

BIOXIS

PHARMACEUTICALS

CYTOSIAL

TRAINING PRESENTATION

TEL AVIV, FEBRUARY 12 2019





AGENDA

- 1 About Hyaluronic Acid
- 2 The Cytosial Range:
The Velvet Technology
- 3 Product characteristics
- 4 Area injections
- 5 Before and after images

1 ABOUT HYALURONIC ACID

Also called Hyaluronan, Hyaluronic Acid is an anionic, nonsulfated glycosaminoglycan like chondroitin sulfate or heparane sulfate, like CS but non-sulfated.

Its molecular weight depends on the length of the molecular chain.

One of the chief components of the extracellular matrix, Hyaluronic Acid can be degraded by a family of enzymes called Hyaluronidases.



1 FOR AESTHETIC USE, WE HAVE TO CROSSLINK HA

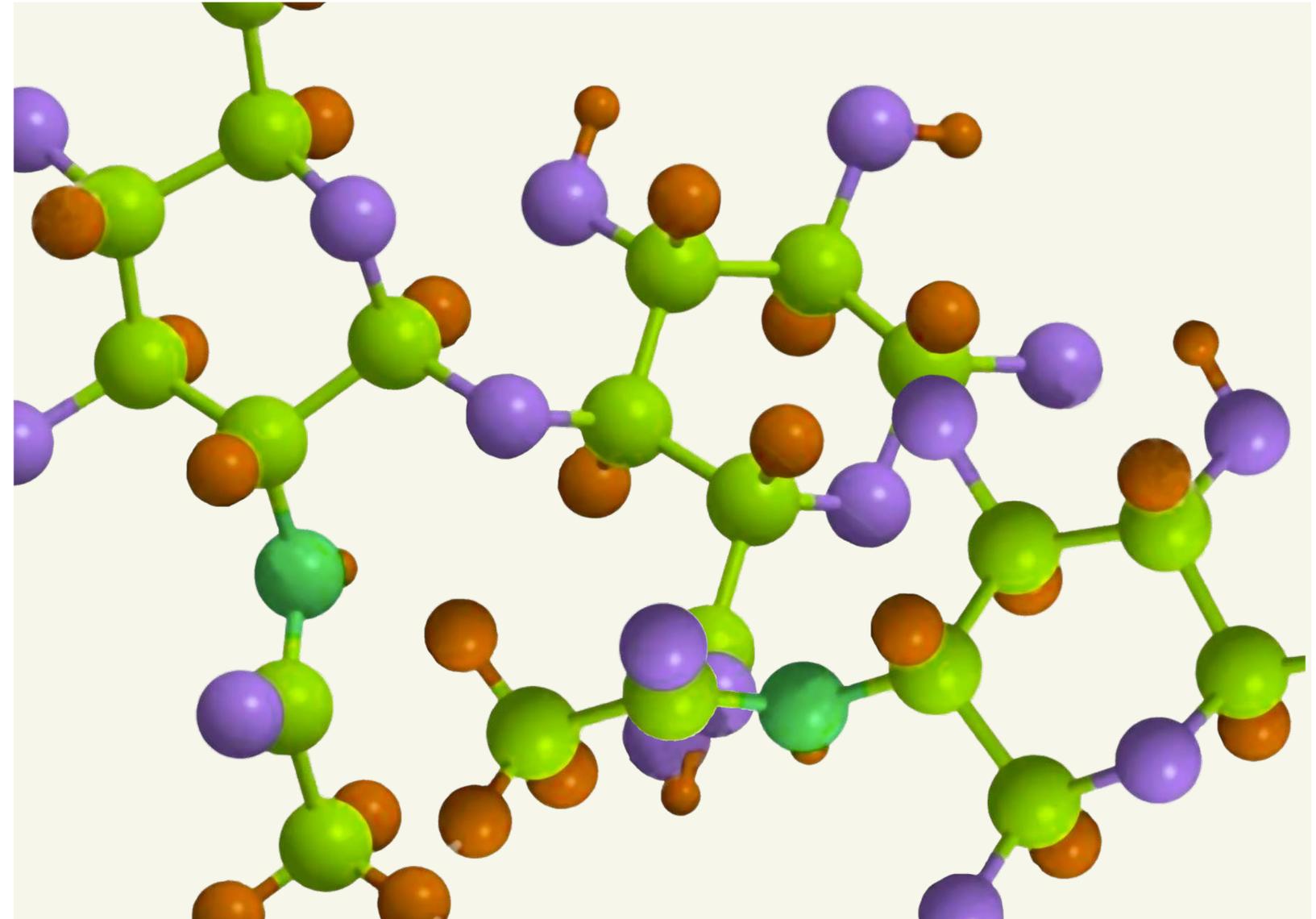
Shelf life of linear (natural) HA in the body is from a few hours to a few days... not enough to ensure a long-lasting effect

Best solution? To cross link linear HA chains

A crosslink is a bond that links one HA polymer chain to another, to create a strong network.

Benefits of cross-linking

- To obtain an HA gel, wider network
- To increase the product shelf life: crosslinking slows down hyaluronidase activity



APPEARANCE OF HA BEFORE AND AFTER CROSSLINKING PROCESS



BEFORE



AFTER

1 HOW DO WE CROSS-LINK OUR HA?



Cross linking process is in common use by all HA manufactory: it is a chemical technique which uses a product called BDDE.

BDDE: *1,4-Butanediol Diglycidyl Ether*

BDDE enables cross-linking of HA chains to increase their mechanical properties: we obtain a gel, viscous and cohesive, with high mechanical properties.

Cross-linking reduces enzymatic and mechanical degradation of HA, in order to obtain long-lasting effects for patients:

- 9 months for Deep Wrinkles formula
- 12 months for Cytosial Volume

1 IS BDDE SAFE?

When BDDE is used to crosslink HA, it must be totally eliminated from the final product. This is what we do at Bioxis Pharma, with our high quality standards.

- Animal studies suggest that BDDE could be cancerogenic, it is not proved for humans.
- When HA is crosslinked, we eliminate BDDE by rinsing with water and filtration by dialysis.
- The Cytosial range of products have a very low rate of BDDE residual, which is measured between the limit of quantification and limit of detection.
- The Cytosial range meets the most stringent criteria.

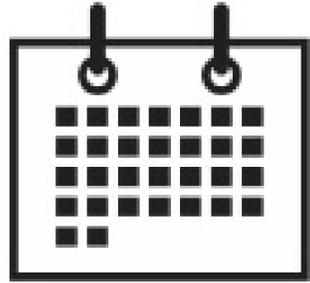


2 THE CYTOSIAL RANGE



A range of new generation, monophasic hyaluronic acid dermal fillers, safe and efficient, that regenerate the skin to wipe away the signs of ageing to produce natural-looking results.

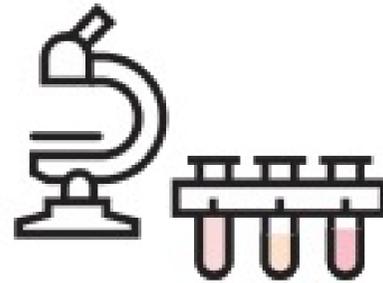
2 CYTOSIAL: THE VELVET TECHNOLOGY IN A FEW KEY FIGURES



5

YEARS OF DEVELOPMENT

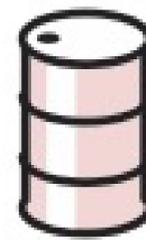
before acquiring CE mark (BSI)



85

FORMULATIONS TESTED

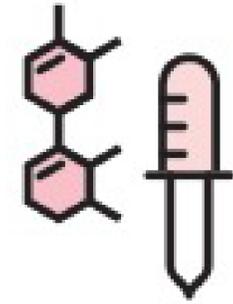
on 60 batches



55

KG OF GEL

to find the best formulation, equivalent to more than 50,000 1.1ml syringes



3

MAIN TECHNOLOGIES

completely designed and evaluated – the best selected for the Cytosial range and named ‘The Velvet Technology’

AH04 – THE VELVET TECHNOLOGY (patented)

- + Monophasic
- + Homogenous network
- + Good cohesivity

2 THE VELVET TECHNOLOGY: A PATENTED PROCESS

HOMOGENOUS

- Optimized linearization process
- Thin layer crosslinking
- Product similar to extracellular matrix

RHEOLOGICAL PERFORMANCE

- Constant force injection
- Less BDDE for the same rheological properties

NATURAL RESULTS

- Low shear rate destructureation
- Slow degradation by hyaluronidase

SAFETY AND TOLERANCE

- Continuous dialysis process to eliminate all residues
- Better conserve HA chains

Easy to inject product

Less pain



Laboratory and manufacturing based in Lyon, France



The highest European standards: ISO 13485 Certification and CE mark from BSI

THE HIGHEST EUROPEAN STANDARDS:
ISO 13485 CERTIFICATION AND CE MARK
BY BSI

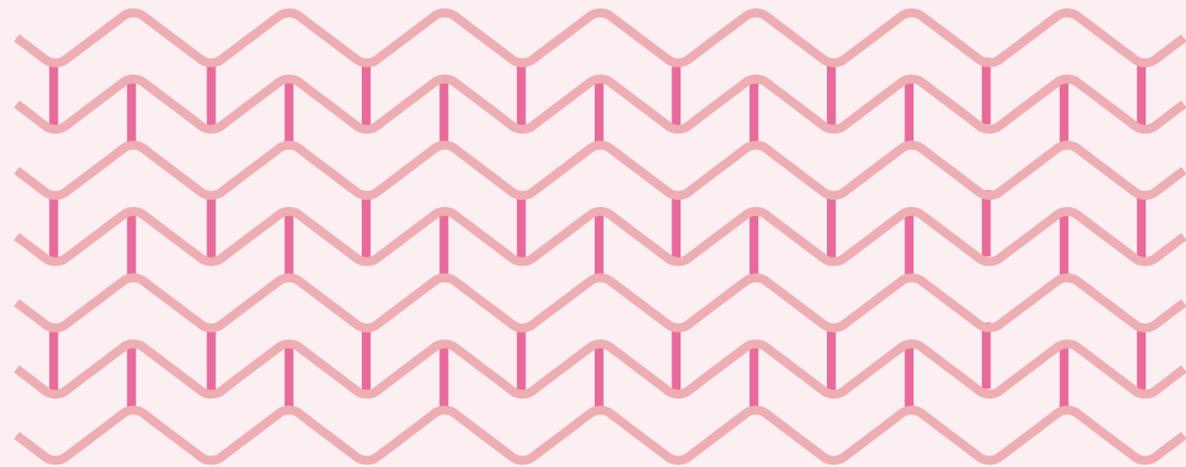


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CYTOSIAL: THE VELVET TECHNOLOGY RAW MATERIAL SELECTION

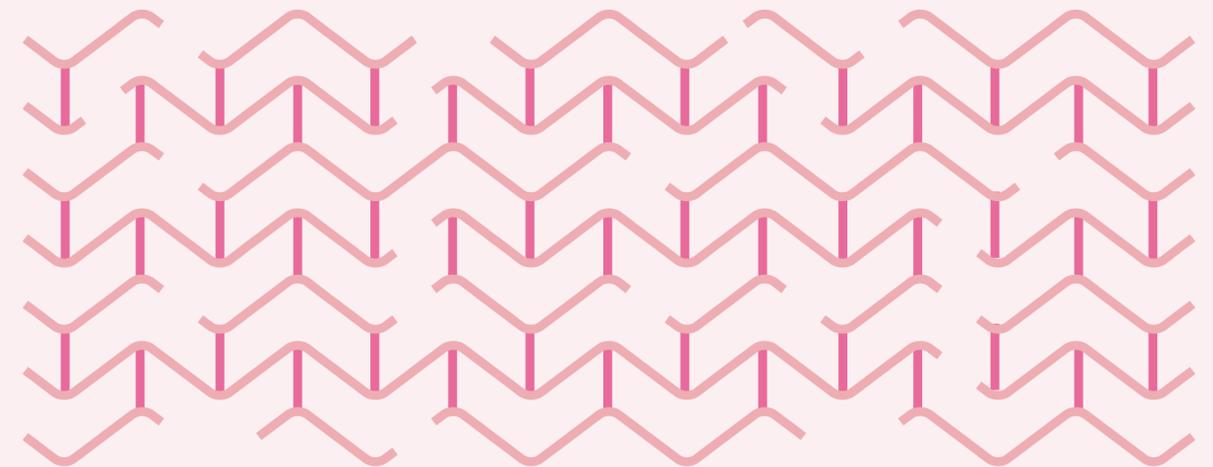
Hyaluronic acid is produced in France with special specifications:

- High molecular weight of HA to improve naturally the gel cohesivity and viscosity
- Low Polydispersity (low difference in HA molecular weight) to involve the regularity of network
- One of the best provider in the world (HTL)



Formulation based on High M_w and Low Polydispersity

VELVET TECHNOLOGY



Formulation based on Low M_w and High Polydispersity

2 CYTOSIAL: THE VELVET TECHNOLOGY

An innovative vision of HA crosslinking:

MIXING AND DISSOLUTION

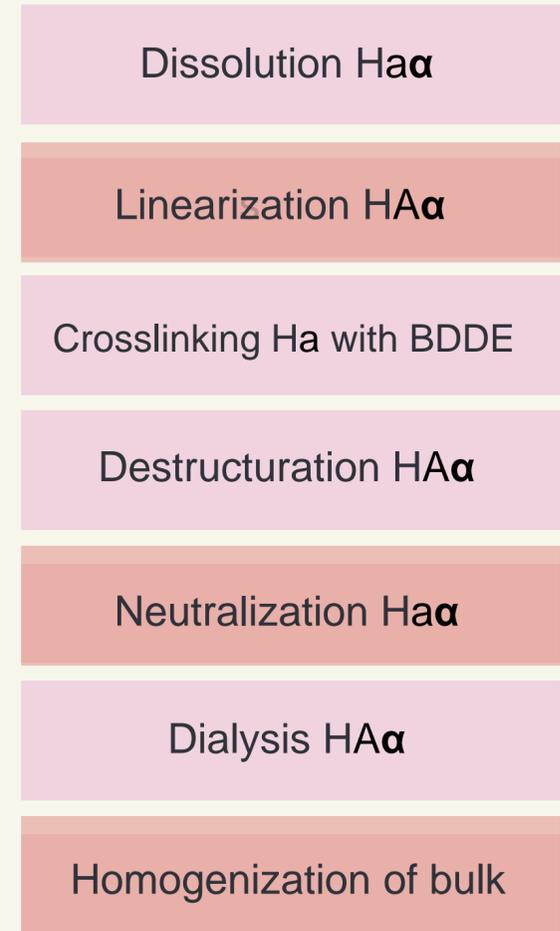
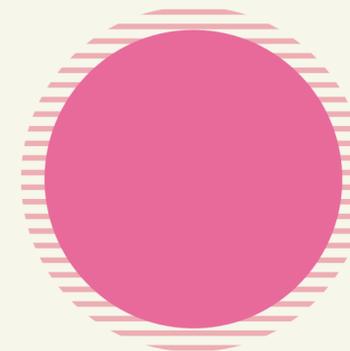
Linearization for better performance

LOW SHEAR RATE DESTRUCTURATION

Improve natural effect

CONTINUOUS DIALYSIS

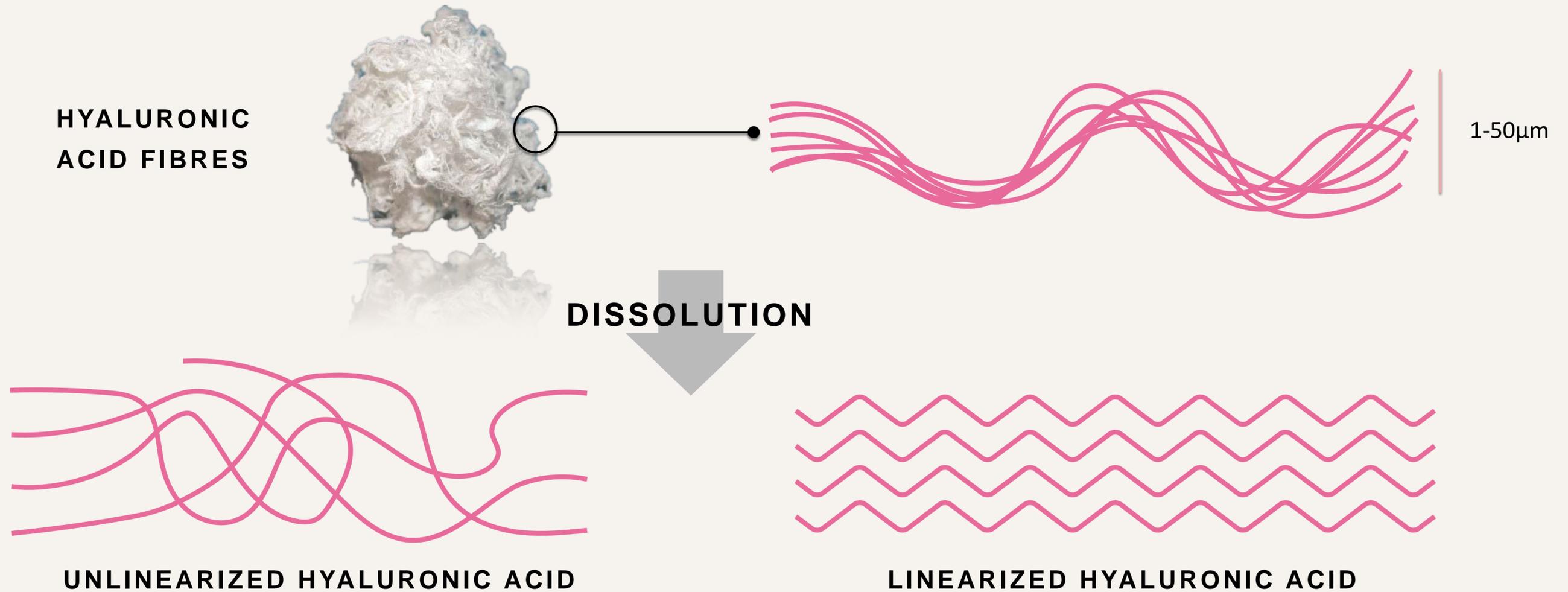
Enhance safety and tolerance



HA manufacturing flowchart

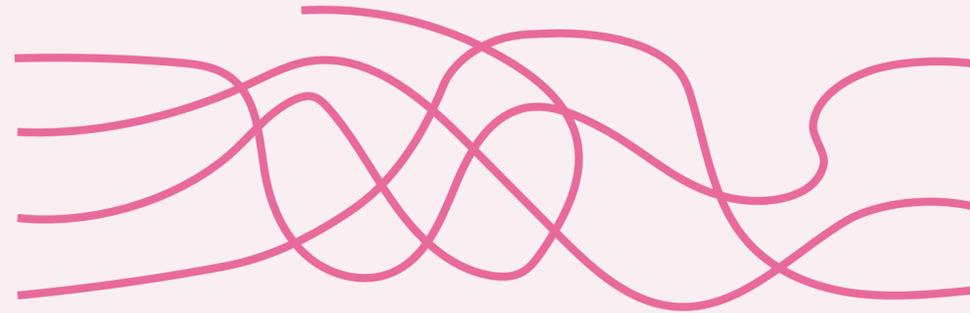
2 CYTOSIAL: THE VELVET TECHNOLOGY

Linearization for better performance



2 CYTOSIAL: THE VELVET TECHNOLOGY

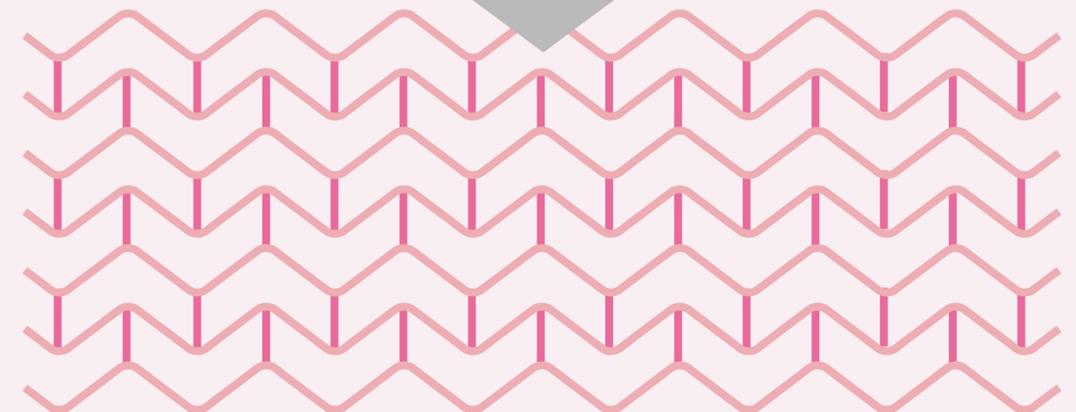
Linearization for better performance



UNLINEARIZED HYALURONIC ACID



LINEARIZED HYALURONIC ACID



HOMOGENOUS GEL

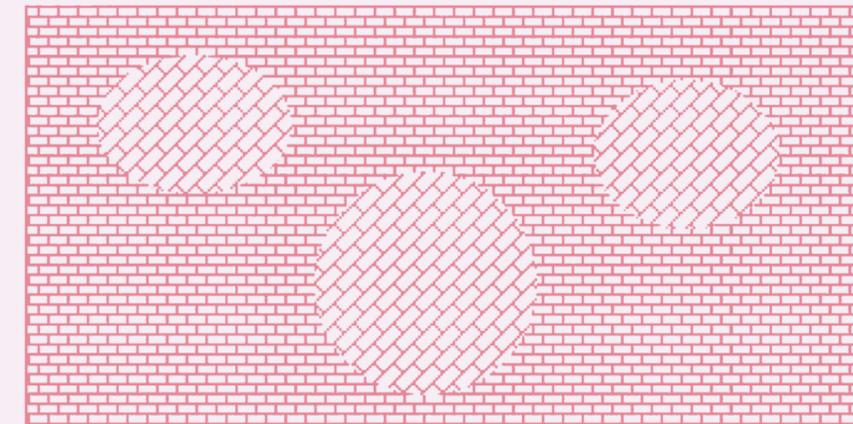
2 CYTOSIAL: THE VELVET TECHNOLOGY

Low Share Rate Homogenization

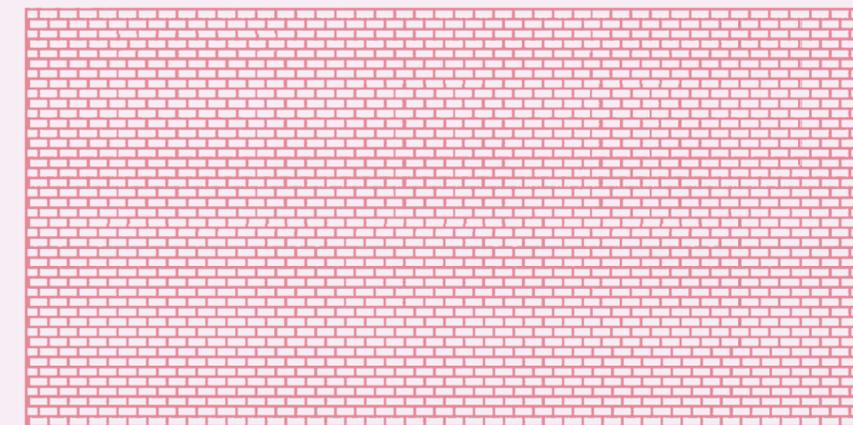
Even with linearization, control of thermal repartition during crosslinking step and the choice of monodisperse HA, some areas of network could exhibit a residual heterogeneity or network bad orientation. In order to ensure perfect homogeneity, Bioxis developed a new technique of homogenization.

Thanks to an innovative **patented** mixing technique:

- Optimizes homogenization
- Limits the destruction of HA/BDDE network
- Favors the purification (Neutralization and extraction of residual BDDE) and the biocompatibility of gel (pH, Osmolarity)



LOW SHARE RATE HOMOGENIZATION



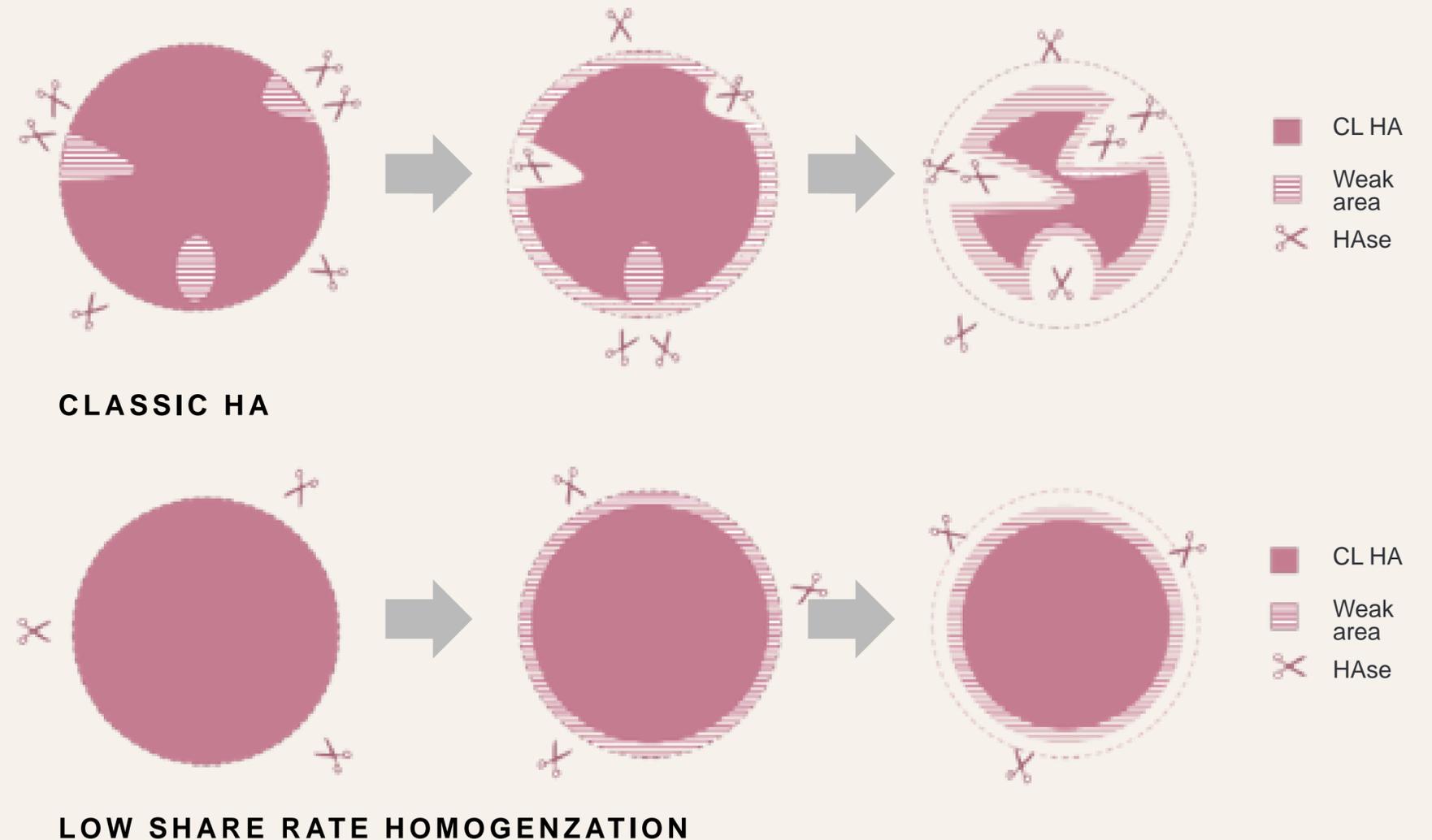
2 CYTOSIAL: THE VELVET TECHNOLOGY

Homogenous matrix

Velvet Technology is focused on the quality of HA network

HOMOGENIZATION MATRIX

- Eases the neutralization and purification
- Smoothness gel
- A very good degradation resistance
- A produce that is easier to inject



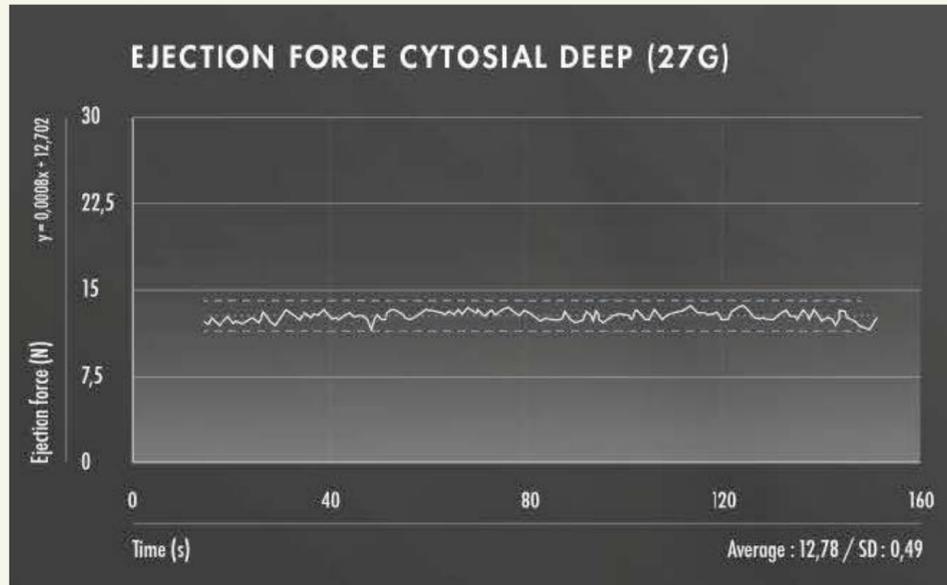
2 CYTOSIAL: HOMOGENOUS FORMULA FOR OPTIMAL COMFORT DURING INJECTION

With Cytosial range, Bioxis Pharma proposes a very stable injection force product like the higher quality standard.

Rheological characteristics of Cytosial: An easy-to-use inject product for the practitioner, an excellent result for the patient, without pain.

CYTOSIAL DEEP WRINKLES

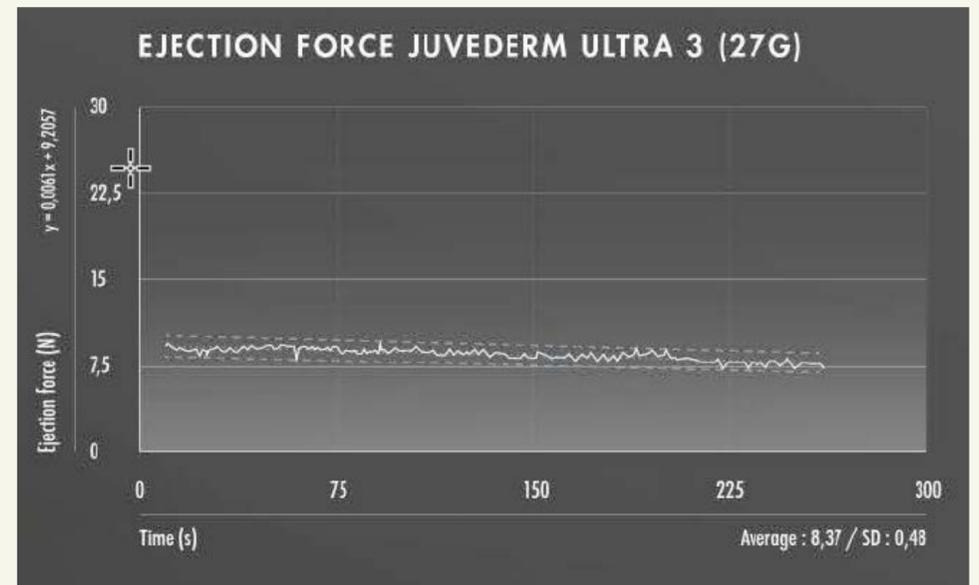
The Cytosial range is characterized by a very subtle injection force without significant variation. This means the gel is homogenous and does not contain any over or under crosslinked areas, particles or bubbles. Given the high rheological properties of the Cytosial range, the ejection force is low.



ELASTICITY (Tan delta): 0.18
 VISCOSITY (Pa.s): 2900

JUVEDERM ULTRA 3

The Juvederm range provides a subtle ejection force, mainly thanks to the syringe design. However, anomalies can be detected and amplified by the large amplitude of the syringe. Moreover, high amplitude syringes can cause discomfort to practitioners with smaller hands.

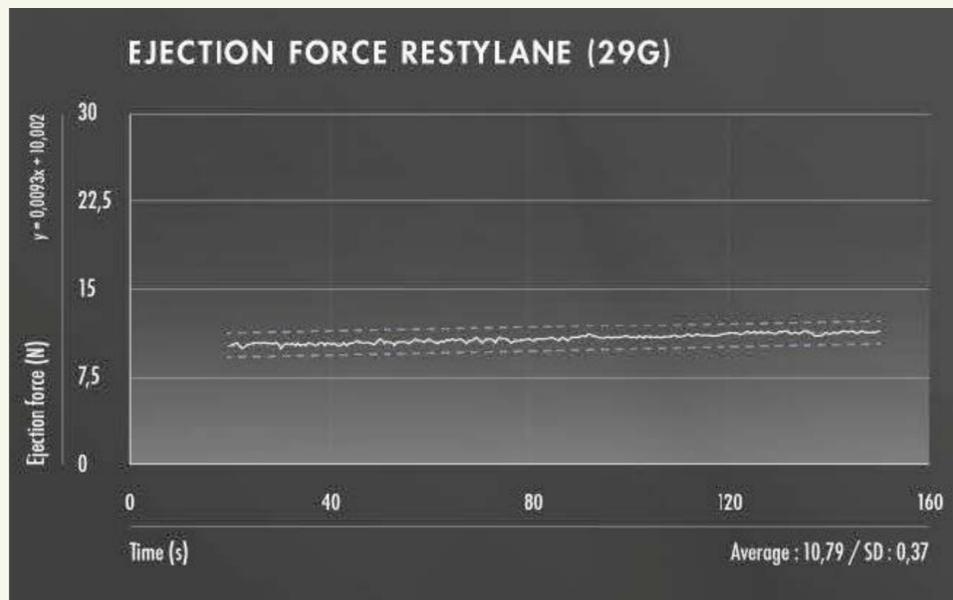


ELASTICITY (Tan delta): 0.21
 VISCOSITY (Pa.s): 2465

2 CYTOSIAL: HOMOGENOUS FORMULA FOR OPTIMAL COMFORT DURING INJECTION

RESTYLANE

Restylane is a biphasic product and therefore always displays low viscosity and low elasticity. Particle migration with the skin can be associated with the rheofluidifying behaviour observed in viscosity.

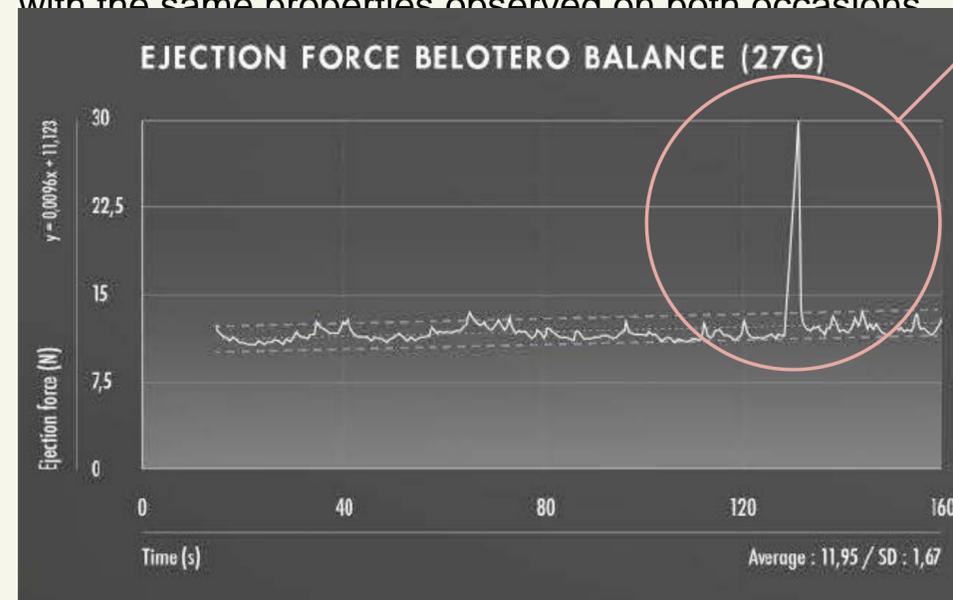


ELASTICITY (Tan delta): 0.32
 VISCOSITY (Pa.s): 1646

Restylane is a registered trademark of Galderma Company

BELOTERO BALANCE

With regards to the ejection force, the rheological properties are very low. The heterogeneity of the gel artificially increases the ejection force. 228 Pa.s is representative of a solution with a low quantity of crosslinking areas. This observation also applies to the elasticity. Due to the unexpected results, the test was carried out on two different batches of Belotero Balance with the same properties observed on both occasions.



ELASTICITY (Tan delta): 0.73
 VISCOSITY (Pa.s): 228

Belotero Balance is a registered trademark of Merz Pharma Company

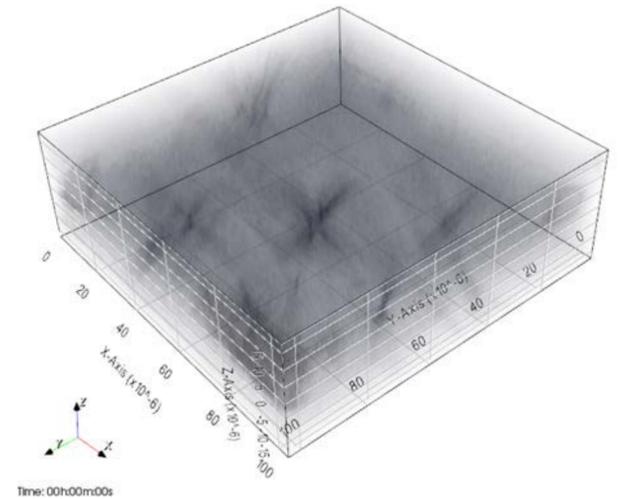
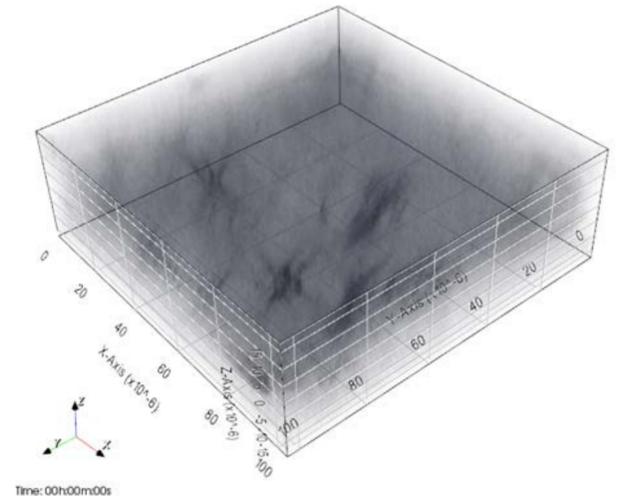
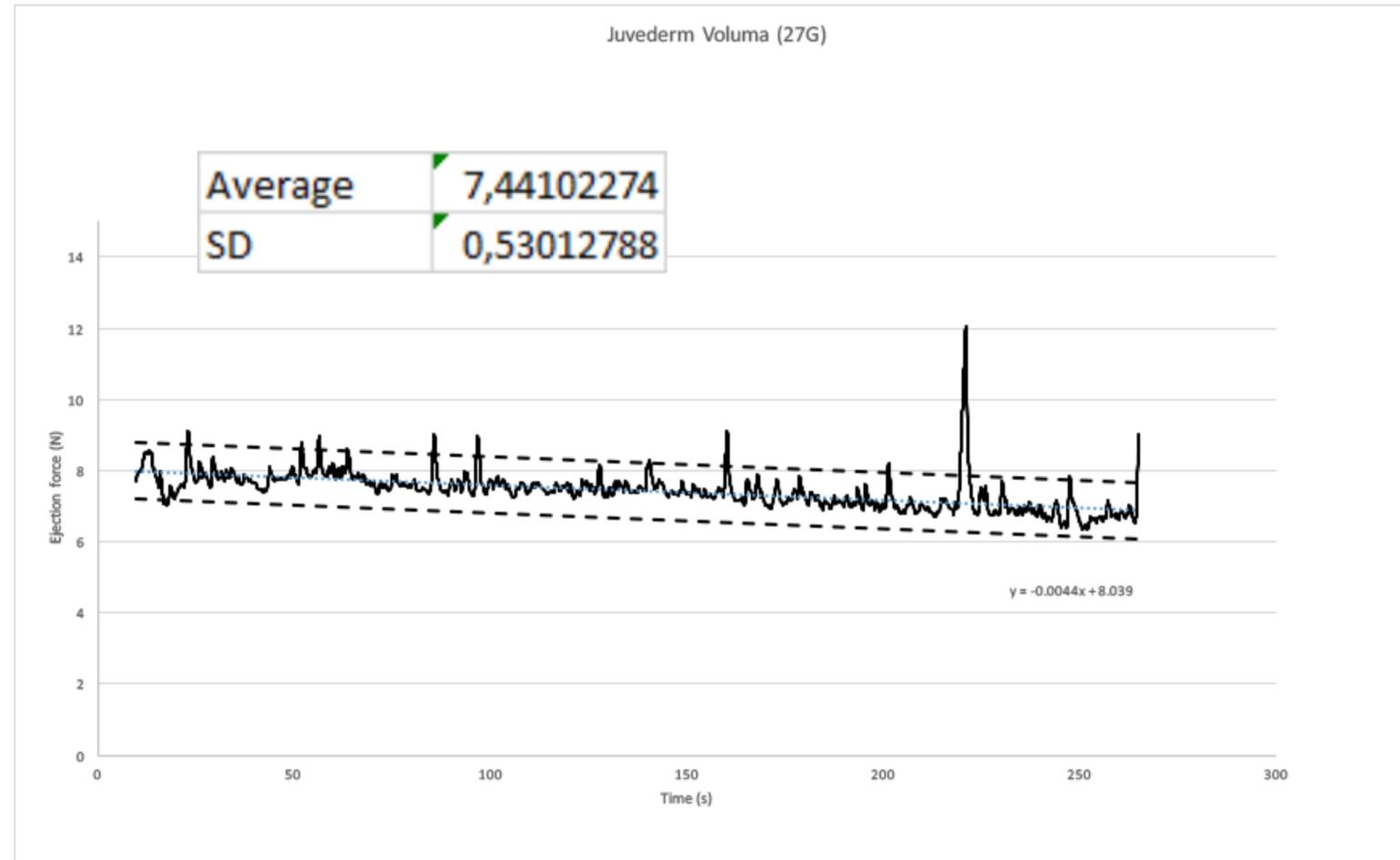
The defect indicates presence of big particles in HA gel (non homogenous)

- Practitioner has to increase pressure to inject product
- Pain for patient

2 CYTOSIAL: THE VELVET TECHNOLOGY

The difference between Velvet Technology and other competitive technologies are:

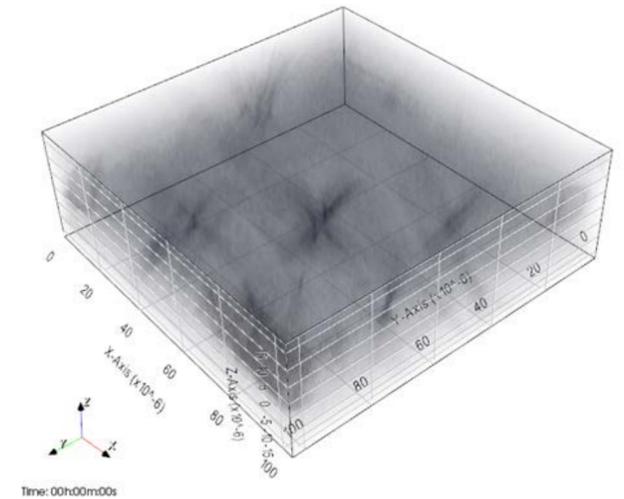
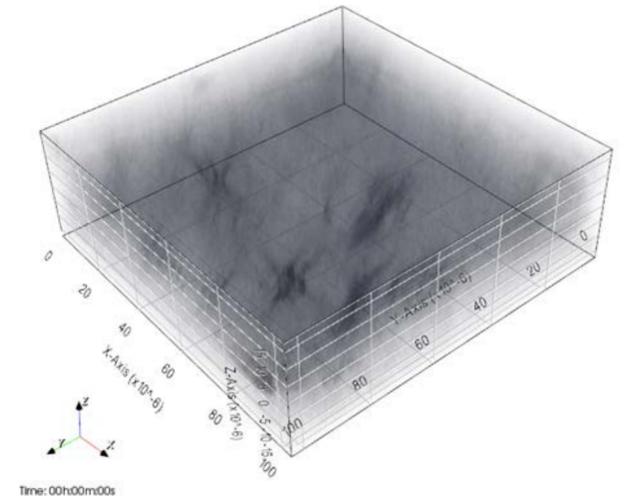
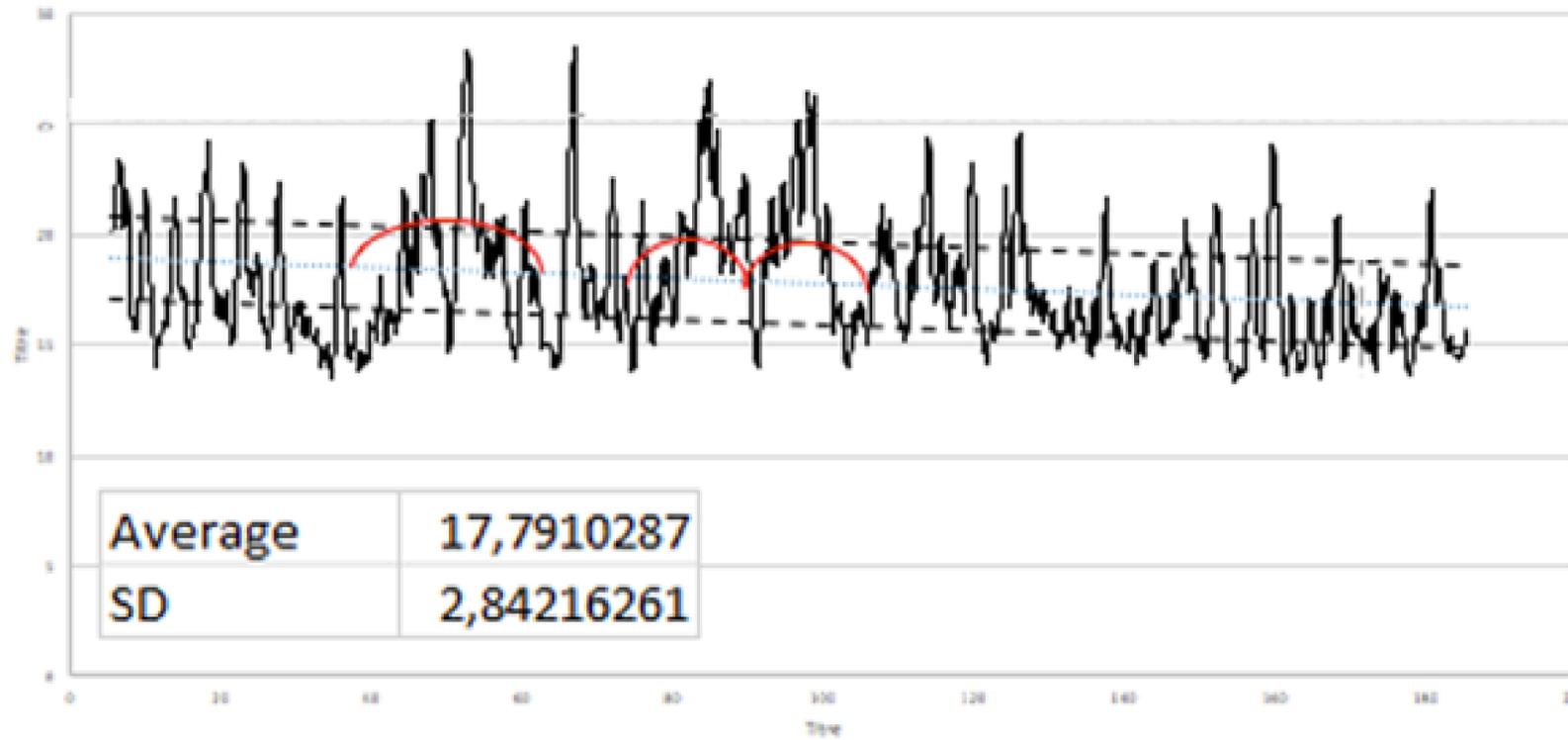
- High ejection force stability
- Higher homogeneity of matrix than competitive technologies



2 CYTOSIAL: THE VELVET TECHNOLOGY

The difference between Velvet Technology and other competitive technologies are:

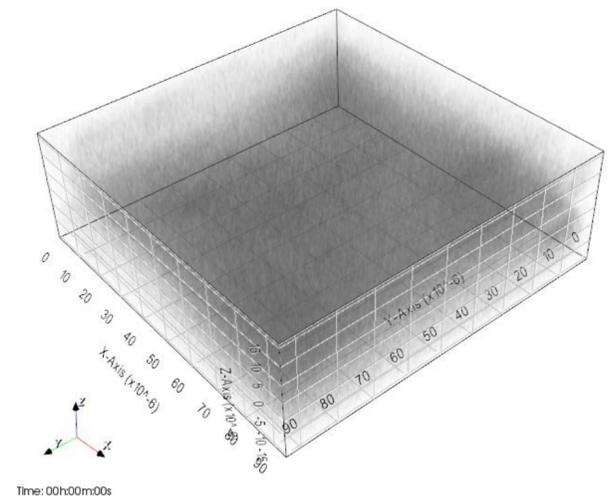
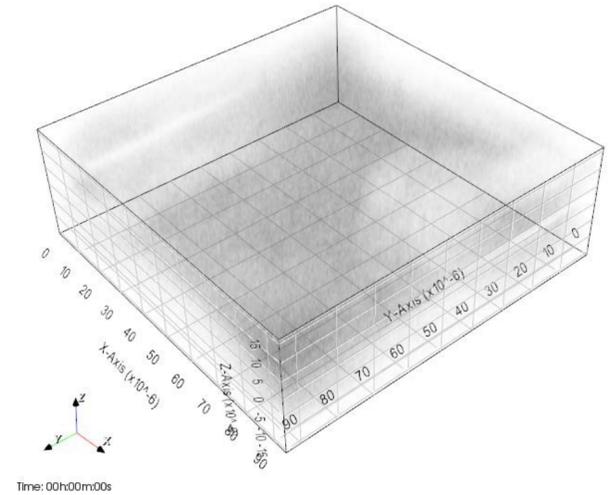
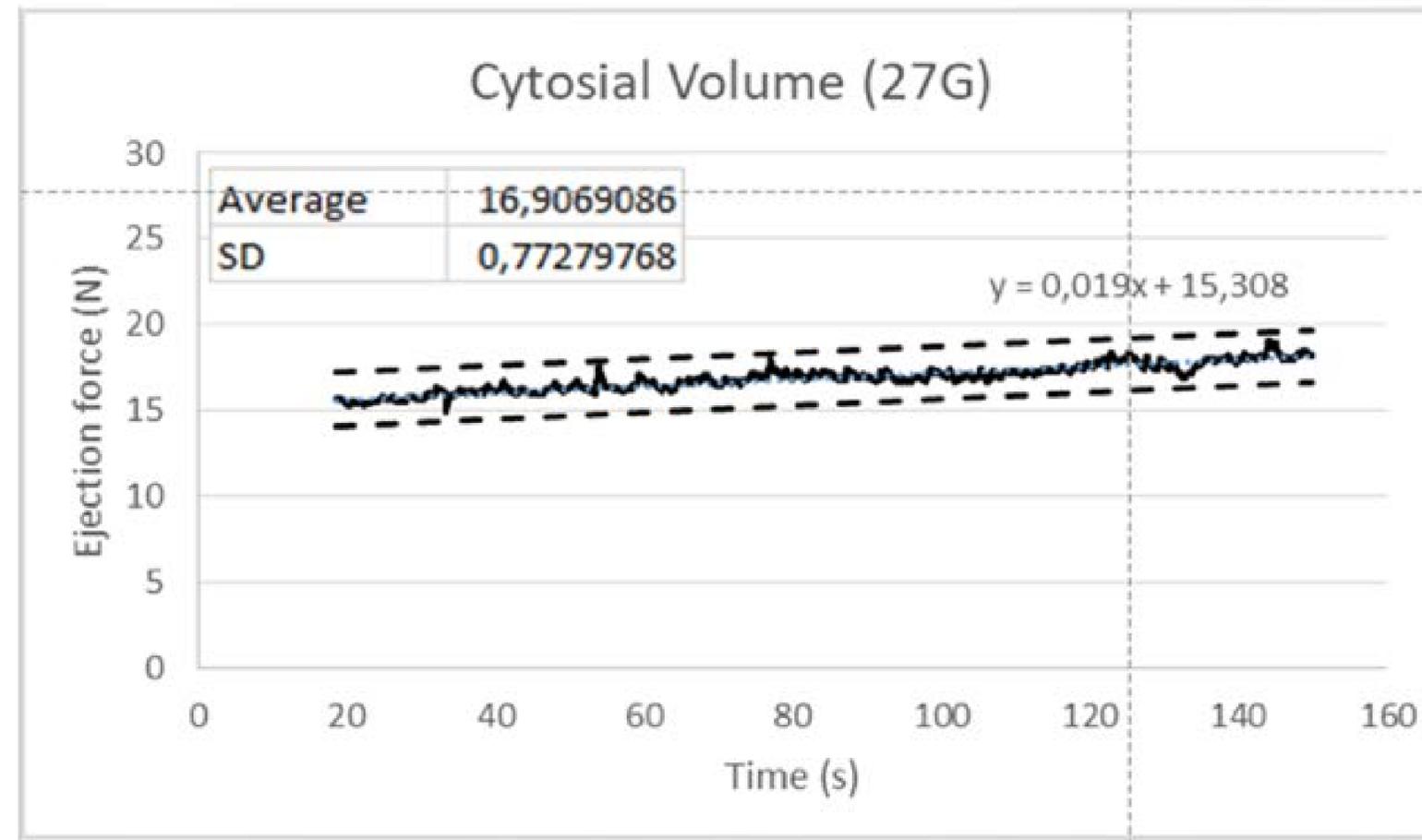
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2 CYTOSIAL: THE VELVET TECHNOLOGY

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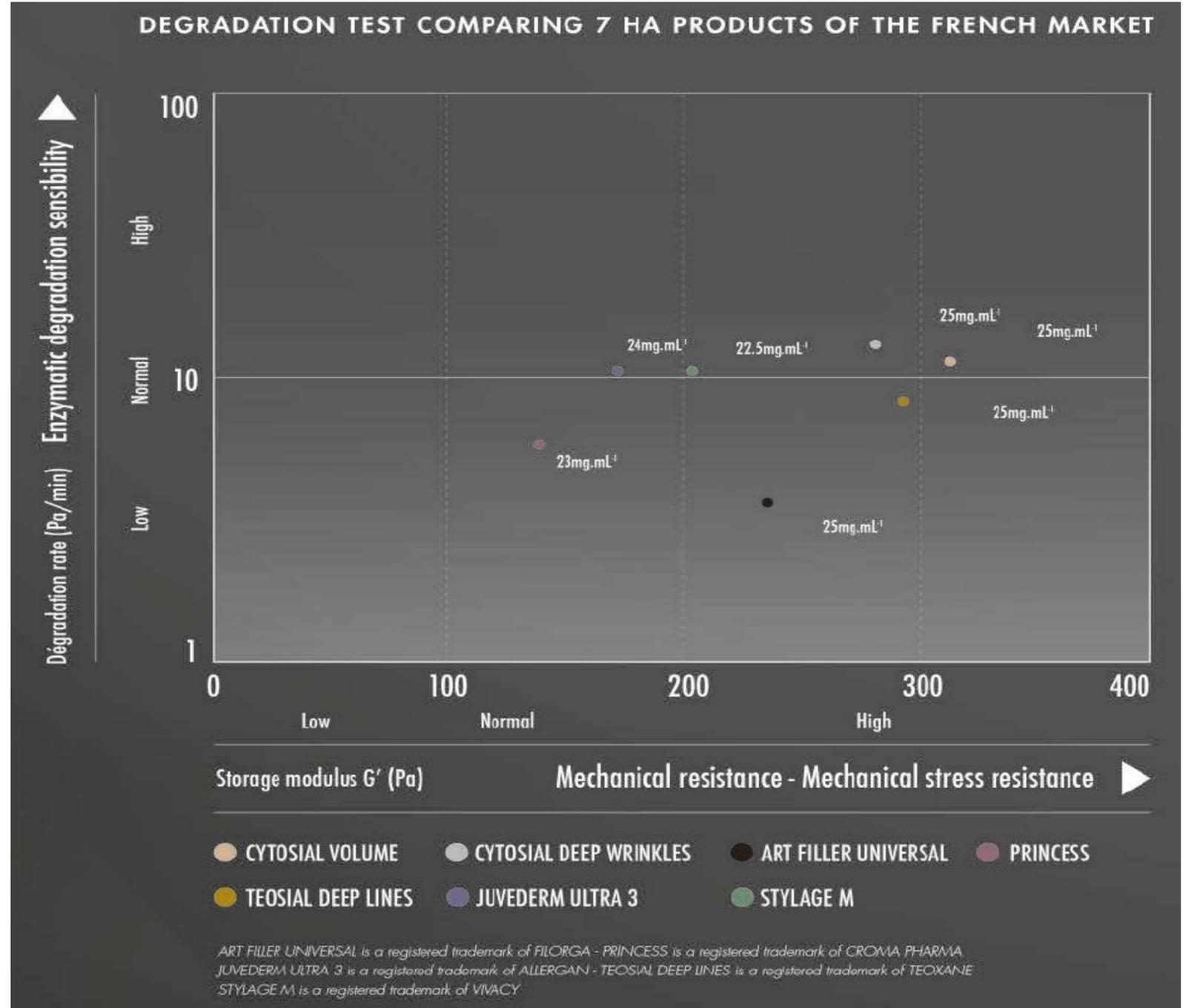
- High ejection force stability
- Higher homogeneity of matrix than competitive technologies



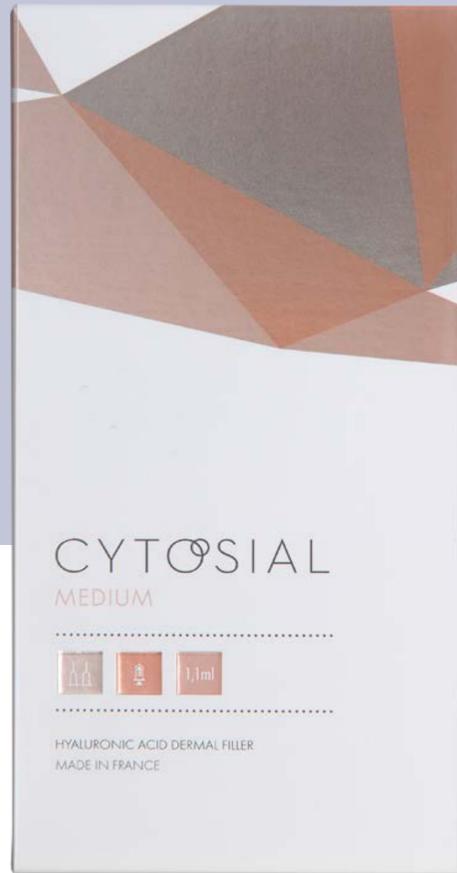
2 CYTOSIAL: HOMOGENOUS FORMULA FOR

LONG-LASTING EFFECTS

Cytosial is easy to inject with a high resistance to enzymatic and mechanical degradation.



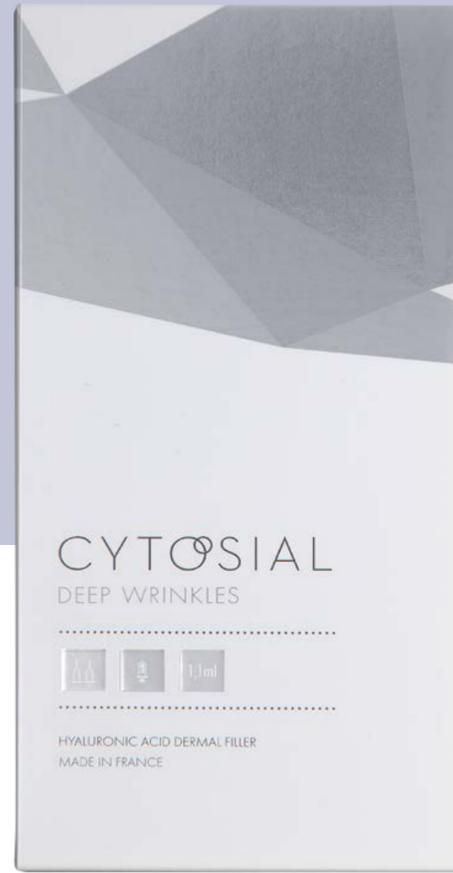
3 CYTOSIAL PRODUCT CHARACTERISTICS



HA concentration:
25mg/ml
Volume: 1.1ml
Needle size: 30G^{1/2}
Injection: Mid dermis

MEDIUM

is indicated for:
The filling of moderate cutaneous depressions as perioral or commissural area



HA concentration:
25mg/ml
Volume: 1.1ml
Needle size: 27G^{1/2}
Injection: Deep dermis

DEEP WRINKLES

Correct deep lines:
Deep nasolabial fold
Deep marionette fold



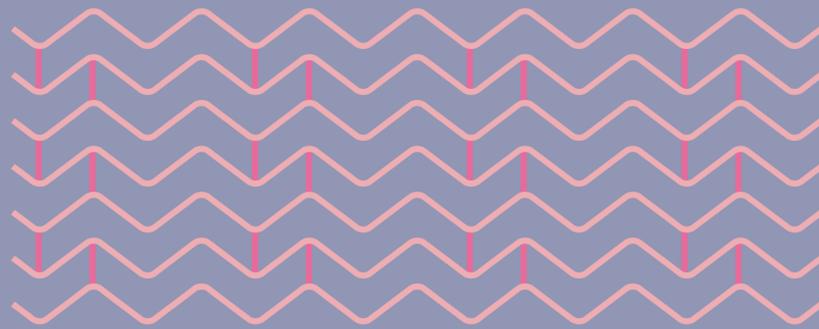
HA concentration:
25mg/ml
Volume: 1.1ml
Needle size: 27G^{1/2}
Injection: Deep dermis or subcutaneous

VOLUME

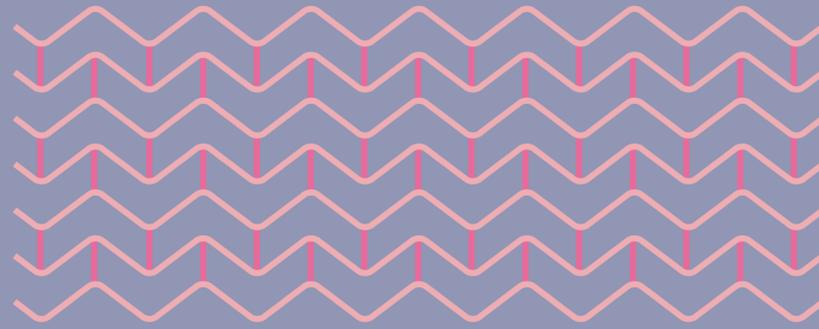
Restore facial volume:
Cheeks and cheekbones, chin, facial volume loss

3 CYTOSIAL: THE VELVET TECHNOLOGY HIGH CONCENTRATION OF HA

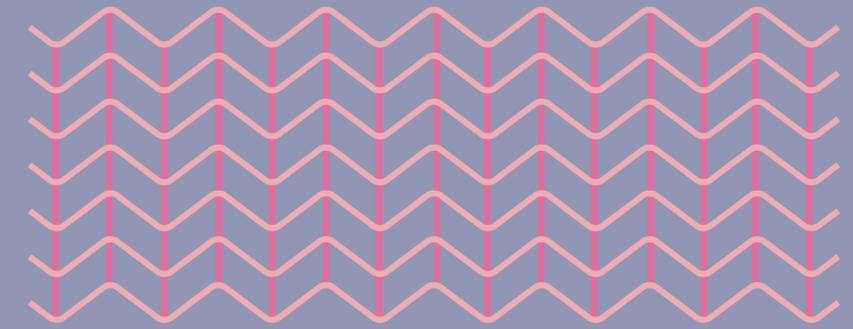
CYTOSIAL MEDIUM



CYTOSIAL DEEP WRINKLES



CYTOSIAL VOLUME



Crosslinking rate

Viscosity

Elasticity

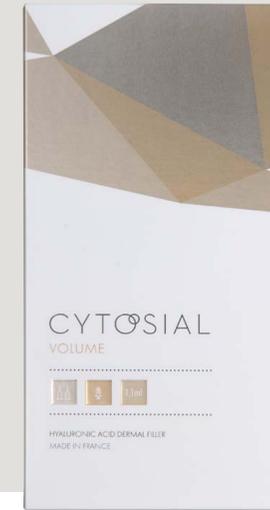
Homogeneity



The originality of Cytosial is related to the high HA concentration of the whole references. All the products contain the same high concentration of HA (25mg.mL¹).

Thanks to Velvet Technology and the great control of crosslinking network, Cytosial range is only based on variation of crosslinking density that modulates the mechanical properties while maintaining the homogeneity of formulation.

3 CYTOSIAL: RANGE TO FULFILL DOCTOR'S NEED



MEDIUM

To target peri-buccal area lines and lips

DEEP WRINKLES

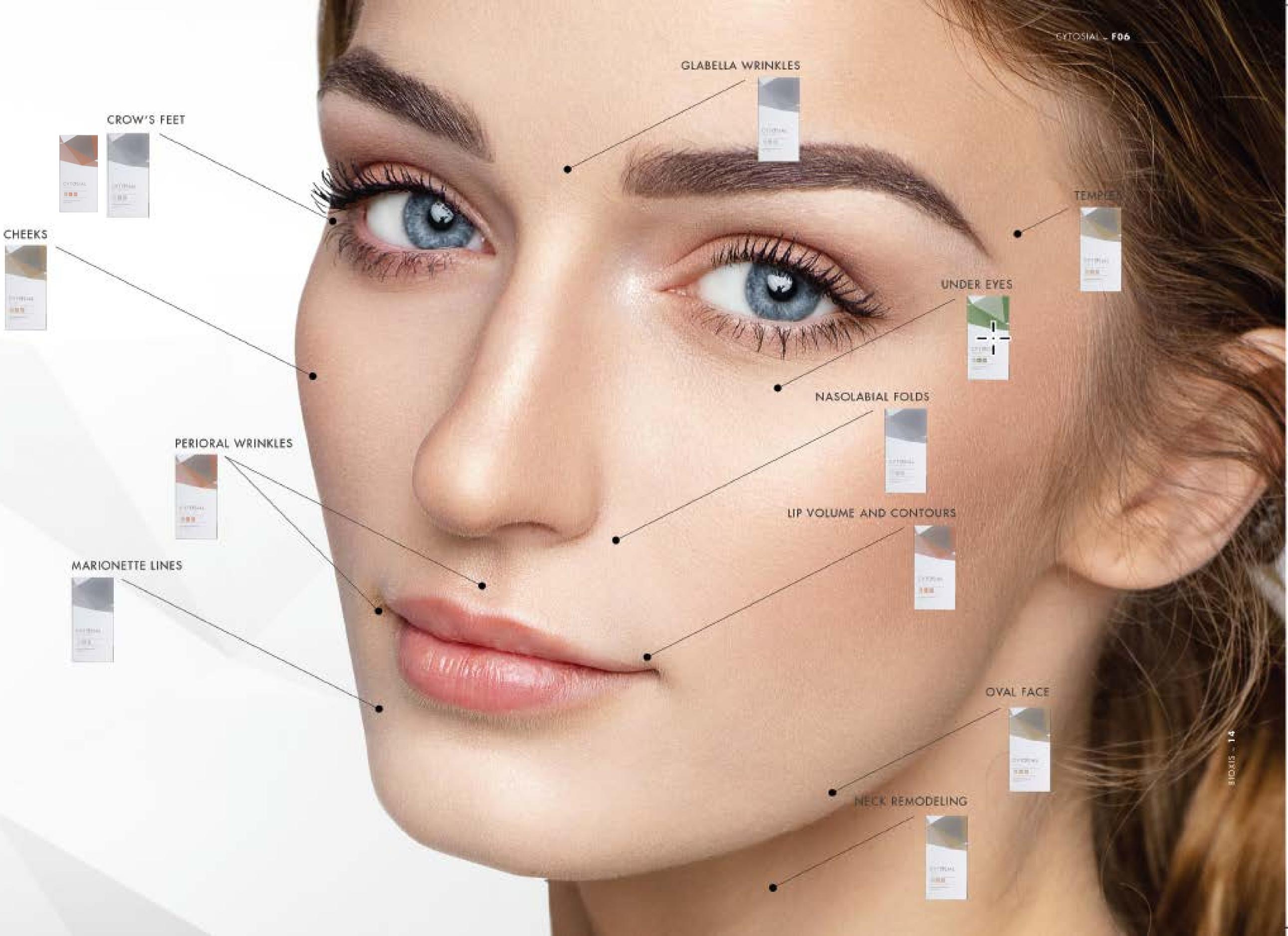
To feel wrinkles over the face

VOLUME

To create volume over the face

HA dosage	25 mg.mL ⁻¹	25 mg.mL ⁻¹	25 mg.mL ⁻¹
BDDE residual rate	≤2 ppm	≤2 ppm	≤2 ppm
BDDE rate	1.15%	1.50%	2.15%
pH	7-7.6	7-7.6	7-7.6
Osmolarity	280 – 360 mOsmol.L ⁻¹	280 – 360 mOsmol.L ⁻¹	280 – 360 mOsmol.L ⁻¹
Viscosity	900 – 2000Pa.s	2300 – 3400Pa.s	3500 – 6000 Pa.s
Elasticity (tanδ)	0.4 – 0.2	0.3 – 0.12	0.25 – 0.08
Ejection Force	10-25 N	10-25 N	10-25 N
Extractable weight	≥1.1 g or ml (d=1)	≥1.1 g or ml (d=1)	≥1.1 g or ml (d=1)

4. Tomorrow



310315 - 14

Before / After: a facial rejuvenation

BIOXIS



PRODUCT USED: CYTOSIAL DEEP WRINKLES (2 SYR.), CYTOSIAL VOLUME (2 SYR.), CYTOSIAL MEDIUM (2 SYR.). PRACTITIONER: H. GALADARI

Before / After: nasolabial injection

BIOXIS

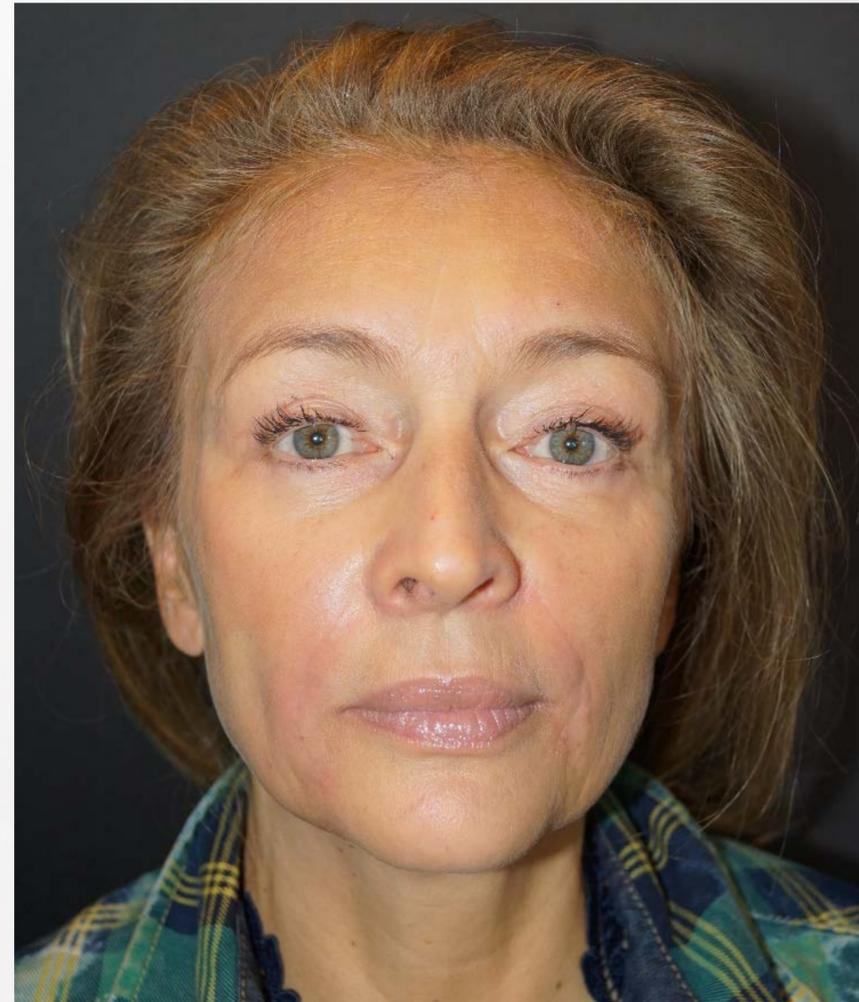
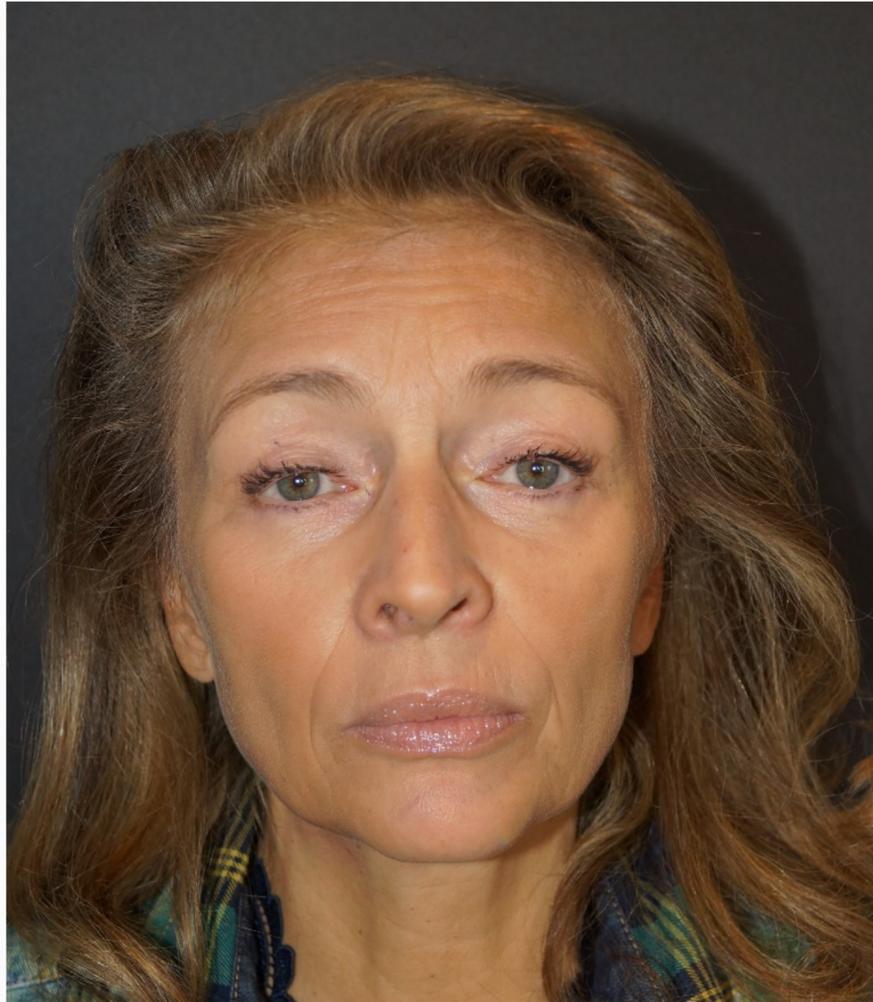


- **PRODUCT USED: CYTOSIAL DEEP WRINKLES**
- **QUANTITY OF PRODUCT: 0.5ML/FOLD**
- **1 SYRINGE FOR TREATMENT**
- **PRACTITIONER: J. LEVY, MD, NICE, FRANCE**



Before / After: nasolabial injection

BIOXIS



- **PRODUCT USED: CYTOSIAL DEEP WRINKLES**
- **QUANTITY OF PRODUCT: 0.5ML/FOLD**
- **1 SYRINGE FOR TREATMENT**
- **PRACTITIONER: J. LEVY, MD, NICE, FRANCE**



An exemple of long lasting effect

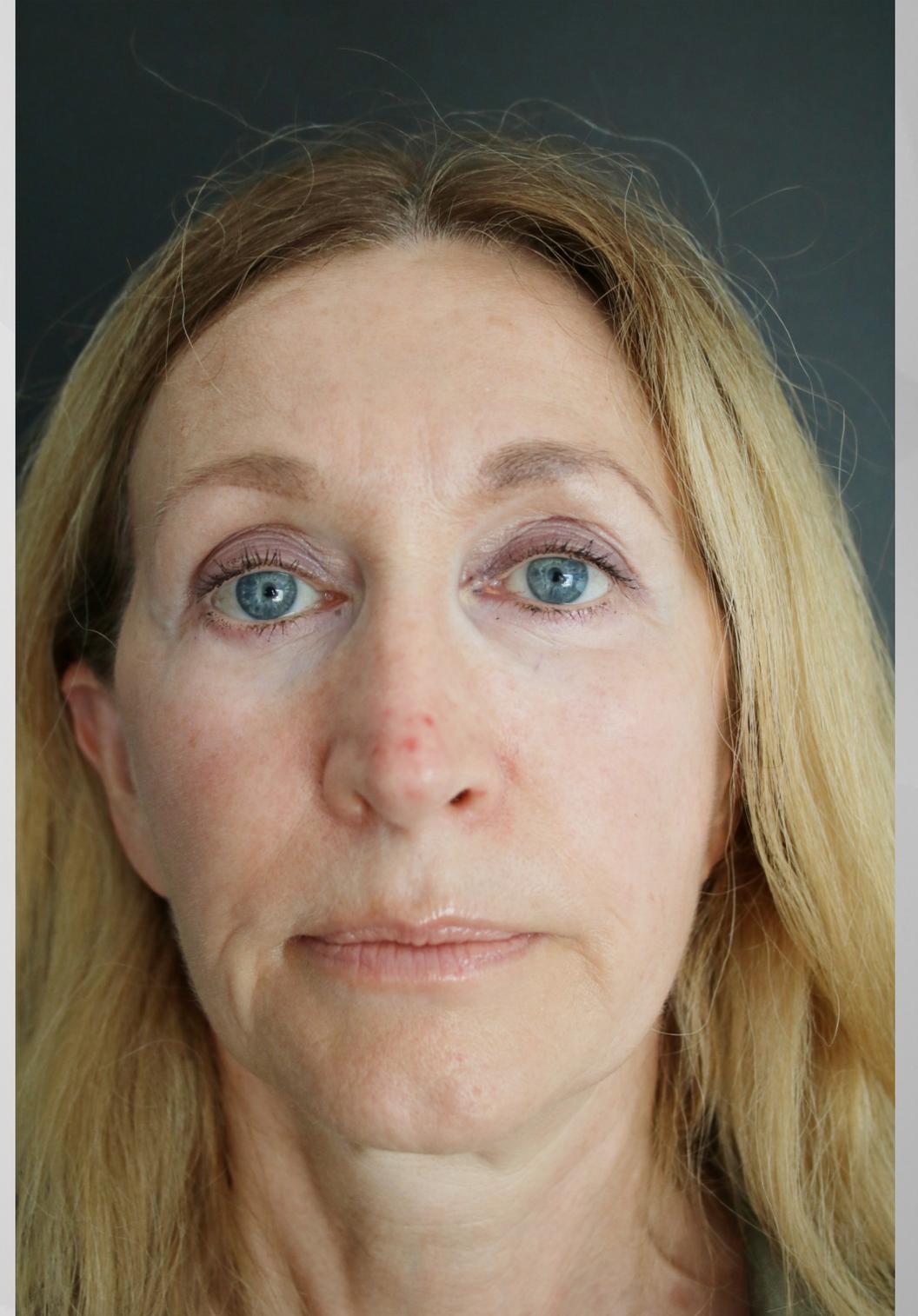
BIOXIS



FEV 17



MAI 17



SEPT 18

Confidential information – do not disseminate



Before / After: a facial rejuvenation



PRODUCT USED: CYTOSIAL VOLUME (1 SYR.), CYTOSIAL MEDIUM (1 SYR.). PRACTITIONER: W. REDKA (GERMANY)



Before / After: marionette line injection



- **PRODUCT USED: CYTOSIAL DEEP WRINKLES**
 - **QUANTITY OF PRODUCT: 0.4 ML**
 - **LESS THAN 1 SYRINGE FOR TREATMENT**
 - **PRACTITIONER: J. LEVY, MD, NICE, FRANCE**
-
- **IMMEDIATE EFFECT POST MARIONETTE LINE INJECTION: TEMPORARY LIGHT REDNESS ONLY.**

Before / After: cheek injection

BIOXIS

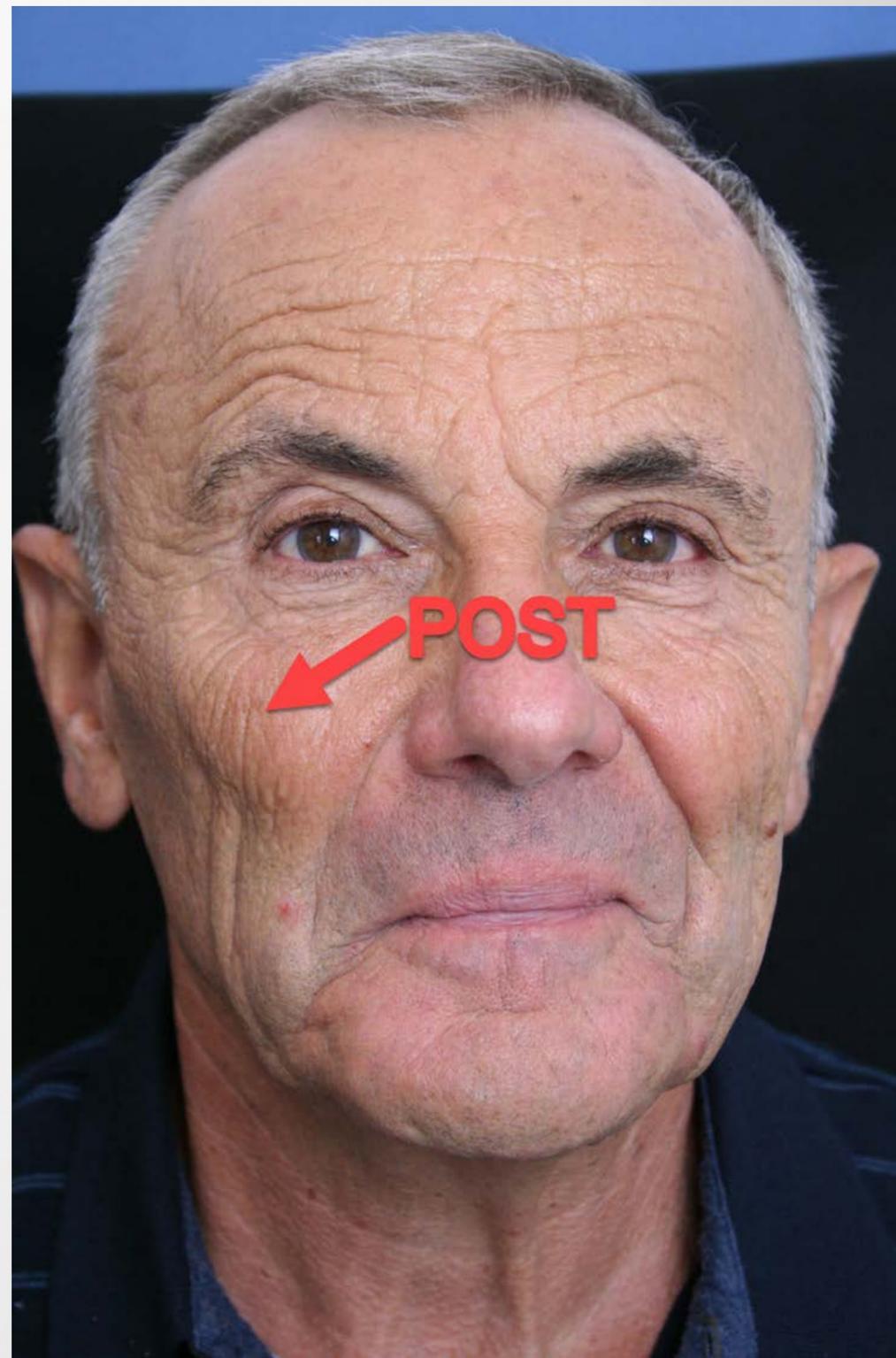
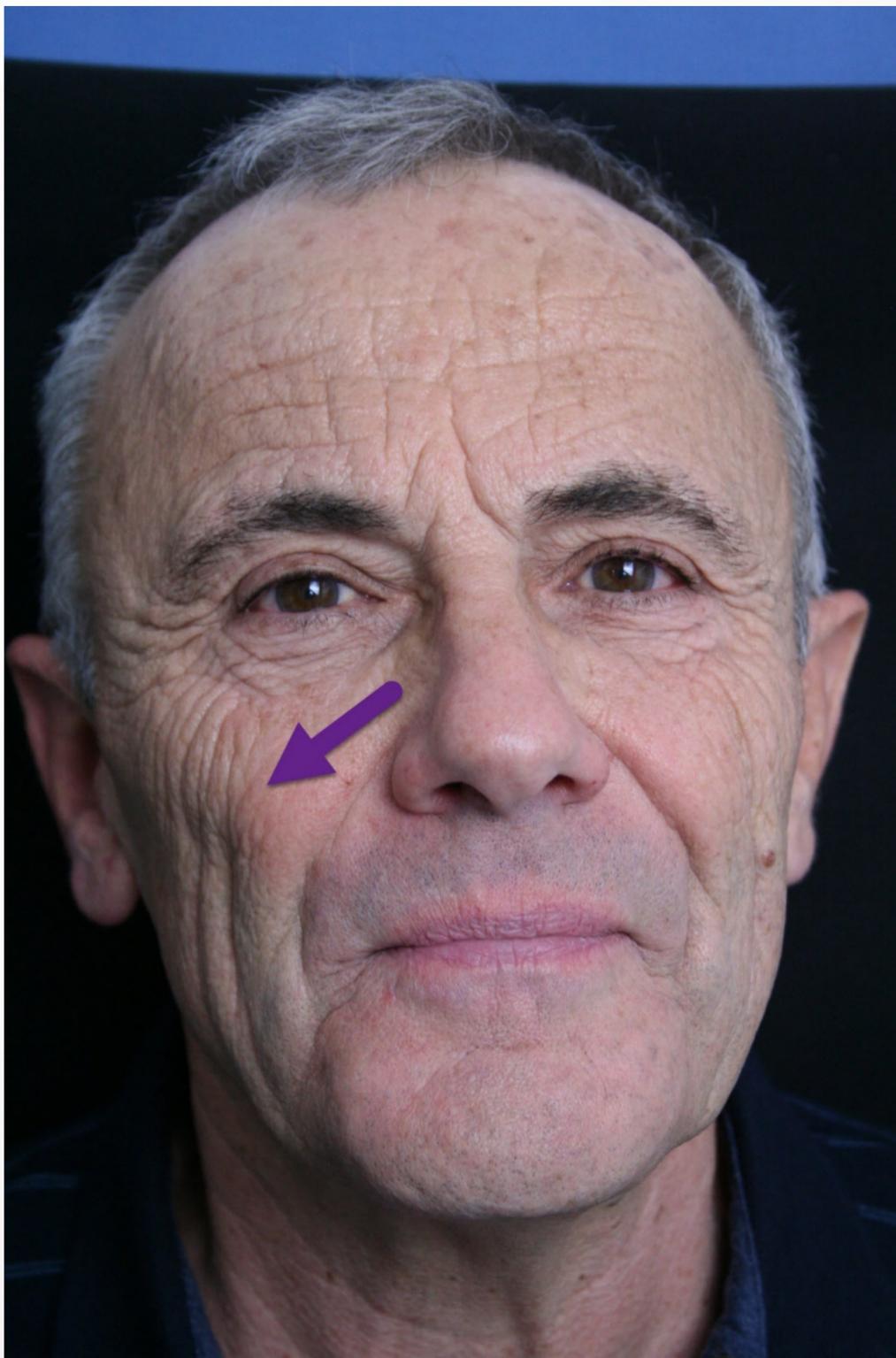


- **PRODUCT USED: CYTOSIAL DEEP WRINKLES**
- **QUANTITY OF PRODUCT: 2ML/SIDE: 1 ML INJECTED IN DEEP LAYER, 1ML DEDICATED TO WRINKLE LOCAL FILLING**
- **4 SYRINGES FOR TREATMENT**
- **PRACTITIONER: J. LEVY, MD, NICE, FRANCE** 

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Before / After: upper cheek area

BIOXIS



- **PRODUCT USED: CYTOSIAL VOLUME**
- **QUANTITY OF PRODUCT: 1ML/SIDE**
- **2 SYRINGES FOR TREATMENT**
- **PRACTITIONER: J. LEVY, MD, NICE, FRANCE**



Before/ after: rejuvenation of hands (2)



- **J1 BEFORE AND AFTER / J15 BEFORE AND AFTER**
- **PRODUCT: CYTOSIAL VOLUME**
- **QUANTITY: 1.1 ML / HAND 1ST DAY AND 1.1 ML/ HAND AT D15**
- **PRACTITIONER: A BRIANT, MD, TOULOUSE, FRANCE**

Before / After: a facial rejuvenation

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PRODUCT USED: CYTOSIAL DEEP WRINKLES (2 SYR.), CYTOSIAL VOLUME (3 SYR.), CYTOSIAL MEDIUM (1 SYR.). PRACTITIONER: H. GALADARI



BIOXIS

PHARMACEUTICALS

Thank you for your attention!
Any question? rhemery@bioxis.com

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CYTOSIAL is manufactured by BIOXIS Pharmaceuticals S.A.S.*

#BIOXIS BEYOND INNOVATION

