Efficacy study of novel monophasic dermal implant containing cross-linked hyaluronic acid associated with amino acids for treatment of the photoaging and its consequences.
Open label observational international multicenter study.

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MATERIAL:
Monophasic gel based on cross-linked hyaluronic acid (HA) with concentration of 7mg/ml associated with a protective buffer of amino acids (taurine, proline, lysine HCl, leucine, glycine, valine, threonine, serine, glutamine, isoleucine, histidine, aspartate of arginine, alanine and phenylalanine, tyrosine) presented in a 3 ml pre-filled syringe (Total concentration of HA 21mg/ml).

TECHNIQUE:
Intradermal injection of 0.2 ml of the product by using 30G needle at 7 specific points on each hemiface (the injection map is presented below in the poster).

OBJECTIVE:
The study has been carried out in normal medical practice with the aim of collecting representative data on the efficacy and safety of the product. Study participants were both men and women over 18 years of age, with indications of photoaging of various severity grades, dermal atrophy.

PROTOCOL:
Day 0. Treatment.
1. Assessment of degree of photoaging according to:
· Classification of wrinkles by Glogau; I-IV
· Wrinkle Severity Rating Scale (WSRS); 1-5
· Midface Volume Deficit Scale (MFVDS); 0-5
2. Skin examination by revision the parameters (texture, skin thickness, skin type, turgor, sagging, actinic elastosis, discoloration, skin atrophy, general skin condition). Parameters were evaluated according to the descriptive scale of 4 degrees.
3. Individual face analysis in aim to evaluate the asymmetries and needs of each patient,
4. Customized mapping of injection sites based on 7-point technique,
5. Treatment performance with a comparative facial analysis of a hemiface after the treatment of one side.
6. Evaluation of treatment result.
7. Monitoring of the adverse events during treatment.

Day 7 and Day 30. Control visits.
1. Evaluation of results using the Global Aesthetic Improvement Scale (GAIS) and the numerical satisfaction scales completed by the doctor and patient.
2. Skin examination.
3. Monitoring of adverse events.

INJECTION MAP
RRS® HA Long Lasting

INJECTION DEPTH	Deep Dermis
VOLUME PER INJECTION	up to 0.2 mL
NEEDLE SIZE	30 G

Injection points:
(1) Zygomatic protuberance. **(2)** Zygomatic area. **(3)** Midcheek groove. **(4)** Nostril angle. **(5)** Nasolabial groove. **(6)** Marionette line. **(7)** Jowl formation.

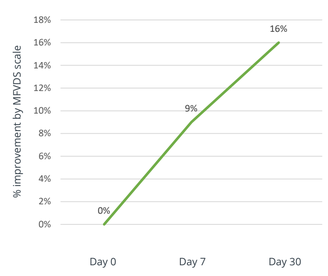
Measure of facial symmetry
(8) Three horizontal lines separating the top third, middle third, and lower third of the face. **(9)** Five vertical lines passing through the center of the face, the center of the pupil, and the lateral corner of the eye. **(10)** Three circular lines in the skin projections of the m. orbicularis oris muscle and m. orbicularis oculi muscles.

RESULTS:
In a clinical study with 43 participants, the following data was observed:

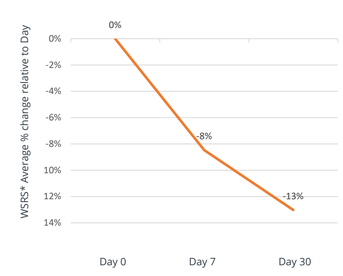
1. MIDFACE VOLUME IMPROVEMENT ACCORDING TO THE MFVDS SCALE* RELATIVE TO DAY 0
Midface volume increase with Validated Midface Volume Deficit Scale (MFVDS) grade reduction of 9% on day 7 after treatment, and 16% on day 30. The volume deficit decreases by an average degree of 2.49 on Day 1 to 2.08 on Day 30.
** The MFVDS scale is a six-point photo numeric scale developed specifically as a scientific assessment tool to evaluate the overall degree of midface volume deficit, with grades ranging from 0 (none) to 6 (severe).*

2. WSRS* GRADE CHANGE RELATIVE TO DAY 0
A reduction in the depth of the nasolabial folds according to the Wrinkle Severity Rating Scale (WSRS) is observed from the mean grade 3.07 on Day 1 to the mean grade 2.67 on Day 30 (-13%).
** WSRS – A validated 5-point photo numeric scale that classifies nasolabial folds, with grades ranging from 1 (absent) to 5 (extreme).*

Grafic. 1 MFVDS



Grafic. 2 WSRS

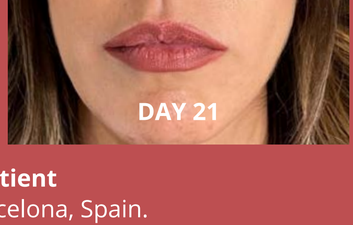


3. RESULTS OF THE CLINICAL EXAMINATION OF THE SKIN PARAMETERS PERFORMED BY CLINICAL INVESTIGATORS
General skin condition
According to clinical examination and evaluation of skin parameters (type, texture, thickness, turgor, dermal atrophy, Glogau grade, flaccidity, actinic elastosis, discoloration) the general condition of the skin has been improved by 9% on Day 7 and 32% on day 30 after treatment (2.41 vs 2.76 vs 3.18).*
** For the evaluation of the skin parameters, the ordinal scales with the following grades were applied: 1- poor, 2 - moderate, 3 - good, 4 - very good.*

Skin Turgor
An increase in skin turgor is detected from a mean grade of 2.71 on Day 1 to 3.18 on Day 7 (17%), and 3.93 on Day 30 (25%).*
** For evaluation of turgor, the ordinal scale was applied with the following grades: 1 - very poor, 2 - poor, 3 - fair, 4 - good.*

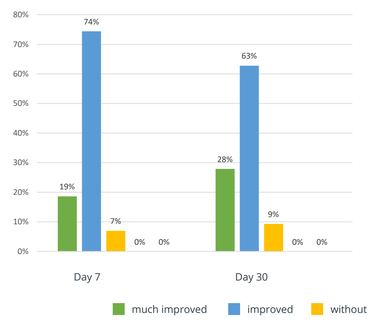
General skin condition

Skin Turgor

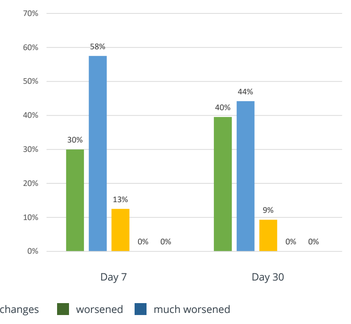


4. RESULTS OF THE SATISFACTION EVALUATION WITH THE TREATMENT ACCORDING TO THE GLOBAL AESTHETIC IMPROVEMENT SCALE (GAIS*)
According to the Global Aesthetic Improvement Scale (GAIS) on the 30th day, 91% of medical practicioners (MP) reported improvement in the appearance of the patients' skin, which coincides with the opinion of patients: 84% of patients reported improvement in their facial appearance.
** GAIS is a 5-point scale that rates overall cosmetic improvement in appearance, compared to pretreatment, at the discretion of the investigator and patient, with grades from 1 (much worse) to 5 (much improved).*

GAIS according to the medical practicioner (MP)



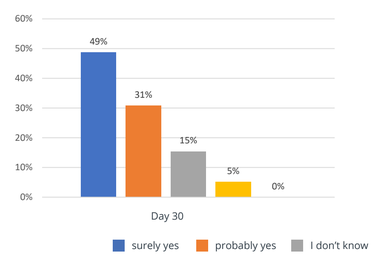
GAIS according to the Patient



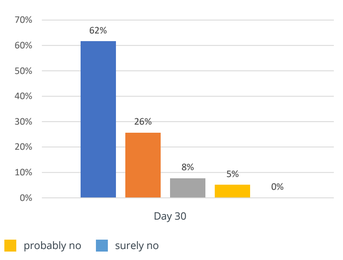
5.RESULTS ACCORDING TO THE PATIENTS SURVEY
Provides skin elasticity
On Day 30 of the study, 80% of the patients agreed that the product provides elasticity to their skin. 15% of the patients neither agreed nor disagreed and 5% disagreed with this statement.

Would you like to repeat the treatment?
88% of patients would like to repeat the treatment in the future. 8% of patients were undecided and 5% of them would not administer the product again.

Provides elasticity



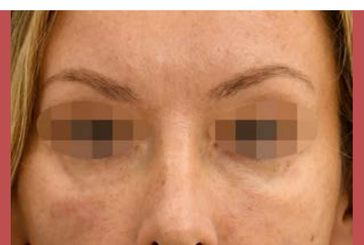
Would you like to repeat the treatment?



6. According to the clinical examination and the evaluation of the skin parameters an improvement of the skin texture is observed from the medium grade 2,22 on Day 1 to 2.65 on Day 7 (20%), and 2.92 on Day 30 (31%).
7. An improvement in the parameter of flaccidity has been reported by physicians increasing from a mean grade of 2.86 on Day 1 to 3.12 on Day 7 (9%), and 3.29 on Day 30 (15%).
8. On Day 30 of the study, 92% of the patients agreed that the administration of the product improves the appearance of their face. 8% of the patients neither agreed nor disagreed and 3% strongly disagreed.
9. On Day 30 of the study, 90% of the patients were satisfied with the product (very satisfied in 54% of cases and satisfied in 36% of cases). 5% of the patients have opted for the "indifferent" option, and 5% for "unsatisfactory" one.

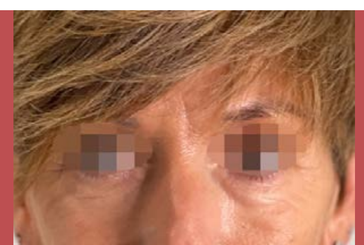
CONCLUSIONS:
1. The intradermal injection of RRS® HA LONG LASTING containing a monophasic gel of high molecular weight cross-linked HA associated with a protective buffer of amino acids is an efficient treatment of skin photoaging and its consequence which provide a skin hydration associate to the loss of volume in the mid-facial area.
2. RRS® HA LONG LASTING containing cross-linked HA improves parameters of the skin such as turgor, elasticity, general skin condition. The aesthetic improvement of the skin is immediate and substantial after one single treatment.
3. Patient selection according to the Glogau grade is the key to successful treatment. The best result was achieved with the patients with I-II Glogau grade.
4. The study reveals a high degree of satisfaction on behalf of the medical practitioners and their patients.

Bibliography: 1. De Boulle K, Glogau R, Kono T, Nathan M, Tezel A, Roca-Martinez JX, Paliwal S. A review of the metabolism of 1,4-butanediol diglycidyl ether-crosslinked hyaluronic acid dermal fillers. Dermatol Surg. 2013 Dec;39(12):1758-66. 2. Chiang YZ, Pierone G, Al-Niaimi F. Dermal fillers: pathophysiology, prevention, and treatment of complications. J Eur Acad Dermatol Venereol. 2017 Mar;31(3):405-413. 3. Fallacara A, Baldini E, Manfredini S, Vertuani S. Hyaluronic Acid in the Third Millennium. Polymers (Basel). 2018 jun 25;10(7):701.4. Urdiales-Gálvez F, Delgado NE, Figueiredo V, Lajo-Plaza JV, Mira M, Moreno A, OrtízMartí F, Del Rio-Reyes R, Romero-Álvarez N, Del Cueto SR, Segurado MA. Treatment of Soft Tissue Filler Complications: Expert Consensus Recommendations. Aesthetic Plast Surg. 2018 Apr;42(2):498-510. 5. Becker LC, Bergfeld WF, Belsito DV, Klaassen CD, Marks JG Jr, Shank RC, Slaga TJ; Cosmetic Ingredient Review Expert Panel, Andersen FA. Final report of the safety assessment of hyaluronic acid, potassium hyaluronate, and sodium hyaluronate. Int J Toxicol. 2009 jul-Aug;28(4 Suppl):5-67.



Clinical Case 1. 38 years old patient
Clínica Hera, Empuriabrava, Spain.
Dra. Evgeniya Ranneva

Clinical Case 2. 36 years old patient
Centro Integrativo de Salud, Barcelona, Spain.
Dra Inma González



Clinical Case 3. 49 years old patient
Centro Integrativo de Salud, Barcelona, Spain.
Dra Inma González