract

There are now many injectable implants for face remodeling since the first product appeared in Europe in 1984. The treatment regions most in demand are the cheeks, jaws, lips, and the oval of the face. The aging process is due to fat resorption over the upper two thirds of the face, in addition to the loss of elasticity. Weakness in the skin and subcutaneous fascia becomes more apparent over the lower third of the face. The fat loss together with the slack skin gives the impression of gauntness and loss of volume under the eyes (i.e., the zygomatic and palpebral areas). Treating the zygomatic bone area and subcutaneous tissue by injecting filler products will increase volume around the zygomatic malar bone and subcutaneous area. To choose an implant, we must take into account the patient's wishes, hopes (whether temporary or long-lasting effects are required), age, skin type (dry, moist, greasy, thick, or thin), and the patient's medical history to prevent obvious contraindications in the choice of implant due to type of product, especially in the case of allergies, inflamed areas, or any suspicion of autoimmune disease or recent infection.

PMID:

19415583

DOI:

10.1055/s-0029-1220655

[Indexed for MEDLINE]

Similar articles

MeSH terms, Substances

-

Select item 19415581 114. **.Include**

Facial Plast Surg. 2009 May;25(2):124-8. doi: 10.1055/s-0029-1220653. Epub 2009 May 4.

The management of dermal filler complications.

Winslow CP[1].

Author information

1

Indiana University School of Medicine, Indianapolis, Indiana, USA.
drwinslow@indyface.com

Abstract

Injectable fillers have gained widespread acceptance among the public and provide a nonsurgical means of rejuvenating the face. As the demand for fillers increases, facial plastic surgeons must become not only expert injectors but also experts in managing the complications of fillers. Little scientific data exists regarding the incidence of complications, and more adverse effects may be

seen with longer-term follow-up of patients. The purpose of this article is to review the most commonly encountered complications and management thereof.

PMID:

19415581

DOI:

10.1055/s-0029-1220653

[Indexed for MEDLINE]

Similar articles

Full text THIEME CONNECT

MeSH terms, Substances

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Select item 19354330 115. **Not relevant**

Am J Clin Dermatol. 2009;10(3):153-68. doi: 10.2165/00128071-200910030-00002.

The Asian dermatologic patient: review of common pigmentary disorders and cutaneous diseases.

Ho SG[1], Chan HH.

Author information

1 Department of Medicine, The University of Hong Kong, Hong Kong SAR, China.

Abstract

The Asian patient with Fitzpatrick skin types III-V is rarely highlighted in publications on cutaneous disorders or cutaneous laser surgery. However, with changing demographics, Asians will become an increasingly important group in this context. Although high melanin content confers better photoprotection, photodamage in the form of pigmentary disorders is common. Melasma, freckles, and lentigines are the epidermal disorders commonly seen, whilst nevus of Ota and acquired bilateral nevus of Ota-like macules are common dermal pigmentary disorders. Post-inflammatory hyperpigmentation (PIH) occurring after cutaneous injury remains a hallmark of skin of color. With increasing use of lasers and light sources in Asians, prevention and management of PIH is of great research interest. Bleaching agents, chemical peels, intense pulsed light (IPL) treatments, and fractional skin resurfacing have all been used with some success for the management of melasma. Q-switched (QS) lasers are effective for the management of epidermal pigmentation but are associated with a high risk of PIH. Long-pulsed neodymium-doped yttrium aluminum garnet (Nd:YAG) lasers and IPL sources pose less of a PIH risk but require a greater number of treatment sessions. Dermal pigmentary disorders are better targeted by QS ruby, QS alexandrite, and QS 1064-nm Nd:YAG lasers, but hyper- and hypopigmentation may occur. Non-ablative skin rejuvenation using a combination approach with

different lasers and light sources in conjunction with cooling devices allows different skin chromophores to be targeted and optimal results to be achieved, even in skin of color. Deep-tissue heating using radiofrequency and infra-red light sources affects the deep dermis and achieves enhanced skin tightening, resulting in eyebrow elevation, rhytide reduction, and contouring of the lower face and jawline. For management of severe degrees of photoaging, fractional resurfacing is useful for wrinkle and pigment reduction, as well as acne scarring. Acne, which is common in Asians, can be treated with topical and oral antibacterials, hormonal treatments, and isotretinoin. Infra-red diode lasers used with a low-fluence, multiple-pass approach have also been shown to be effective with few complications.
Fractional skin resurfacing is very useful for improving the appearance of acne scarring. Hypertrophic and keloid scarring, another common condition seen in Asians, can be treated with the combined used of intralesional triamcinolone and fluorouracil, followed by pulsed-dye laser. Esthetic enhancement procedures such as botulinum toxin type A and fillers are becoming increasingly popular. These are effective for rhytide improvement and facial or body contouring. We highlight the differences between Asian skin and other skin types and review conditions common in skin of color together with treatment strategies.

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Mesotherapy for skin rejuvenation: assessment of the subepidermal low-echogenic band by ultrasound evaluation with cross-sectional B-mode scanning.

Lacarrubba F[1], Tedeschi A, Nardone B, Micali G.

Author information

1

Dermatology Clinic, University of Catania, Catania, Italy.

Abstract

Skin-targeted ultrasound is a noninvasive technique that has been extensively used to evaluate age-related dermal changes, and the presence of a subepidermal low-echogenic band (SLEB) has been related to chronic UVR exposure in several studies. Since SLEB echogenicity is photoage-related, the aim of this study was to evaluate, through ultrasound imaging, the effects on skin photoaging of mesotherapy, a treatment approach currently used in cosmetic dermatology for skin rejuvenation. Twenty women (mean age: 46.7 range 40-60 years) with physical signs of moderate photoaging on the dorsum of the hands were enrolled and treated with multiple microinjections of hyaluronic acid (HA) salts of biotechnological origin (1.000 Kd) every week for 4 weeks. In all subjects, ultrasound evaluation was performed at each visit and 1 week after the last treatment to evaluate SLEB echogenicity changes during treatment. At the end of study, a statistically significant ($p < 0.001$) increase of SLEB echogenicity (with a mean increase of pixel numbers equal to 31.3%) was observed in 15 of 19 subjects who completed the study. Our preliminary study suggests that mesotherapy with HA may be an effective treatment for skin photoaging, as confirmed by ultrasound. Follow-up investigations on larger series of patients are necessary to further evaluate the safety, effectiveness, and duration of effect of this possible therapeutic approach to skin photoaging.

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Graz, July 2016

Curriculum Vitae

Born	April 19, 1960, Graz, Austria
Studies	Medical College Karl-Franzens-University Graz 1978-1984, Graduation M.D. 13.4.1984 Gerontology 2007-2009 Karl-Franzens-University Graz Management EMBA 2009-2011, Donau University Krems Geragogy M.Ed. 2011-2013, KPH Wien
Medical Curriculum	Internship 1984 – 1987 (various hospitals and clinics) Specialisation in Dermatology 1988 – 1992, Department of Dermatology, University of Graz, Austria Head of Center of Aesthetic Medicine (Laser treatment, Acne and Facial Dermatoses, Hair& Scalp Diseases), Department of Dermatology, Medical University, Graz, Austria.
Scientific Curriculum	Dept. of Gynecology, Univ. Graz 1987/88 (in vitro fertilisation, Andrology) Department of Dermatology, University of Regensburg, Germany, 1995 (Laser) **Investigator in various clinical studies according to GCP guidelines since 1990 (Hairloss, Aesthectic Dermatology, Infectious Diseases in Dermatology)** **Primary Investigator in clinical studies since 1994** Professor of Dermatology 16.6.1998 (assoc. prof.) Clinical research in Laser Surgery, Aesthetic Dermatology and Infectious Skin Diseases, Skin Aging and prevention of uv-induced skin cancer.
Current Position	Associate Professor of Dermatology, Chair: Center of Aesthetic Medicine, Department of Dermatology, Medical University Graz, Graz, Austria. in charge of **hair and scalp disorders, facial dermatoses, aging skin, aesthetic laser treatments, skin aging, photodamaged skin, rejuvenation, prevention.** Private Consultant for Dermatology+Aesthetic Dermatology.

Daisy Kopera, M.D., Prof. of Dermatology

25.7.16

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Declaration of Interests of the Evaluators

Herewith we declare that involved evaluator Prof. Dr. Daisy Kopera (place and date of birth: 19-06-1960; Graz, Austria), Associate Professor of Dermatology, Medical University Graz, Austria is not employed by CROMA.

Prof. Dr. Daisy Kopera received grants from CROMA for principal investigator role in four post-marketing studies with dermal fillers from CROMA, for consultancy advice on treatment methods, procedures and techniques with dermal fillers and for presentation of clinical study results at scientific conference.

Prof. Dr. Daisy Kopera does not receive any other benefits from CROMA and holds no interest in connection with the manufacturing of the device or its constituents, nor with intellectual property. There are no other interests or sources of revenues that could be possibly affected by the result of the evaluation.

Neither Prof. Dr. Daisy Kopera nor any of CROMA personnel involved with creation or review and evaluation of this CER is having any ownership or holds any shares of CROMA.

AGREED TO AND ACCEPTED

BY: _____
NAME: Prof. Dr. Daisy Kopera

TITLE: Associate Professor of Dermatology
DATE: 17 OCT 2017

BY: _____
NAME: Mag. Martin Prinz

TITLE: Managing Director of CROMA GmbH
DATE: 23/10/2017

№				
	Аналіз нейрохімічних механізмів нейропротекторної дії діакамфу гідрохлориду	Фармаком №4. С.88 №4 . p.88		O.A. Shatilova,
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	Зміни рівня моноамінів головного мозку в мишей під впливом нового протидіабетичного засобу діакамфу	Український біофармацевтичний журнал. № 2(7) 2010. . № 2(7) 2010.		O.A. Shatilova,
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	Психотропні властивості протидіабетичного засобу діакамф при хронічній алкогольній інтоксикації у мишей / The psychotropic	Український біофармацевтичний журнал. том I. . №2. . С.15. 18./ vol I. . №2. . 18	8	O.A. Yesyeva*,
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8	Ноотропний ефект протидіабетичного засобу діакамф/ Nootropic effect of an	Клінічна фармація . Том 13,№2. С.59 vol.13,№2	8	O.A. Yesyeva*,
	Церебропротекторні властивості нового проти діабетичного засобу діакамфу/	Фармаком №2. С.110 №2		O.A. Yesyeva*,
	Антидепрессивные и антиагрессивные свойства диакамфа/	Український журнал клінічної та лабораторної медицини. 2008.. том 3 (№3).. С.60 2008. (№3).		O.A. Yesyeva*,
	Експериментальні моделі церебральної ішемії у мишей: порівняльна характеристика гравітаційного перевантаження та каротидної оклюзії/	Клінічна фармація.. 2008.. Т.12. №2. 2008. №2.		O.A. Yesyeva*,
	Антіалкогольний єфект діакамфу/	Ліки України.. червень №112 (додаток).. С.86. 87/Medicine of №112 (addition p 86. 87		O.A. Yesyeva*,

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	Експериментальне вивчення церебропротекторних та психотропних властивостей діакамфу та його солей при нормо глікемії та цукровому діабеті/ Experimental study	Обзоры по клинической фармакологии и лекарственной терапии . том 11 (спецвыпуск).. С.156./		
	Дослідження впливу діакамфу на перебіг черепно мозкової травми у щурів /	Актуальні питання створення нових лікарських засобів: Матер. Всеукр. наук.. практ. конф. студентів та молодих вчених, 21. 22 квітня 2010 р.. Х.: Вид во НФаУ, 2010.. С.		

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	Порівняльний аналіз впливу діакамфу на рівень нейромедіаторів головного мозку в мишей / Comparative	Матер. XI Міжнародного медичного конгресу студентів та молодих вчених, 13 квітня 2010 р.. Тернопіль, С. 315./		
	Протидіабетичний засіб діакамф як потенційний алкопротектор/ Antidiabetic	Матеріали Всеукраїнської науково практичної конференції з міжнародною участю «Сучасні проблеми судово токсикологічної науки і практики» 9 10 квітня 2009 р.. Харків: Вид во НфаУ.. С.104		Yesyeva * O.A.,
	Діакамф зменшує порушення з боку центральної нервової системи при хронічній алкогольній інтоксикації у мишей/ Diacamph reduces	Актуальні питання створення нових лікарських засобів: Матер. Всеукр. науково практичної конф. студентів та молодих вчених 23 24 квітня 2009 р.. Харків: Вид во НФаУ, 2009.. С.220/		Yesyeva * O.A.,
	Діакамф є агоністом імідазолінових рецепторів/	Клінічна фармація в Україні. Матеріали всеукраїнської науково практичної конференції за участю міжнародних спеціалістів. Харків, 6 7 листопада 2008 р. . С.88 / Clinical Pharmacy in 7, 2008 . p.88		Yesyeva * O.A.,
	Розробка та вивчення експериментальної гравітаційної моделі повної церебральної ішемії у мишей. / Design	Актуальні питання створення нових лікарських засобів: Матер. Всеукр. науково практичної конф. студентів та молодих вчених 16 17 квітня 2008 р.. Харків: Вид во НФаУ, 2008.. С.230 /		Yesyeva * O.A.

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		17 April 2008 2008.		
8	Захисний ефект діакамфу на моделі церебральної ішемії у щурів / The protective effect	Актуальні питання створення нових лікарських засобів: Матер. Всеукр. науково практичної конф. студентів та молодих вчених 16 17 квітня 2008 р.. Харків: Вид во НФаУ, 2008.. С.195./ 17 April 2008 2008.		Yesyeva * O.A.,
	Вивчення психотропних ефектів діакамфу / Studying	Актуальні питання створення нових лікарських засобів: Матер. Всеукр. науково практичної конф. студентів та молодих вчених 17 18 травня 2007 р.. Харків: Вид во НФаУ, 2007.. С.173./ 18,		Yesyeva * O.A.,
	Фармакоэкономическая оценка лечения диабетической ретинопатии /	Матеріали V Всеукраїнської науково практичної конференції «Клінічна фармація в Україні» 18 листопада 2004 р.. Харків: «Золоті сторінки», 2005.. С. in Ukraine" November 18		Yesyeva * O.A.,
	Фармацевтическая опека больных с рвотой, индуцированной химиотерапией /	Матеріали V Всеукраїнської науково практичної конференції «Клінічна фармація в Україні» 18 листопада 2004 р.. Харків: «Золоті сторінки», 2005 С. in Ukraine" November 18		Yesyeva * O.A.,

№				
	Фармацевтична опіка хворих з онкопатологією	Актуальні питання створення нових лікарських засобів. . Тези доп. міжвузівської студентської науково практичної конф. 14 квітня 2004 р. . Харків: НФаУ, 2004. . С.228 / Current issues of p.228		Yesyeva * O.A.,
	Кардіопротекторні якості глюкозамінів / Glucosam	Тези доповідей міжвузівської студентської наукової конференції, 17. 18 квітня 2003 р. . Харків: НФаУ, 2003. . С.162. / Abstracts 18, 2003.		* O.A.,
	Наркоманія та вагітність /	Тези доповідей наукової студентської конференції НФАУ. . Харків: НФАУ. . С.307. / Abstracts of		Yesyeva * O.A.,

№				
	Патент на корисну модель № 39780, Україна МПК С07Д 235/00, А61К 31/4164, А61Р 3/00. Застосування цис бензімідазоліл) триметилциклопентанкарбонової кислоти як засобу, що підвищує чутливість тканин до інсуліну та проявляє антиатерогенну, нефропротекторну, церебропротекторну, ноотропну, антидепресивну та репаративну дію 1 model № 39780,	Заявка № u 2008 12308; Заявл. 20.10.2008; Опубл. 10.03.2009. – Бюл. № 5. – 14 с/ Application № u 2008 12308; Announced 20.10.2008; Published. № 5.		O.A. Yesyeva*,

	Патент на корисну модель №33367, Україна 23/28. Спосіб моделювання глобальної церебральної ішемії у мишей model № 33367, Ukraine UA33367 U G09B 23/28. A	Заявка № u 200714635; Заявл. 24.12.07; Опубл. 25.06.2008. – Бюл. №12. – 13 с./ Application № u 25.06.2008. №12.		O.A. Yesyeva*, O.A. V.S.

Note: *

Arkan Zwick

Cell: +43 676 84 6868 242

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CV executive summary – Status May 2015

Regulatory and legal executive with a consistent record of increasing shareholder value in public sector and medical device / pharmaceutical companies. Result driven personality with the ability to build peak performing teams. Background includes hands-on experience in strategic planning and implementation of international market authorization projects, change management and restructuring of teams, acquisition and sales projects, management of regulatory, labelling and legal teams, raising capital and asset building.

CROMA Pharmaceuticals Ltd, Vienna Austria – since 2007

Private medical device / pharmaceutical company which develops and markets medical devices, drugs, cosmetics, food supplements for the global orthopaedic, aesthetic dermatology and ophthalmology markets. Employees total 450. Director of legal and regulatory department comprising 13 staff members for regulatory, legal and labelling services.

- ✓ Overall responsibility for strategy and reporting of department targets, instruments and budget.
- ✓ Implemented processes and build the teams for an effective regulatory & legal department including processes for regulatory compliance, contract management, IP rights, STED / CTD / Cosmetic / Food supplement file and regulatory body management, international registrations. The team managed a portfolio of approx. 90 products including OTC and prescript drugs, medical devices (all classes – including high risk), food supplements and cosmetics with a global geographical coverage including EU, Canada, LATAM, Russia, Asia-Pacific including China, Japan and Australia.
- ✓ Implemented legal and regulatory asset and share acquisition project: integration of IOL and ophthalmic instrument portfolio of Corneal France / Allergan (project value EUR 50+ million). This project included due diligence, contract negotiations, share and asset closings, regulatory body approvals in EU and ROW of CE transfers and restructuring of RA/Labelling team.
- ✓ Implemented legal and regulatory asset and share sale project (project value EUR 60+ million): sale of OVD, IOL, instruments and orthopaedic portfolio of CROMA to Valeant/Bausch & Lomb. This project included contract negotiations, share and asset closings and purchaser support during transition period.
- ✓ Developed the strategic plan and implemented medical device and cosmetics market authorization projects in more than 60 countries including Canada, BRIC, other LATAM countries, Russia and Middle East, Australia.
- ✓ Positioned RA as a profit centre through invoicing consulting services to OBL customers and distributors.

- ✓ Due diligence and negotiations of various agreements including contract manufacturing supply agreement for OTC dry Eye product from Gedeon Richter (HU), hydrophobic intraocular lens (IOL) from Nidek Co Ltd (JP) and Own brand Label (OBL) sales and distribution agreements with Pierre Fabre (FR), Zimmer (GER), Merckle Recordati (IT) and other customers.
- ✓ Regulatory coordination of an NSAID eye drop project Yellox (post cataract anti-inflammatory drug). This project included: national and EMA scientific advice meetings, regulatory and labelling pathway, EMA submission and deficiency answers, negotiation of co-promotion agreement with Bausch & Lomb, pricing and reimbursement strategy in Austria and France.
- ✓ Implementation of drug vigilance compliance processes: This project consisted in outsourcing vigilance activities to contract partners including EU QPPV function in order to comply to MA holder responsibilities and save costs.

City of Vienna / Vienna Business Agency, Vienna Austria – 2000 to 2007

Public private partnership company founded by the City of Vienna Government and banks (UNI Credit and ERSTE Bank) with the aim of developing and promoting the business location Vienna and its enterprises. The agency is financed both by private and public (EU) funds. Employees total 150. Head of European (EIC) team comprising 4 staff members with focus on accessing of EU funds.

- ✓ Overall responsibility of yearly work programme, budget and reporting to European Commission DG-Enterprise.
- ✓ Strategy and implementation of an EU co-financed IT cluster infrastructure. The project consisted in project drafting and insuring financial participation (EUR 1.2 million) of the European Regional Development Fund (EFRE) to the infrastructure investment.
- ✓ Consulting and training of small and medium sized (SME) enterprises on how to access EU funds such as 6th research framework programme (FP6), EFRE funds, EU tenders. Organisation of EU co-financed business and technology cooperation fairs for SME´s in Vienna and Brussels. Seminars on lobbying and decision making in the EU. Trainings for EU Commission DG enterprise on project management.

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Declaration of Interest of a creator

I, Olga Shatilova, born on 21.05.2019 at Ismail (Ukraine), am employed as a Senior Medical Writer at Croma-Pharma GmbH (address: Industriezeile 6, 2100 Leobendorf, Austria) (the "**CROMA**"). As CROMA's employee, I participate in the preparations of clinical evaluation reports (the "**Clinical Evaluation Reports**") for the evaluation of CROMA's and CROMA's affiliated company Croma GmbH's (address: Industriezeile 6, 2100 Leobendorf, Austria) products (the "**Evaluations**") as a creator.

To the best of my knowledge, I hereby declare that besides my reasonable interests as an employee, there are no financial interests of my family members included in the Evaluation.

Furthermore, I do not possess

- any ownership or shareholding possibly affected by the outcome of the Evaluation;
- any interests in connection with intellectual property possibly affected by the outcome of the Evaluation;
- any other interests or sources of revenues possibly affected by the result of the Evaluation.

Creator

Signature: _____

Name: Dr. Olga Shatilova

Title: Senior Medical Writer

Date 07.11.2019

Confirmed by Management:

Croma-Pharma GmbH

Signature: _____

Mag. Martin Prinz

Managing Director

Date: 07. Nov. 2019

Signature: _____

Mag. Martin Schöller

Managing Director

Date: 07. Nov. 2019

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Declaration of Interest of a reviewer

I, Arkan Zwick, born on 15.12.1971 at Vienna, Austria, am employed as Regulatory Affairs Director at Croma-Pharma GmbH (address: Industriezeile 6, 2100 Leobendorf, Austria) (the "**CROMA**"). As CROMA's employee, I participate in the preparations of clinical evaluation reports (the "**Clinical Evaluation Reports**") for the evaluation of CROMA's and CROMA's affiliated company Croma GmbH's (address: Industriezeile 6, 2100 Leobendorf, Austria) products (the "**Evaluations**") as a reviewer.

To the best of my knowledge, I hereby declare that besides my reasonable interests as an employee, there are no financial interests of my family members included in the Evaluation.

Furthermore, I do not possess

- any ownership or shareholding possibly affected by the outcome of the Evaluation;
- any interests in connection with intellectual property possibly affected by the outcome of the Evaluation;
- any other interests or sources of revenues possibly affected by the result of the Evaluation.

Reviewer

Signature: _____

Dr. Arkan Zwick

Regulatory Affairs Director

Date: 03.10.2019

Confirmed by Management:

Croma-Pharma GmbH

Signature: _____

Mag. Martin Prinz

Managing Director

Date: 09. Okt. 2019

Signature: _____

Mag. Martin Schöller

Managing Director

Date: October 8, 2019

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Declaration of Interest of reviewer

I, Marion Pucher, born on 24.05.1983 at [Hollabrunn, Austria], am employed as Teamleader GCP/Clinical Project Manager at Croma-Pharma GmbH (address: Industriezeile 6, 2100 Leobendorf, Austria) (the "**CROMA**"). As CROMA's employee, I participate in the preparations of clinical evaluation reports (the "**Clinical Evaluation Reports**") for the evaluation of CROMA's and CROMA's affiliated company Croma GmbH's (address: Industriezeile 6, 2100 Leobendorf, Austria) products (the "**Evaluations**") as a reviewer.

To the best of my knowledge, I hereby declare that besides my reasonable interests as an employee, there are no financial interests of my family members included in the Evaluation.

Furthermore, I do not possess

- any ownership or shareholding possibly affected by the outcome of the Evaluation;
- any interests in connection with intellectual property possibly affected by the outcome of the Evaluation;
- any other interests or sources of revenues possibly affected by the result of the Evaluation.

Reviewer

Signature: _____

Name: DI Dr. Marion Pucher

Title: Teamleader GCP/Clinical Project Manager

Date: 04.02.2020

Confirmed by Management:

Croma-Pharma GmbH

Signature: _____

Mag. Martin Prinz

Managing Director

Date: 04.02.2020

Signature: _____
ppa. MARTIN PRINZ, GL, 04.02.2020, MAS.

Mag. Martin Schöller

Managing Director

Date: 04.02.2020

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Declaration of Interest of an expert

I, Dr. Verena Proell, born on 25.12.1977 at St. Pölten, Austria, am employed as Deputy Global Director Research and Development at Croma-Pharma GmbH (address: Industriezeile 6, 2100 Leobendorf, Austria) (the "**CROMA**"). As CROMA's employee, I participate in the preparations of clinical evaluation reports (the "**Clinical Evaluation Reports**") for the evaluation of CROMA's and CROMA's affiliated company Croma GmbH's (address: Industriezeile 6, 2100 Leobendorf, Austria) products (the "**Evaluations**") as an expert.

To the best of my knowledge, I hereby declare that besides my reasonable interests as an employee, there are no financial interests of my family members included in the Evaluation.

Furthermore, I do not possess

- any ownership or shareholding possibly affected by the outcome of the Evaluation;
- any interests in connection with intellectual property possibly affected by the outcome of the Evaluation;
- any other interests or sources of revenues possibly affected by the result of the Evaluation.

Expert

Signature: 

Name: Verena Proell

Title: Dr. rer. nat.

Date: 05.02.2020

Confirmed by Management:

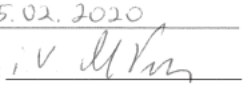
Croma-Pharma GmbH

Signature: 

Mag. Martin Prinz

Managing Director

Date: 05.02.2020

Signature: 

Mag. Martin Schöller

Managing Director

Date: 05.02.2020

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Declaration of Interest of an Approver

I, Michael Henkel, born on 26 May 1963 at Vienna, am employed as Clinical Documentation Review Manager at Croma-Pharma GmbH (address: Industriezeile 6, 2100 Leobendorf, Austria) (the "**CROMA**"). As CROMA's employee, I participate in the preparations of clinical evaluation reports (the "**Clinical Evaluation Reports**") for the evaluation of CROMA's and CROMA's affiliated company Croma GmbH's (address: Industriezeile 6, 2100 Leobendorf, Austria) products (the "**Evaluations**") as an approver.

To the best of my knowledge, I hereby declare that besides my reasonable interests as an employee, there are no financial interests of my family members included in the Evaluation.

Furthermore, I do not possess

- any ownership or shareholding possibly affected by the outcome of the Evaluation;
- any interests in connection with intellectual property possibly affected by the outcome of the Evaluation;
- any other interests or sources of revenues possibly affected by the result of the Evaluation.

Approver

Signature: _____

Mag. Michael Henkel

Clinical Document Review Manager

Date: 27/01/2020

Confirmed by Management:

Croma-Pharma GmbH

Signature: _____

Mag. Martin Prinz

Managing Director

Date: 30. Jan. 2020

Signature: _____

Mag. Martin Schöller

Managing Director

Date: 30. Jan. 2020

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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

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Journal of Cosmetic Dermatology

Instructions for authors:

SECTIONS OF THE JOURNAL TO WHICH SUBMISSIONS ARE ACCEPTED

Original Articles

Peer reviewed submissions of high quality that have not been published elsewhere. International submissions from all parts of the globe are encouraged as the Associate Editors are international in scope. Reviewers will be encouraged to submit commentaries to accompany the accepted article they evaluated. The title page should contain the author's name(s), appointments and place of work at the relevant time. A full and a short running title should be given, together with no more than six keywords for indexing purposes.

Dermatologic Surgery

Edited By: William P. Coleman III, M.D.

Impact Factor: 1.798

ISI Journal Citation Reports © Ranking: 2011: 23/58 (Dermatology); 67/199 (Surgery)

Online ISSN: 1524-4725

Overview

Exclusively devoted to dermatologic surgery, *Dermatologic Surgery* publishes the most clinically comprehensive and up-to-date information in its field. This unique monthly journal provides today's most expansive and in-depth coverage of cosmetic and reconstructive skin surgery and skin cancer, through peer-reviewed original articles, extensive illustrations, case reports, ongoing features, literature reviews, and correspondence. The journal provides information you need to know about the latest scientific information for all types of dermatologic surgery such as:

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Clinical, Cosmetic and Investigational Dermatology

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ISSN 1178-7015

Editor-in-Chief:
Dr Jeffrey M Weinberg

An international, peer-reviewed, open access journal that focuses on the latest clinical and experimental research in all aspects of skin disease and cosmetic interventions. Normal and pathological processes in skin development and aging, their modification and treatment, as well as basic research into histology of dermal and dermal structures that provide clinical insights and potential treatment options are key topics for the journal.

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Aesthetic Surgery Journal is a peer-reviewed international journal focusing on scientific developments and clinical techniques in aesthetic surgery. An official publication of the American Society for Aesthetic Plastic Surgery (ASAPS), *ASJ* is also the official English-language journal of many major international societies of plastic, aesthetic and reconstructive surgery representing South America, Central America, Europe, Asia, and the Middle East. It is also the official journal of The Rhinoplasty Society.

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Journal of Cosmetic and Laser Therapy

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All manuscripts will be subjected to confidential peer review by experts in the field and, on the basis of reviewers' feedback, papers will be accepted unconditionally, accepted subject to revision or rejected.

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INSTRUCTIONS FOR AUTHORS

MISSION STATEMENT

To provide independent, unbiased and high-quality content that is validated by rigorous peer review. PRIME's aim is to serve the information needs of the aesthetic and anti-ageing medicine community, to help translate medical advances into patient care and be a leader in transparency/disclosure by facilitating a collaborative and honest approach to publication.

AIMS AND SCOPE

PRIME – The World Journal of Aesthetic and Anti-Ageing Medicine – is a peer-reviewed journal focused on all aspects of aesthetics and anti-ageing medicine in today's ageing population.

The publication contains original research papers, reviews and commentaries across all anti-ageing therapeutic specialties, providing a single source of high-quality research for all who work in the field of anti-ageing.

The Journal welcomes reports describing new anti-ageing treatments, innovative delivery or applications of existing treatments, and review articles on developments in anti-ageing medicine within specific therapeutic areas.

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2011	2011-222	Princess Rich	403004/1	Product did not spread as usual, but made "lumps". Patient now has "Dippel" in these places. AD has been contacted by a physician regarding post-treatment of the patient (US, cupping massage, ...).	Lumps not justified	1	Adverse event Complaint
2011	2011-272	M-HA18	403007/2	Instead of 2 there was only 1 blister in the folding box	Missing component	1	Product Quality Complaint
2012	2012-043	Genyal Genyalift	403009/4	Bent plungers/luer lock problems & needle going out of plastic part --> genaue Zuordnung nach Erhalt der Muster	Bent plunger rod, luer lock issue	2	Product Quality Complaint
2012	2012-188	Princess Rich	403010/2, 3	The needle comes off at injection	Luer lock BD	10	Product Quality Complaint
2012	2012-219	Princess Rich	403010/2	1ml Princess Rich injected into both lower lid regions using nappage technique (superficial setting of small depots). The patient had a persistent swelling of the lacrimal sacs (eye rings) for over a week.	swelling	1	Adverse event Complaint
2012	2012-220	Princess Rich	403008/3	Luer lock went off during the injection and the gel was coming out.	Luer lock BD	1	Product Quality Complaint
2012	2012-221	Princess Rich	403009/1	Luer lock went off during the injection and the gel was coming out.	Luer lock BD	1	Product Quality Complaint
2013	2013-175	Princess Rich	403013/4	In most (85%) of the cased neither needle fell off neither luer lock. Just because of high pressure product goes out between plastic luer lock and glass syringe. In few cases needle stayed in body and in few luer lock fell of together with needle.	Luer lock BD	1	Product Quality Complaint
2013	2013-176	Princess Rich	403013/1	In most (85%) of the cased neither needle fell off neither luer lock. Just because of high pressure product goes out between plastic luer lock and glass syringe. In few cases needle stayed in body and in few luer lock fell of together with needle.	Luer lock BD	1	Product Quality Complaint
2013	2013-177	Princess Rich	403013/5	In most (85%) of the cased neither needle fell off neither luer lock. Just because of high pressure product goes out between plastic luer lock and glass syringe. In few cases needle stayed in body and in few luer lock fell of together with needle.	Luer lock BD	3	Product Quality Complaint

Year	Complaint no/ form	Product name	Serial / Lot n°	Description of the Event	Complaint cause	Affected items	Product Quality / Adverse event complaint
2009	2009-307	Princess Rich	403001/3	During a workshop 2 patients had been injected with Princess Rich in the decollete. They both compained that the injection was very painful and they blead (a lot) on all the injection points. It was so painful that they refused to be injected in the neck (as planned). The surgeon thinks this event was due to not adapted needle (too long for a 30G 1/2).	Pain and bleeding	2	Adverse event Complaint
2010	2010-149	Princess product line	403004/1	Princess Line: Blister opens itself when the box is shaken, as the lid lasts badly. Open appearance makes a delicate impression.	Blister opened itself	1.	Product Quality Complaint
2010	2010-472	M-HA 18	403007/2	2 lid pockets with "yellow liquid" + important oedema of crows feet immediately after injection	oedema	1	Adverse event Complaint
2011	2011-073	Princess Rich	403007/1 403008/1 403008/3 403008/4	BD Medical informed us that the needle which is supplied with our product Princess RICH is recalled because of a blocking problem.	Blocking needle	4.	Product Quality Complaint
2011	2011-088	Princess Rich	403007/1	Totally bent plungers; at the moment 10 pieces of this batch concerned	Bent plunger rod	61	Product Quality Complaint
2011	2011-093	Princess Rich	403003/1	3 hours after injection of Princess Rich (on many places of the face) the patient developed papules on each injection point. The doctor gave her Solupred and within 3 days all papules disappeared. The patient already had NaHa injections (Juvederm) but didn□t tell the surgeon if she ever had problems in the past. She also informs the doctor (only after the papules appeared) that she was highly allergic to many things and that she already had a Quinck Oeadema (angiodema).	papules	1	Adverse event Complaint
2011	2011-173	Princess Rich	unknown	1 Princess Rich pattern of AD smelled when opening the pack extremely after fish; Especially after the syringe has been opened. Unfortunately the syringe and the packaging were disposed of, the product was not used	others	1	Product Quality Complaint

2016	CF-2016-018	Princess Rich	unknown	client inject princess rich, and have this result ...on the neck --> bleeding	bleeding due to wrong injection technique	1	Adverse event Complaint
2016	CF-2016-026	M-HA18	403036	During the control of received products we found some non-compliant X-HA3 and M-HA18 products: The products sealing label is broken	label torn	237	Product Quality Complaint
2016	CF-2016-033	Hyalstyle Light	403016/6	Already in 2014, the patient was treated by a curative practitioner in Germany, shortly thereafter, granulomas developed, which were apparently not treated correctly. A legal dispute has arisen from the whole case, but Mr Mrad-Agua is the owner of the Hyalstyle brand. As a "reasoning document" in court, it would be good for him if we could write a report that the batch was all right and could also prove this with test reports. We do not need any treatment suggestions from our side.	granuloma	1	Adverse event Complaint
2016	CF-2016-096	M-HA18	403036	Broken sealing label. The transport is made by specialized companies and the sealing label shouldn't break during the distribution of products.	label torn	15	Product Quality Complaint
2016	CF-2016-097	M-HA18	403037	Broken sealing label. The transport is made by specialized companies and the sealing label shouldn't break during the distribution of products.	label torn	12	Product Quality Complaint
2016	CF-2016-127	Jalor Re-style	403037	luer lock problems	luer lock BD	1	Product Quality Complaint
2016	CF-2016-192	Princess Rich	403022	When doctors wanted to apply the products the luer lock adapter of the syringe came loose and all the product ran out of the syringe.	luer lock BD	1	Product Quality Complaint
2016	CF-2016-232	Princess Rich	403039	Unfortunately we just received a notification from a big client in France that the RICH syringes do not have a bar code. This is the second time we have this problem.	labelling	1	Product Quality Complaint
2016	CF-2016-241	Zfill Refresh	403043	Wir haben in der letzte Lieferung unterschiedlich bedruckte Filler gefunden. (Farbe ist dunkler.) / Darker color of folding box.	different folding box - colour	2	Product Quality Complaint
2016	CF-2016-324	Princess Rich	403028	The luer lock adapter went off. We don□t heard about any harm of patient	luer lock BD	1	Product Quality Complaint
2016	CF-2016-325	Princess Rich	403038	The luer lock adapter went off. We don□t heard about any harm of patient	luer lock BD	1	Product Quality Complaint

2016	CF-2016-326	Princess Rich	403039	The luer lock adapter went off. We don□t heard about any harm of patient	luer lock BD	3	Product Quality Complaint
2017	CF-2017-022	Princess Rich	403028	I would like to report an incident of a syringe. A doctor called and told me that the syringe broke while using it on a patient. The black plastic (in between the needle and the syringe) popped out with the result that the HA poured all out.	luer lock BD	1	Product Quality Complaint
2017	CF-2017-110	Princess Rich	403041	After using Princess Rich, papules of the face did not disappear after 72 hours. Today after 25 days, the skin is rough, without natural glow, with the appearance of acne	nodules and appearance of acne not justified	1	Adverse event Complaint
2017	CF-2017-114	Zfill refresh²	403034 SAP Nr.:31176	we have the problem with the luer lock, which went off.	luer lock BD	1	Product Quality Complaint
2017	CF-2017-126	Princess Rich	unknown	a doctor used princess rich and he reported us that after use inflammario reactions are observed and fine lines are more visible.	inflammation	1	Adverse event Complaint
2017	CF-2017-160	Princess Rich	403034	The luer lock is broken	broken luer lock BD	1	Product Quality Complaint
2017	CF-2017-161	Princess Rich	403045	The luer lock is broken	broken Luer lock Gerresheimer	1	Product Quality Complaint
2017	CF-2017-209	Pluryal Booster	unknown	a case about patients allergies with Pluryal Booster: After treatment 2 days, the erythema with swelling all body. She must go to hospital & testing generality.	Erythema swelling not justified	1	Adverse event Complaint
2018	REK-18-00008	unknown	unknown	I recently got 1ml of princess lip filler injected, and unfortunately had an allergic reaction to this. I was unable to leave my house for a week, or eat anything. The swelling occurred within hours of having the procedure done, where I was rushed into the clinic for two steroid injections. I was told that this sort of reaction was unheard of by my aesthetic doctor. I just wanted to know what is exactly in this filler? What has caused me to have this reaction	swelling	1	Adverse event Complaint

				and does this now mean that I will react in the same way to other fillers in the future?			
2018	REK-18-00050	Princess Rich	unknown	I have used princess rich for eyeshadows at the same day to my 2 patients 7 days ago , but they are very unhappy about swelling. Remark ike/QA: we tried several times to contact the complainant in order to receveive further information (especially in regard to the current health status of the patient). However no answer was received from the complainant	swelling	1	Adverse event Complaint
2018	REK-18-00051	Princess Rich	unknown	I have used princess rich for eyeshadows at the same day to my 2 patients 7 days ago , but they are very unhappy about swelling. Remark ike/QA: we tried several times to contact the complainant in order to receveive further information (especially in regard to the current health status of the patient). However no answer was received from the complainant.	swelling	1	Adverse event Complaint
2018	REK-18-00085	Princess Rich	403051	One of our Doctors sent us a picture of a patient who had Princess Rich treatment done 4 weeks ago and the product still didn□t absorbed completely. Same patient had this treatmet already several time and before the product was absorbing up to one week. Can you help us? Do you know what could be the reason why? The series nr of Rich was as follows: 403051 According to picture provided the following can be observed: edema, induration, nodules, papules. Additional information received on 02.07.2018: Currently the patient is feeling good. The papulas have despaired, but only after two series of hyaluronidase	edema, induration /nodules, papules	1	Adverse event Complaint
2018	REK-18-00124	Princess Rich	403058	Few of our clients informed us that the cover of the part in which syringe and needles are packed seems to open much, much easier than in the past. It seems like the glue is not as strong as used to be. It give an impression like the packaging was opened and	Blister sealing inconsistent	4	Product Quality Complaint

				closed again. It raised a question if the product is still protected well enough and sterile. There was no harm to the patient.			
2018	REK-18-00154	M-HA18	403050	During process of extrusion from the piston, the rubber tip separated from the plunger. The complainant used the needles in the package M-HA 18. There was no harm to the patient. additional Information received on 05.09.2018 and 08.10.2018: the complainant means that the Plunger rod went off the Plunger stopper during application and the luer lock adapter went off during injection	luer lock Gerresheimer and plunger rod went off	1	Product Quality Complaint
2018	REK-18-00155	M-HA18	403053	During process of extrusion , the needle and luer lock section separated from the syringe, and the preparation expelled. There was no harm to the patient. The procedure outlined in the information leaflet being followed. The operator/nurse used this product before. Needles from set have been used. Additional information received on 05.09.2018: The complainant confirms that the luer lock adapter including needle went off the syringe during applic	luer lock Gerresheimer	1	Product Quality Complaint
2018	REK-18-00168	Princess Rich	403045	I would like to share with you a problem appeared with some of our customers during the injection of Princess Rich, the compressor is separated from the needle . No harm to the patient was reported.	others	1	Product Quality Complaint
2018	REK-18-00169	Princess Rich	unknown	I would like to share with you a problem appeared with some of our customers during the injection of Princess Rich, sometimes the material is released alone from the sides . No harm to the patient was reported.	leakage at luer lock Gerresheimer	1	Product Quality Complaint
2018	REK-18-00232	Princess Rich	unknown	crack on the syringe	Complaint Cause is unknown to this time	1	Product Quality Complaint
2018	REK-18-00235	Princess Rich	403056	ripped off the thread	Complaint Cause is unknown to this time	1	Product Quality Complaint

2018	REK-18-00237	Princess Rich	403057	the needle flew off	Complaint Cause is unknown to this time	1	Product Quality Complaint
2018	REK-18-00242	Pluryal booster	403057	we received an email from our distributor with the attached pictures: the client opened a Pluryal Booster box and inside there was a Princess filler Batch 903182. We cannot check other boxes in our stock as we sold all the lot. Remark ike/QA:no specific Information regarding patient impact could be provided by the complainant, however it can be assumed that the customer did not use the Syringe as the customer reconized it when he screwed in the needle an	mixed up product	1	Product Quality Complaint
2018	REK-18-00258	unknown	unknown	I have a Patient who has used filler for her lips and apparently develop some small lumps on site. Additional Information received on 29.11.2018: So far the reason for the complain has disappeared as the injection of hyalurinasa has dissolved the lumps.	lumps	1	Adverse event Complaint
2018	REK-18-00277	unknown	unknown	Again we have a dislodge of the plastic o ring	Complaint Cause is unknown to this time	1	Product Quality Complaint
Complaint ratio: / release units*100= 52/1.617.859 *100= 0,0032%							

REK-19-00089	12.04.2019	M-HA 18	403071	unknown	CROMA received an e-mail conversation between Filorga and Regulatory Affairs. Filorga complained about an writing mistake on the folding boxes of M-HA 18. Instead of "1 x 1 ml Hyaluronic Acid with Glycerol" it was stated " 1 x 1 ml Cross-linked Hyaluronic Acid". Filorga now had receive a complaint from a customer, who received the same product with two different packaging. Filorga Regulatory Department noticed this issue in December. ABW_18-00156: "Error in 34838 FB M-HA18 TQ FMM000A1a" additional information received on 29.05.2019: This complaint concerns batch 403076 and 403071.		France	Product Quality Complaint	**major**	labeling		
REK-19-00139	29.05.2019	M-HA 18	403076	unknown	CROMA received an e-mail conversation between Filorga and Regulatory Affairs. Filorga complained about an writing mistake on the folding boxes of M-HA 18. Instead of "1 x 1 ml Hyaluronic Acid with Glycerol" it was stated " 1 x 1 ml Cross-linked Hyaluronic Acid". Filorga now had receive a complaint from a customer, who received the same product with two different packaging. Filorga Regulatory Department noticed this issue in December. ABW_18-00156: "Error in 34838 FB M-HA18 TQ FMM000A1a" additional information received on 29.05.2019: This complaint concerns batch 403076 and 403071.		France	Product Quality Complaint	**major**	labeling		

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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

Complaint ID	QA received date	Brand name	Lot / serial #	N° complained items	Description of the Event (issue)	harm to the patient	Country	Complaint type	major/ minor	Complaint issue	Adverse event outcome	Update of RiA necessary
REK-19-00026	24.01.2019	Apriline Hydro	403059	1	Side effect appearing on the skin of patient (inflammatory reaction). Photos attached on the day of onset and from the following day. Consecutive treatments and measures: No hospitalization; Antibiotics – ceftriaxone + antihistamine. Current Status of the Patient: Recovering Additional information received on 25.01.2019: The patient started treatment on the fourth day after the injection procedure. The reaction, if it is defined by inflammation, lasted for 10 days. However, papules are still present on the face. The information about a dental treatment will be requested. Additonal information received on 04:04.2019: The patient didn't undergo any dental treatment during this period.		Georgia	Adverse event Complaint	minor	inflammation, papules - derma		no. Known adverse event listed in the IFU.
REK-19-00067	02.03.2019	Princess Rich	unknown	1	remark aps/COP 11.03.2019: the complaint was forwarded to Marzena Piwowarska (CROMA Poland) for translation on 06.03.2019 remark aps/COP 22.03.2019: Marzena Piwowarska (CROMA Poland) answered that this complainant is not a customer of them and provided a translation: Three days ago i performed mesotherapy treatment for the first time with Princess RICH. After the treatment papules appeared and these are still visible. Is it a regular reaction? Or maybe I injected too superficially or too much of the product? How much time does it take the product to absorb totally, and if there is any risk, that the skin will not absorb the product totally?		Poland	Adverse event Complaint	minor	papules - derma		no. Known adverse event listed in the IFU.

REK-19-00153	18.06.2019	Princess Rich	403062	5	Here is a message I received from the trusted branch manager of a high end clinic in Dubai: "Omar don't get the fillers we tried..both patients got infected with a lot of pain..dr manar was told that obaji was using it before but the complications are high...dr fadi dissolved it for both patients!" My team thinks your manufacturing process might not be sterile and that bacteria was inside the product. remark aps/COP: further information about the affected product and the complaint form is missing.		Dubai	Adverse event Complaint	major	infection, pain - not confirmed		no. Known adverse event listed in the IFU.
REK-19-00183	18.07.2019	M-HA 18	403059	1	Leackage due to bad connection between luer lock and needle. When a doctor screwed the needle on the syringe, she noticed that the lock rotates. The doctor did not attach any importance to this fact, introduced the needle, pressed the plunger of the syringe, the needle remained in the tissue, and the syringe separated from it and all the gel spilled on the therapy bed. update 18.SEP2019: - How many syringes were complained? One - From which country was the complaint reported? Russia - Was there any harm to the patient? No (for health) punctured skin only	no	Russia	Product Quality Complaint	minor	luer lock Gerresheimer - derma	n.a	no

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C_CT_CER_005_05	09.03.2020	08.06.2025	09.04.2020

REK-19-00229	19.09.2019	Saypha RICH 1ml R1 FP	403088	1	During the review of a patient who received the injection of 0.5 mL saypha rich per site with 25G cannula in deep dermis, the doctor noticed a granuloma in the area. Doctor is requesting an advise from CROMA for treatment: e.g. hyalurinidase, corticoids, physiological serum, etc.. Complainant is an aesthetic Doctor with more than 15 years of experience. She has attended to some of Croma workshops in the past.	no	Portugal	Adverse event Complaint		Indurations or nodules at the injection site - derma		no. Known adverse event listed in the IFU. Off label use

Clinical Investigation Report - Interim Report

Sponsor:	**CROMA-PHARMA GmbH**
Clinical investigation plan (CIP) identification:	CPH-401-201364 RICH
Title:	A Prospective Open-label, Multicenter Study Evaluating Princess® RICH in Correction of Fine Lines
Investigational medical device (IMD):	Princess® RICH [1.8% Sodium Hyaluronate with 2% Glycerol i.d.]
Classification:	Class III medical device
Coordinating investigator (CI):	Univ. Prof. Dr. Daisy Kopera Medical University Graz- Dermatology and Venerology Clinic Auenbruggerplatz 8, 8036 Graz, Austria Tel. general: +43 316 385 12423 FAX: +43 316 385 12466 Email: daisy.kopera@medunigraz.at
Sponsor	CROMA-PHARMA GmbH Industriezeile 6, 2100 Leobendorf, Austria Phone: +43 2262 684 680 Email: office@croma.at
Biostatistician	Agnes Himmelmann, M.S. bioskin GmbH Burchardstrasse 17, 20095 Hamburg, Germany
Author of the report	Ragna Williams, M.S. bioskin GmbH Burchardstrasse 17, 20095 Hamburg, Germany
Clinical investigation period	25OCT2018 (first subject in, Visit 1/Screening) to 12JUN2019 (last subject last Week 16 visit, Visit 6)
Date of report:	28OCT2019

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

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Summary

Title

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

Purpose

1. To assess the effectiveness of Princess® RICH to correct fine lines on the face including lateral canthal lines (LCL) also called "Crow's Feet" and perioral rhytids (PR) also called "smile lines" or "smoker's lines"
2. To assess safety
3. To assess the ability of Princess® RICH to improve skin hydration, skin tone and skin elasticity in the treatment areas
4. To assess subject satisfaction with treatment
5. To assess the aesthetic effect of Princess® RICH

Introduction

Princess® RICH has been approved in 2009 for the replenishment of hyaluronic acid (HA) loss due to aging, to improve hydration, tone and elasticity of the skin and to act as a filler for small lines such as LCL also called "Crow's Feet", smile lines and PR also called "smile lines" or "smoker's lines". The approval was based on clinical experience with similar devices. The present investigation was undertaken to support these claims by providing evidence of Princess® RICH performance and safety in subjects undergoing up to three treatments with the device and followed for 16 weeks. The study follow-up period was prolonged up to week 52, but these results are not part of this report.

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

Design and methodology

This was an open label, single treatment arm study.

All subjects were evaluated by the treating physician, at their initial clinic visit. Subjects deemed by treating physician to have sufficient severity to merit treatment of either their LCL or PR or both were enrolled in 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. 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 next injection. An assessment for concomitant medication and adverse events were done. 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 the end of the study (independent of whether the subject participates in the 52-Week follow-up period), all necessary study closeout procedures were performed and the subjects

	were discharged from the study. Formal interim analysis (IA): An IA was performed after all subjects have completed the follow-up visit at Week 16. End of Study: The duration of the clinical investigation was planned for 52 Weeks at a maximum. In case it was observed by the investigator that at a given visit no aesthetic effect was any more visible in approximately 75 % of the subjects participating the follow-up period of 52 Weeks, the study could have been terminated at an earlier time point.
Population (planned/analyzed)	100 male and female subjects aged 18 years or older were planned; 102 subjects were screened and enrolled in this clinical investigation. Data of all 102 subjects were valid for the safety-analysis-set. Data of 101 subjects were valid for intent-to-treat-population (ITT). 84 subjects were included in the per-protocol (PP) population (valid cases set = VCS). 18 subjects in total were excluded from PP population. For 17 of the 18 subjects the primary exclusionary reason was categorized as "Subject with protocol deviation (PD) interfering with the evaluation for GAIS at Week 8". 1 of the 17 subjects withdrew from the investigation after Visit 4/Week 8 due to personal reasons. For the remaining 1 subject, the primary exclusionary reason from the PP was categorized as "Other". This subject suffered from familial catastrophes and discontinued the investigation after Visit 1. The 2 subjects with premature discontinuation after Visit 4 and Visit 1 were the only 2 dropouts in this investigation.

Results and conclusions

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

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

The ability of Princess® RICH to improve skin tone and skin elasticity in the treatment areas was confirmed by cutometry. The cutometric measurements revealed mean lower R0 values (skin tone) and mean higher R2 (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 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.

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

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

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

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

In total, 42 treatment-emergent adverse events (TEAEs) were reported in 26 subjects (25%). 2 of the TEAEs were SAEs (Neuropathia vestibularis right and meniscus partial rupture left knee), which were considered to be unlikely or not related to IMD or procedure. All other TEAEs were non-serious TEAEs, mostly located at treatment area or just around treatment area (31 TEAES in 20 subjects) and considered to be related to study procedure (mainly 'injection site haematoma' with 25 events, otherwise 4 events of 'injection site oedema' and 1 event of 'injection site swelling')'. The causal relationship to IMD was considered to be probable for 1 TEAE (injection site swelling), and definite for 6 TEAEs (5 events of 'injection site oedema', 1 event of 'injection site haematoma').

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

	In comparison to approximately 80% described in literature (Succi et al, 2012; Uth, Elberg and Zachariae, 2016), only 5 of subjects (5%) in this clinical investigation presented swelling or oedema. None of the TEAEs led to subject's withdrawal and the outcome of the TEAEs was 'resolved' within a few days to one week in most cases, corresponding to other HA described in literature (Abduljabbar and Basendwh, 2016). 'Ongoing' was noted for 2 TEAEs (PTs: gastrooesophageal reflux disease and seasonal allergy) and 'resolved with sequelae' for 1 TEAE (PT: shoulder operation). 8 subjects took a medication for treatment of AE. 1 of these subjects took rescue medication hyaluronidase once at Week 3 for treatment of injection site oedema. None of the other subjects took a rescue medication. 44.1%, 22.4%, and 48.8% took an additional anaesthetic medication on Day 0, Week 3 and Week 6, respectively. Furthermore, no device deficiencies were reported in this clinical investigation. On the basis of the present results no specific risks or precautions are required to be mentioned over those already known and described. There were no safety concerns based on the results of this clinical investigation. Overall, the IMD poses a well-tolerated, safe and effective alternative to current use of other comparable dermal fillers in the treatment of LCL and PR. Princess® RICH as a non-cross-linked hyaluronic dermal injectable convinced with its performance on improving skin tone and elasticity and to act as an filler for small lines such as LCL and PR lasting for a satisfactory duration.
Initiation/completion date of investigation	25OCT2018 (first subject in, Visit 1/Screening) 12JUN2019 (last subject last Week 16 visit, Visit 6)

1. Introduction

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

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

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

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

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

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

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

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

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

Princess® RICH is a viscoelastic solution used to replenish the loss of HA due to aging to improve hydration, tone and elasticity of the skin and to act as a filler for lateral canthal lines (LCL) also called "Crow's Feet" and perioral rhytids (PR) also called "smile lines" or "smoker's lines".

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

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

2. Investigational medical device (IMD) and methods

Details of the IMD are given in Table 1.

Table 1: Details of the IMD

Brand name	Princess® RICH
Formulation	Hyaluronic Acid
Functional components	Sodium hyaluronate (17.72 mg/mL) as Active ingredient Citric acid monohydrate (0.06 mg/mL) as Buffer salt Glycerol (21.16 mg/mL) as Stabilizer Di-sodiumhydrogen phosphate dodecahydrate (1.31 mg/mL) as Buffer salt Water for injection (970.76 mg/mL) as Solvent
Shelf life	36 months
Intended use	Initial intended use: To replenish the loss of HA due to aging to improve hydration, tone and elasticity of the skin and to act as a filler for lateral canthal lines (LCL) also called "Crow's Feet" and perioral rhytids (PR) also called "smile lines" or "smoker's lines". The intended use was updated in April 2019 as follows: To replenish the loss of hyaluronic acid due to ageing, to improve hydration, tone and elasticity of the skin.
Amount per unit	30G ½ per syringe
Packaging	A folding box containing two sterile single use needles (30G ½) per syringe and the IFU
Storage	2–25 °C / 36–77°F
Manufacturer	Princess® RICH is manufactured by Croma-Pharma GmbH, Industriezeile 6, 2100 Leobendorf, Austria. Enclosed needles are manufactured by TERUMO Europe N.V., Interleuvenlaan 40, 3001 Leuven, Belgium.

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

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

3. Clinical investigation plan (CIP)

3.1 Clinical investigation objectives

The objective of the clinical investigation was

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

3.2 Clinical investigation design

3.2.1 Overall clinical investigation design and plan - description

The present clinical investigation was designed as an open label, prospectively designed trial using a single investigational product, Princess® RICH, for the treatment of small lines such as crow's feet and smile or smoker's lines around the mouth and to improve skin hydration, tone and elasticity. The clinical investigation was performed in 102 male or female subjects with a single investigational product, Princess® RICH.

All subjects were evaluated by the physician, at their initial clinic visit. Subjects deemed by treating physician to have sufficient severity to merit treatment of either their LCL or PR or both were enrolled in the study. Documentation of the evaluation was done by photographs taken with the 3D LifeViz micro camera-Quantificare, and measurements for skin hydration, tone and elasticity was done using the corneometer and cutometer devices (Courage & Khazaka). Subjects were treated with the investigational product, Princess® RICH at Weeks 0, 3 and 6.

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

A subject treatment satisfaction questionnaire was collected at Weeks 8, 12 and 16

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

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

3.2.2 Efficacy/ performance and safety variables

Primary efficacy variable / Primary performance endpoint:

Primary efficacy assessment was:

- Percentage of responders at Week 8 after initial treatment point. Responder was defined as at least "improved" versus baseline in the fine lines of the LCL on both sides and/or the PR as assessed with the GAIS, based on the investigator assessment.

Secondary efficacy variable / Secondary performance endpoints:

Secondary efficacy assessments were:

- Percentage of responders. Responder was defined as at least "improved" versus baseline in the fine lines of the LCL on both sides and/or PR, as assessed with the GAIS and based on the investigator's assessment, at Weeks 12 and 16 after initial treatment.
- Change from baseline at Weeks 3, 6, 8, 12 and 16 in skin hydration assessed with the corneometer device.
- Changes from baseline at Weeks 3, 6, 8, 12, 16 in skin tone assessed with the cutometer device.
- Change from baseline at Weeks 3, 6, 8, 12 and 16 in skin elasticity as assessed with the cutometer device.
- Subject satisfaction with treatment at Weeks 8, 12 and 16 using one of the following categories: "Very unsatisfied", "Unsatisfied", "Neither unsatisfied nor satisfied", "Satisfied", or "Very satisfied".
- Percentage of subjects demonstrating an aesthetic effect at Weeks 12 and 16 based on the investigator's assessment.

Safety variables

Medical and aesthetic history and demographic data

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

Adverse events

All AEs were assessed in terms of seriousness (yes/no), severity, relationship to the IMD or clinical investigation procedures, and outcome (for details see CIP, Section 14.4 "AE/SAE assessment") from the beginning of treatment on Day 0 onwards.

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

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

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

Laboratory variables

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

Safety endpoints

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

- Occurrence and frequency of adverse events.

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

[0] Prior to application of the investigational device.

[**] From beginning of the treatment onwards.

[a] Includes year of birth, gender and race.

[b] All medication taken/received within the previous 10 days.

[c] In women of child-bearing potential only, including those who were postmenopausal for less than 12 months. Urine dipstick test was used.

[d] Investigator evaluation to determine baseline status of subject's LCL and/or PR and the baseline status regarding skin hydration, tone and elasticity.

[e] Photography was to be taken before application of the investigational device.

[f] Investigator's assessment of improvement in wrinkle severity using the Global Aesthetic Improvement Scale (GAIS).

[g] Measurements for skin hydration, tone and elasticity using the corneometer and cutometer devices.

[h] Evaluated by the subject using the Subject's Treatment Satisfaction Questionnaire.

[i] Optional visits (only applicable for subjects willing to participate in the prolonged follow-up): The duration of the clinical investigation was planned for 52 Weeks at a maximum. In case it was observed by the investigator that no aesthetic effect was any more visible in approximately 75 % of the subjects participating the follow-up period of 52 Weeks, the study could have been terminated at an earlier time point.

Table 2: Clinical investigation flow chart

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

3.2.2.2 Assessments/Measurements

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

- Investigator's assessment of improvement in wrinkle severity using the Global Aesthetic Improvement Scale (GAIS)
- Measures of skin hydration, skin tone and skin elasticity
- Subject's Treatment Satisfaction Questionnaire
- Aesthetic effect assessed by the investigator

Aesthetic improvement/GAIS assessment

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

Table 3: Global Aesthetic Improvement Scale (GAIS)

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

Skin hydration

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

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

Skin tone and skin elasticity

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

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

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

Subject's treatment satisfaction questionnaire

Each subject was asked to grade their satisfaction with the treatment using one of the following categories: "Very unsatisfied", "Unsatisfied", "Neither unsatisfied nor satisfied", "Satisfied", or "Very satisfied".

Aesthetic effect

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".

3.2.2.3 Photographic documentation

Photographic documentation was performed on Visit 1 to Visit 9.

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

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

3.2.2.4 Measurement of safety parameters

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

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