REGENflex
PROJECT



ACTION & PREVENTION

HYALURONIC ACID FOR JOINTS, TENDONS, MUSCLES & LIGAMENTS

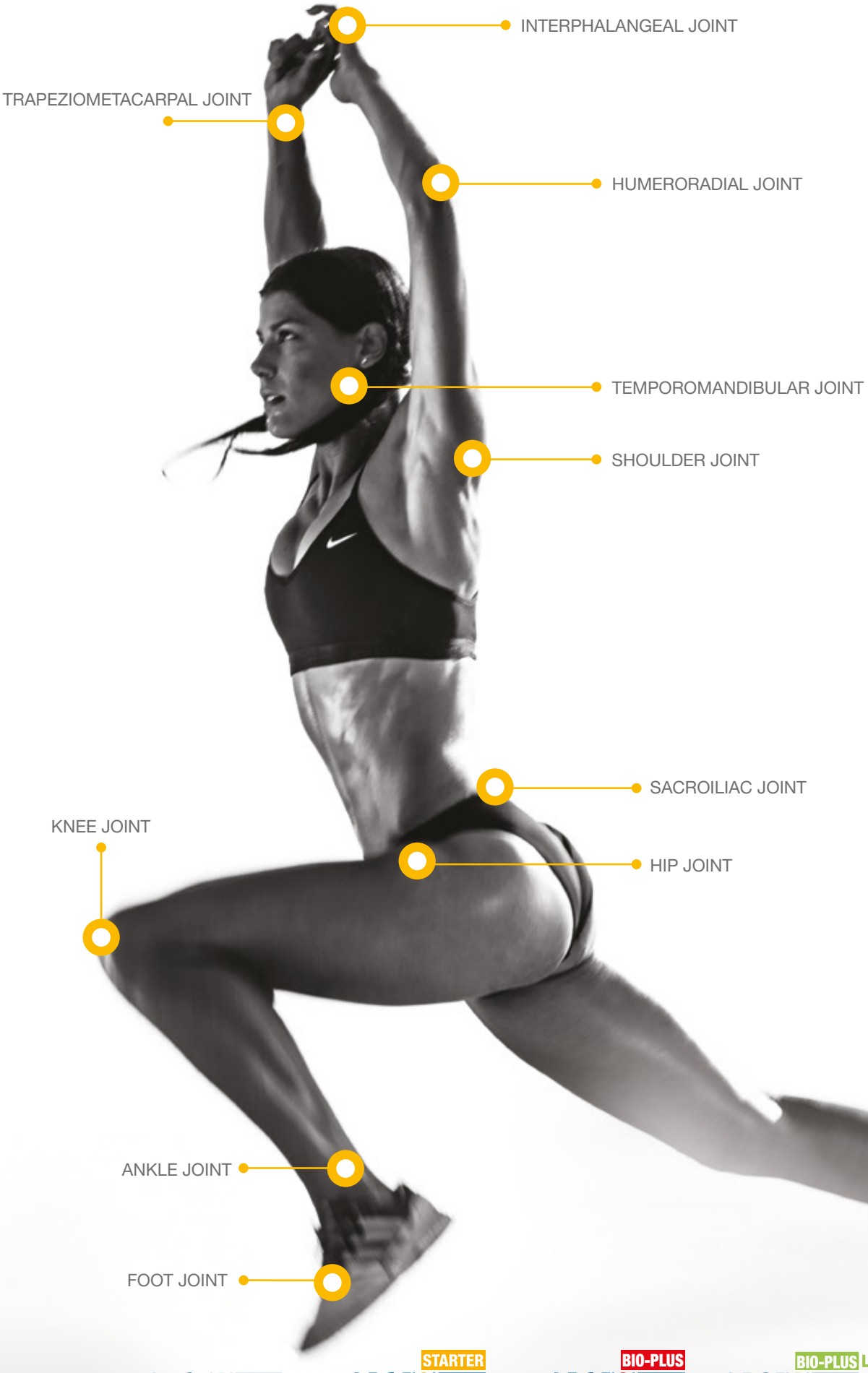
REGENYAL
LABORATORIES

TENDONS - MUSCLES - LIGAMENTS



T&M REGENflex

JOINTS



REGENflex STARTER REGENflex BIO-PLUS REGENflex BIO-PLUS LIGHT REGENflex



HYALURONIC ACID

- NATURAL COMPONENT OF CONNECTIVE TISSUE
- FUNDAMENTAL COMPONENT OF LARGE MOLECULAR COMPLEXES SUPPORTING THE EXTRACELLULAR MATRIX
- FUNDAMENTAL COMPONENT OF SYNOVIAL FLUID
- LUBRICATES JOINTS AND CUSHIONS MECHANICAL STRESSES
- PROTECT CARTILAGE FROM THE PENETRATION OF INFLAMMATORY CELLS AND LYTIC ENZYMES
- BINDS TO LUBRICIN (A GLYCOPROTEIN THAT PROTECTS JOINT SURFACES)
- PERFORMS A FUNDAMENTAL ROLE IN OSTEOARTHRITIS AND TENDINOPATHIES

JOINTS

In traumatic and degenerative joint diseases, there is a decrease in the amount of hyaluronic acid in situ, leading to a reduction in the viscosity of synovial fluid. This deficit results in compromised joint function and pain.

ACTIONS OF HYALURONIC ACID

- ALLEVIATING PAIN AND INFLAMMATION
- IMPROVING JOINT MOBILITY
- PREVENTING JOINT DEGENERATION
- RESTORING VISCO-ELASTIC PROPERTIES OF SYNOVIAL FLUID

TENDONS, MUSCLES AND LIGAMENTS

In traumatic and degenerative pathologies of the tendon body of the muscle-tendon and osteo-tendon transition zone, the administration of multifractionated hyaluronic acid, consisting of 5 progressive molecular weight fractions, performs a bio-induction and results in improved muscle contractility.

ACTIONS OF HYALURONIC ACID

- PROTECTION
- RESTORATION OF ELASTICITY
- REVASCULARISATION
- NEOANGIOGENESIS
- ACTIVATION OF BIOLOGICAL FACTORS

REGENflex



1 syringe
16 mg/2 ml
HYALURONIC ACID
SODIUM SALT

0.8%
concentration
HA

LINEAR HA

- MAINTENANCE OF THE RHEOLOGY AND METABOLIC HOMEOSTASIS OF THE JOINT CHAMBER
- NORMALISATION OF MATRIX METALLOPROTEASE CONCENTRATION
- INTERLEUKIN INHIBITION
- ANTIPHLOGISTIC EFFECT ALSO IN RHEUMATOLOGY PATIENTS UNDERGOING ASSOCIATED CORTISONE TREATMENT
- RAPID FUNCTIONAL RECOVERY
- MAINTENANCE OF RESULTS

STARTER REGENflex



1 syringe
32 mg/2 ml
HYALURONIC ACID
SODIUM SALT

1.6%
concentration
HA

LINEAR HA

- INTERLEUKIN INHIBITION
- IMMEDIATE REDUCTION IN PAIN AND INFLAMMATORY STATE
- INHIBITION OF ACID PHOSPHATASES
- VISCO-SUPPLEMENTATIVE AND ANTALGIC EFFECT
- RAPID FUNCTIONAL RECOVERY

BIO-PLUS REGENflex



1 syringe
75 mg/3 ml
CROSS-LINKED
HYALURONIC ACID
3 MOLECULAR WEIGHTS

2.5%
concentration
HA

CROSS-LINKED HA + INTERCALATED HA

1+2 MDa cross-linked + 500 kDa intercalated

- **VISCOSUPPLEMENTATION** - HIGH MOLECULAR WEIGHT
- **VISCOINDUCTION** - LOW MOLECULAR WEIGHT
- STIMULATES SYNOVIOCYTES TO PRODUCE ENDOGENOUS HYALURONIC ACID
- RAPID PAIN REDUCTION
- PROTECTS THE CARTILAGE - 500 kDa MOLECULAR FRACTION
- HIGH DWELL TIME IN THE ARTICULAR ENVIRONMENT
- GRADUAL RELEASE OVER TIME HA MW 500 KDa
- SPECIFIC FOR WEIGHT-BEARING JOINTS

BIO-PLUS LIGHT REGENflex



1 syringe
40 mg/1.6 ml
CROSS-LINKED
HYALURONIC ACID
3 MOLECULAR WEIGHTS

2.5%
concentration
HA

CROSS-LINKED HA + INTERCALATED HA

1+2 MDa cross-linked + 500 kDa intercalated

- **VISCOSUPPLEMENTATION** - HIGH MOLECULAR WEIGHT
- **VISCOINDUCTION** - LOW MOLECULAR WEIGHT
- STIMULATES SYNOVIOCYTES TO PRODUCE ENDOGENOUS HYALURONIC ACID
- RAPID PAIN REDUCTION
- PROTECTS THE CARTILAGE - 500 kDa MOLECULAR FRACTION
- HIGH DWELL TIME IN THE ARTICULAR ENVIRONMENT
- GRADUAL RELEASE OVER TIME HA MW 500 KDa
- SPECIFIC FOR NON WEIGHT-BEARING JOINTS

T&M REGENflex



1 syringe
32 mg/2 ml
HYALURONIC ACID
SODIUM SALT
5 MOLECULAR WEIGHTS

1.6%
concentration
HA

MULTIFRACTIONATED LINEAR HA

2 kDa + 100 kDa + 200 kDa + 500 kDa + 1 MDa

- INTERLEUKIN INHIBITION
- IMMEDIATE REDUCTION IN PAIN AND PROTECTION AGAINST INFLAMMATION
- PROTECTION
- RESTORATION OF ELASTICITY
- REVASCULARISATION
- RAPID FUNCTIONAL RECOVERY

REGENflex PROJECT



HYALURONIC ACID-BASED INJECTIONS INDICATED IN THE PREVENTION AND TREATMENT OF DEGENERATIVE AND TRAUMATIC JOINT, TENDON, MUSCLE AND LIGAMENT PATHOLOGIES

	REGENflex	REGENflex STARTER	REGENflex BIO-PLUS	REGENflex BIO-PLUS LIGHT	REGENflex T&M
COMPOSITION	SODIUM SALT OF HYALURONIC ACID IN BUFFERED SALINE SOLUTION	SODIUM SALT OF HYALURONIC ACID IN BUFFERED SALINE SOLUTION	CROSS-LINKED AND INTERCALATED HYALURONIC ACID	CROSS-LINKED AND INTERCALATED HYALURONIC ACID	SODIUM SALT OF HYALURONIC ACID IN BUFFERED SALINE SOLUTION
DOSAGE	2 ML	2 ML	3 ML	1,6 ML	2 ML
MOLECULAR WEIGHT	800 KDa 1.200 KDa	800 KDa 1.200 KDa	1 MDa 2 MDa CROSS-LINKED + 500 kDa INTERCALATED	1 MDa 2 MDa CROSS-LINKED + 500 kDa INTERCALATED	2 kDa 100 kDa 200 kDa 500 kDa 1 MDa
HA CONCENTRATION	0.8% 16 MG / 2 ML	1.6% 32 MG / 2 ML	2.5% 75 MG / 3 ML	2.5% 40 MG / 1,6 ML	1.6% 32 MG / 2 ML
CROSS-LINKING AGENT	NOT-CROSSLINKED	NOT-CROSSLINKED	BDDE	BDDE	NOT-CROSSLINKED
MAIN INDICATIONS	ALL JOINTS	ALL JOINTS	KNEE HIP ANKLE	SHOULDER ELBOW HAND TEMPOROMANDIBULAR	TENDONS LIGAMENTS MUSCLES
WEIGHT-BEARING JOINTS	**YES**	**YES**	**YES**	**NO**	
NON WEIGHT-BEARING JOINTS	**YES**	**YES**	**NO**	**YES**	
DEGENERATIVE PATHOLOGIES	**NO**	**YES**	**YES**	**YES**	**YES**
TRAUMATIC PATHOLOGIES	**NO**	**YES**	**YES**	**YES**	**YES**
ACUTE PATHOLOGIES	**YES**	**YES**	**YES**	**YES**	**YES**
CHRONIC PATHOLOGIES	**NO**	**YES**	**YES**	**YES**	**YES**

ALL JOINTS



REGENflex

FAST ACTING

5 INFILTRATIONS / ONE EVERY 7 DAYS - INFILTRATION CYCLE EVERY 6 MONTHS

T 0 days — T 7 days — T 14 days — T 21 days — T 28 days



✓ACTION ON PAIN

IMMEDIATE RESULTS

RAPID ACTION ON PAIN AND INFLAMMATION

✓PROTECTS

AGAINST THE DAMAGE OF NSAIDs AND CORTISONE

✓LINEAR HYALURONIC ACID

VISCO-SUPPLEMENTATIVE FOR ALL JOINTS

0.8%
16 mg/2 ml

PREVENZIONE E TERAPIA

ALL JOINTS



STARTER REGENflex

FAST ACTING

3 INFILTRATIONS / ONCE EVERY 7 DAYS - INFILTRATION CYCLE EVERY 6 MONTHS

T 0 days — T 7 days — T 14 days



✓ ACTION ON PAIN

IMMEDIATE RESULTS

RAPID ACTION ON PAIN AND INFLAMMATION

✓ PROTECTS

AGAINST THE DAMAGE OF NSAIDs AND CORTISONE

✓ LINEAR HYALURONIC ACID

VISCO-SUPPLEMENTATIVE FOR ALL JOINTS

1.6%
32 mg/2 ml

PREVENZIONE E TERAPIA

KNEE • HIP • ANKLE



BIORIVOLUMETRIA®

BIO-PLUS
REGENflex

LASTING ACTION

BIORIVOLUMETRIA - BIO-SYNCHRONISATION

1 INFILTRATION / ONCE EVERY 6 MONTHS



✓ ACTION ON PAIN

VISCO-SUPPLEMENTATION - HIGH MOLECULAR WEIGHT

VISCO-INDUCTION - LOW MOLECULAR WEIGHT

IMMEDIATE RESULTS

REDUCTION OF INFLAMMATION OVER TIME

PROTECTS AGAINST DAMAGE FROM NSAIDs AND CORTISONE

SLOW-RELEASE ACTION (LINEAR HA)

✓ CROSS-LINKED AND INTERCALATED HYALURONIC ACID

3 MOLECULAR WEIGHTS CROSS-LINKED HA (HA 1+2 MDa) + INTERCALATED LINEAR HA (500 KDa)

VISCO-SUPPLEMENTATIVE AND VISCO-INDUCTIVE FOR JOINTS SUBJECT TO BEARING WEIGHT

2.5%
75 mg/3 ml

PREVENZIONE E TERAPIA

SHOULDER • ELBOW • HAND • TEMPOROMANDIBULAR



BIORIVOLUMETRIA®

BIO-PLUS LIGHT REGENflex

FAST ACTING

BIORIVOLUMETRIA - BIO-SYNCHRONISATION

1 INFILTRATION / ONCE EVERY 3 MONTHS

T 0 days — T 3 months



✓ ACTION ON PAIN

VISCO-SUPPLEMENTATION - HIGH MOLECULAR WEIGHT

VISCO-INDUCTION - LOW MOLECULAR WEIGHT

IMMEDIATE RESULTS

REDUCTION OF INFLAMMATION OVER TIME

PROTECTS AGAINST DAMAGE FROM NSAIDs AND CORTISONE

SLOW-RELEASE ACTION (LINEAR HA)

✓ CROSS-LINKED AND INTERCALATED HYALURONIC ACID

3 MOLECULAR WEIGHTS **CROSS-LINKED HA (HA 1+2 MDa) + INTERCALATED LINEAR HA (500 KDa)**

VISCO-SUPPLEMENTATIVE AND VISCO-INDUCTIVE FOR JOINTS NOT SUBJECT TO BEARING WEIGHT

2.5%
40 mg/1.6 ml

PREVENZIONE E TERAPIA

BIORIVOLUMETRIA: BIO-PLUS & BIO-PLUS LIGHT

BIORIVOLUMETRIA®

BIO
BIOCOMPATIBLE AND BIO-ABSORBABLE SUBSTANCES

RI
RESTRUCTURING

VOLUMETRIA
CREATION OF NEW VOLUMES

CROSS-LINKED AND LINEAR INTERCALATED HYALURONIC ACID

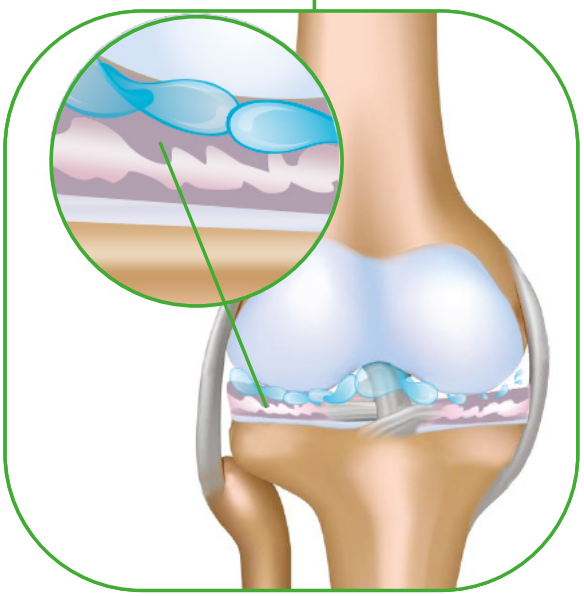
BIORIVOLUMETRIA is an innovative concept in the field of injectable medical devices based on HYALURONIC ACID, which identifies a new category of treatments capable of ensuring both visco-supplementation and visco-induction. BIO-PLUS and BIO-PLUS LIGHT are the two Biorevolumetric products of the Regenflex Project line. Thanks to their patented formula, it is possible to restore the volume of the joint chamber through the introduction of CROSS-LINKED HYALURONIC ACID (VISCO-SUPPLEMENTATION) and a simultaneous receptor stimulating action on synoviocytes and chondrocytes, provided by the linear fraction of intercalated HA (VISCO-INDUCTION), released gradually over time.

VOLUME
NORMALISES HYDROSTATIC PRESSURE
IN THE JOINT CHAMBER

+

REGENERATION
STIMULATES SYNOVIOCYTES
TO PRODUCE ENDOGENOUS HA





VISCO-SUPPLEMENTATION
HYDROSTATIC AND LUBRICATING ACTION

VISCO-INDUCTION
CELLULAR STIMULATION

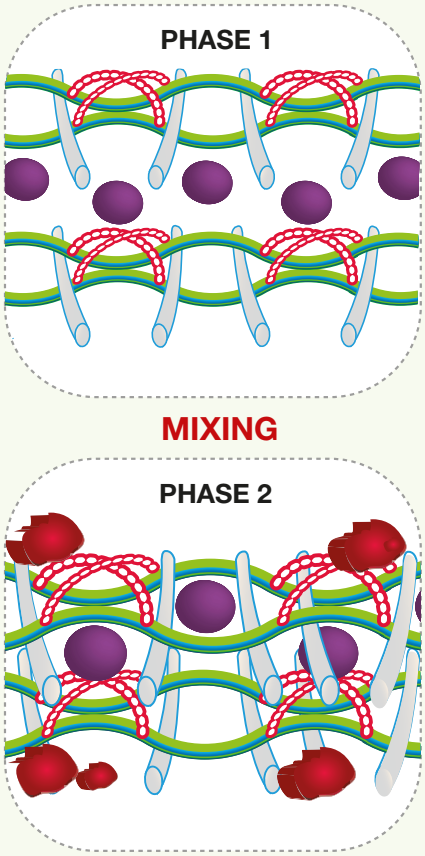
EXCLUSIVE PATENTED FORMULA

PATENT **NO. 0001408222**
GENTLE CROSS-LINKING PRODUCTION TECHNOLOGY

Biorevolumetric products are uncut MONOPHASIC GELS obtained by "gentle crosslinking", a low-temperature and prolonged duration cross-linking process. Slow mixing allows the cross-linking agent (BDDE) to distribute itself better and more evenly. 30% less BDDE is used compared to the majority of other products, with the same viscosity, on the market and the free residual is lower than 0.1ppm. In Regenflex BIO-PLUS 3 molecular weights of Hyaluronic Acid are used, of 1 MDa, 2 MDa (cross-linked) and 500 kDa. The latter, linear and intercalated, corresponds to 10% of the total Hyaluronic Acid. HA chains of different length allow for a better calibration of product viscosity. Linear Hyaluronic Acid is released gradually over time with a prolonged biological action (visco-induction).

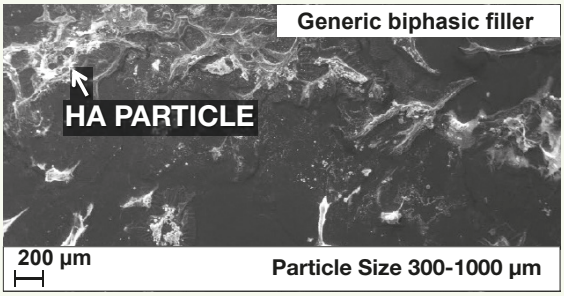
Intercalation process

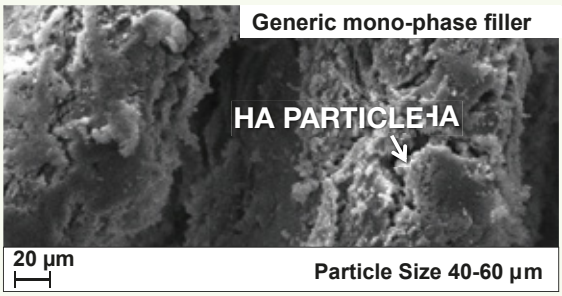
Intercalation is carried out during one of the last production phases and consists in alternating very thin layers of linear sodium hyaluronate with thicker layers (of a few millimetres) of cross-linked hyaluronic acid inside special containers in the absence of oxygen. Everything is left resting for 12 hours at low temperature so as to form weak bonds (hydrogen and Van der Waals bonds). After 12 hours we proceed with a homogenization carried out with the use of an orbital mixer equipped with special blades designed specifically for this purpose. After some hours of mixing, micro-aggregates are obtained, formed on the outside by cross-linked hyaluronic acid and on the inside by linear sodium hyaluronate.

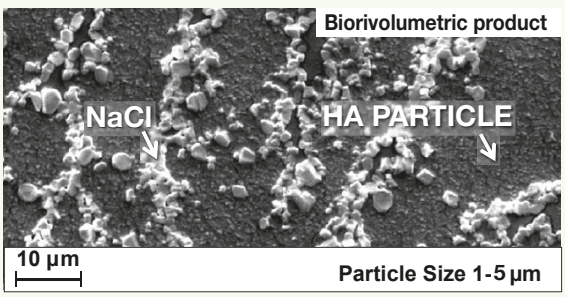


Hyaluronic acid microparticles

Images obtained with the scanning electron microscopy (SEM) technique reveal how BIOREVOLUMETRIC PRODUCTS are MORE COMPACT and HOMOGENEOUS than sized monophasic gels and biphasic gels* due to the smaller particle size of cross-linked hyaluronic acid. Smaller particles allow a better distribution of the gel in the articular chamber, with a better distribution of the compression forces.





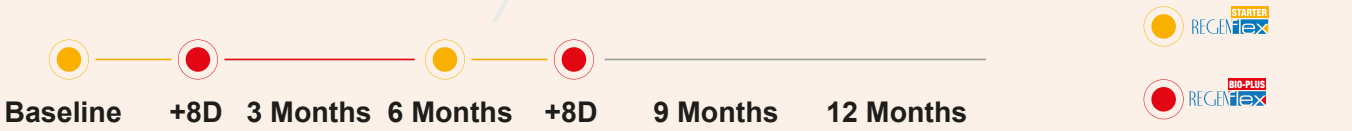


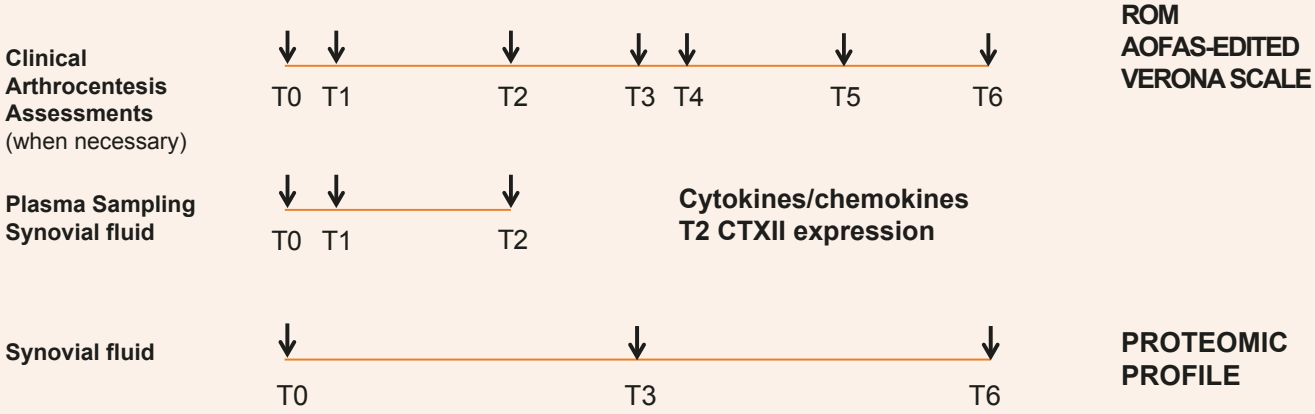
Observational study

The **University of Urbino Carlo Bo** conducted an observational clinical study on the combined protocol of STARTER and BIO-PLUS. They enrolled 53 patients, 35 of them were eligible, in order to evaluate the clinical and biochemical effects on patients with osteoarthritis.

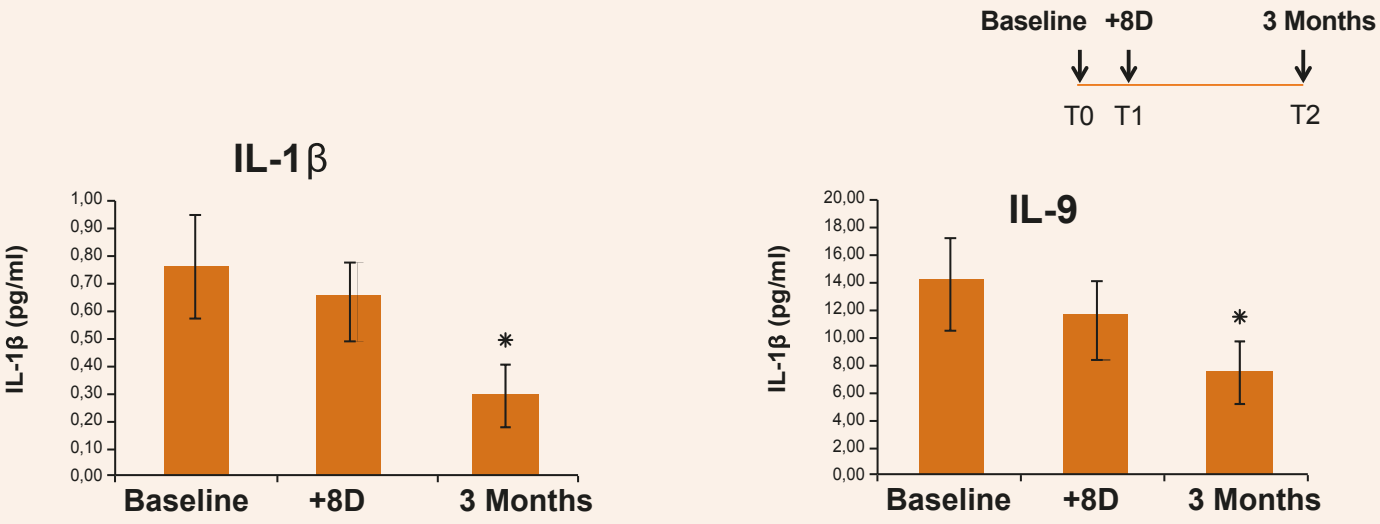
RESEARCH STUDY
"CLINICAL ADVANTAGE AND EVALUATION OF BIOCHEMICAL PARAMETERS AFTER TREATMENT WITH INTRA-ARTICULAR INJECTION OF HYALURONIC ACID IN PATIENTS WITH KNEE OSTEOARTHROSIS WITH INTERVALS OF 6 MONTHS".

Experimental design





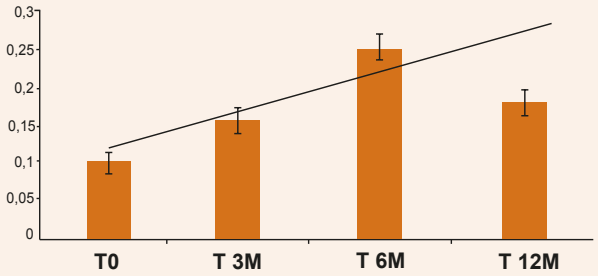
Plasma



Three months after the second infiltration, there is a significant decrease in pro-inflammatory interleukins.

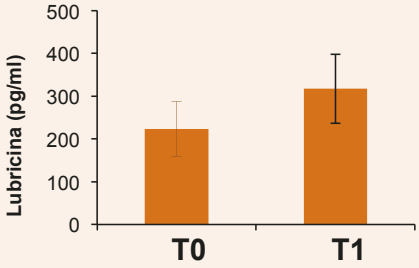
Transthyretin

Transthyretin is a constitutive inhibitor of interleukin-1 (IL-1) production. It carries out a physiological and Anti-aging function.



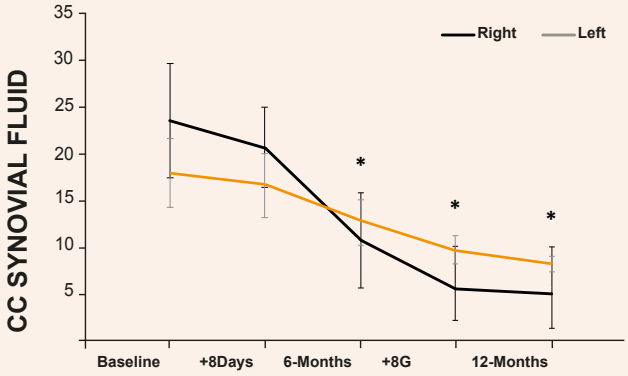
Lubricin

Lubricin is a glycoprotein that carries out a cartilage protective action.
There is an increase already after 8 days.

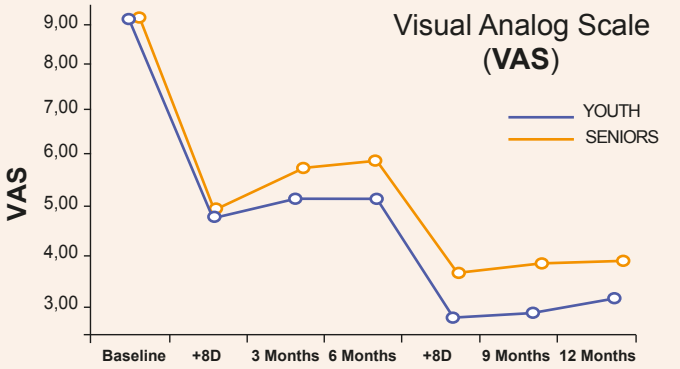


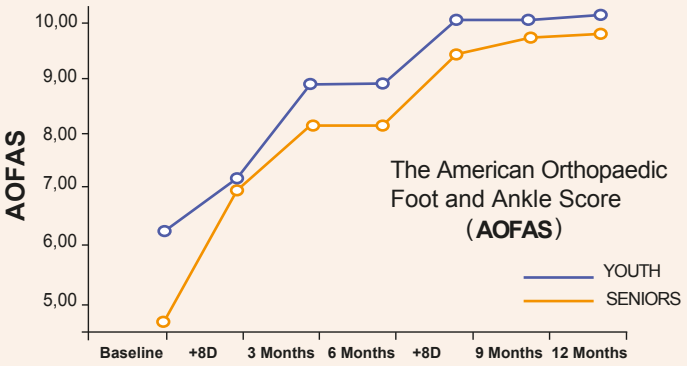
Arthrocentesis

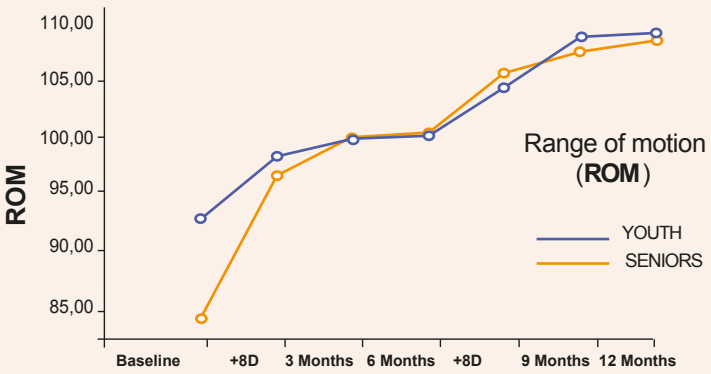
Arthrocentesis shows a very significant decrease in joint effusion over time, indicating a marked improvement in joint condition.



VAS and ROM + AOFAS double







Conclusions

Regenflex Starter + Bio-Plus protocol has been demonstrated to be effective on both mild and high-grade chondropathies with a clinical improvement in articular function and a slowing of disease progression.

TENDONS • LIGAMENTS • MUSCLES

T&M REGENflex

FAST ACTING

MULTIFRACTIONAL BIO-INDUCTION

3 INFILTRATIONS / ONCE EVERY 15 DAYS

T 0 days — T 15 days — T 30 days



✓ACTION ON PAIN

HYDRATION AND PROTECTION

PROTECTION AND ELASTICITY

IMPROVEMENT OF MICROCIRCULATION

RAPID REDUCTION OF PAIN AND INFLAMMATION

✓ MULTIFRACTIONATED LINEAR HYALURONIC ACID

5 MOLECULAR WEIGHTS 2 kDa / 100 kDa / 200 kDa / 500 kDa / 1 MDa

1.6%
32 mg/2 ml

PREVENZIONE E TERAPIA

MULTIFRACTIONAL BIO-INDUCTION

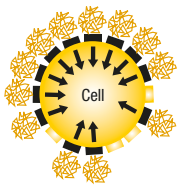
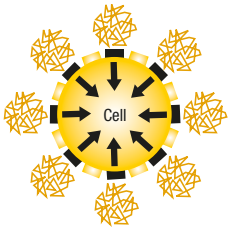
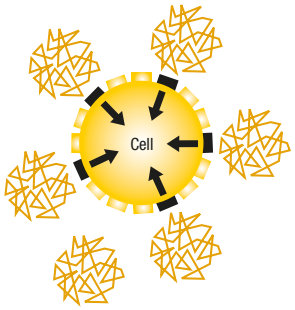
Regenflex T&M is an injectable product indicated in tendinopathies in which there is a decrease in the amount of hyaluronic acid, resulting in a reduction in the viscosity of synovial fluid. This deficit results in compromised tendon function and pain. The administration of hyaluronic acid by injection can restore the viscoelastic properties of the tendon fluid, with a clear anti-inflammatory response and pain relief, resulting in improved mobility.

5 MOLECULAR WEIGHTS

In a single fragmentation process, several molecular fractions can be obtained, each with a targeted action. The process is carried out by implementing HEAT and ULTRASOUND in a highly alkaline environment, starting with 1000 kDa fractions.

2 K Da	100 K Da	200 K Da	500 K Da	1 MDa

3 ACTIONS

1	**STIMULATING** STIMULATES ENDOTHELIAL CELLS, PROMOTES NEO-ANGIOGENESIS AND COLLAGEN PRODUCTION	**LOW** **MOLECULAR WEIGHT**	
2	**RESTRUCTURING** INCREASES THE PROLIFERATION OF FIBROBLASTS AND TENOCYTES WITH PRODUCTION OF COLLAGEN, ELASTIN AND ENDOGENOUS HA	**MEDIUM** **MOLECULAR WEIGHT**	
3	**ANTIOXIDANT AND MOISTURISING** ATTRACTS AND RETAINS WATER MOLECULES, REALIGNS TENDON BANDS, VISCO-SUPPLEMENTATION	**HIGH** **MOLECULAR WEIGHT**	

Observational pilot study

The **University of Urbino Carlo Bo** conducted a real-life pilot study on amateur marathon runners, who had been diagnosed with unilateral AT and had been prescribed three local injections of Regenflex T&M by the specialist doctor.

THE AIM OF THE OBSERVATIONAL PILOT STUDY WAS TO EVALUATE THE CLINICAL AND BIOCHEMICAL EFFECTS ON PATIENTS SUFFERING FROM TRAUMATIC AND/OR DEGENERATIVE TENDON PATHOLOGIES.

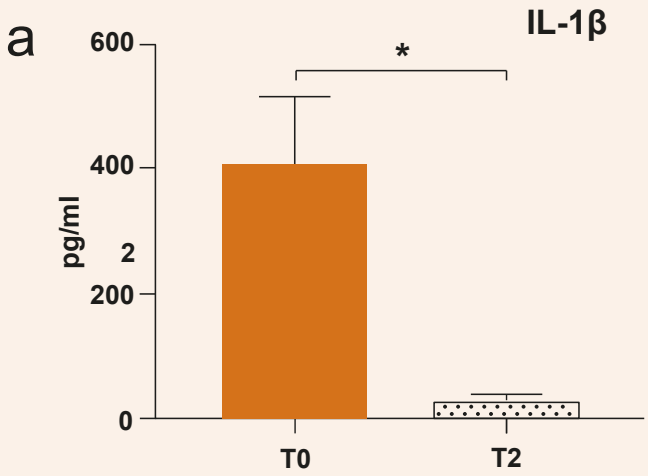
Treatment of Achilles Tendinopathy in Recreational Runners with Peritendinous Hyaluronic Acid Injections: A Viscoelastometric, Functional, and Biochemical Pilot Study

Marco Gervasi 1,* , Elena Barbieri 1,2 , Italo Capparucci 1, Giosuè Annibalini 1 , Davide Sisti 1 , Stefano Amatori 1 , Vittoria Carrabs 1, Giacomo Valli 1, Sabrina Donati Zeppa 1 , Marco Bruno Luigi Rocchi 1 , Vilberto Stocchi 1 and Piero Sestili 1

Experimental design

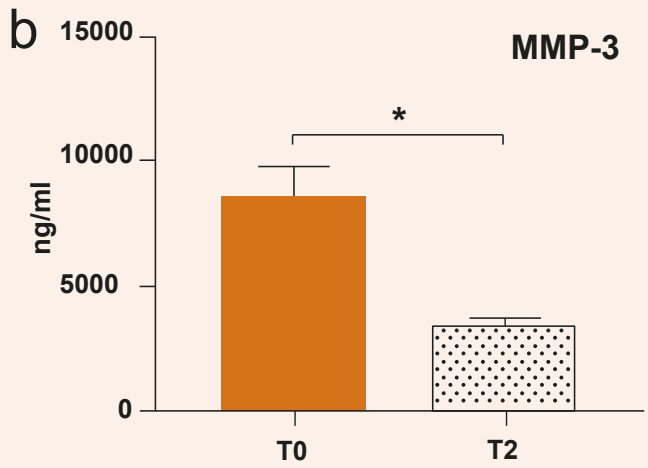


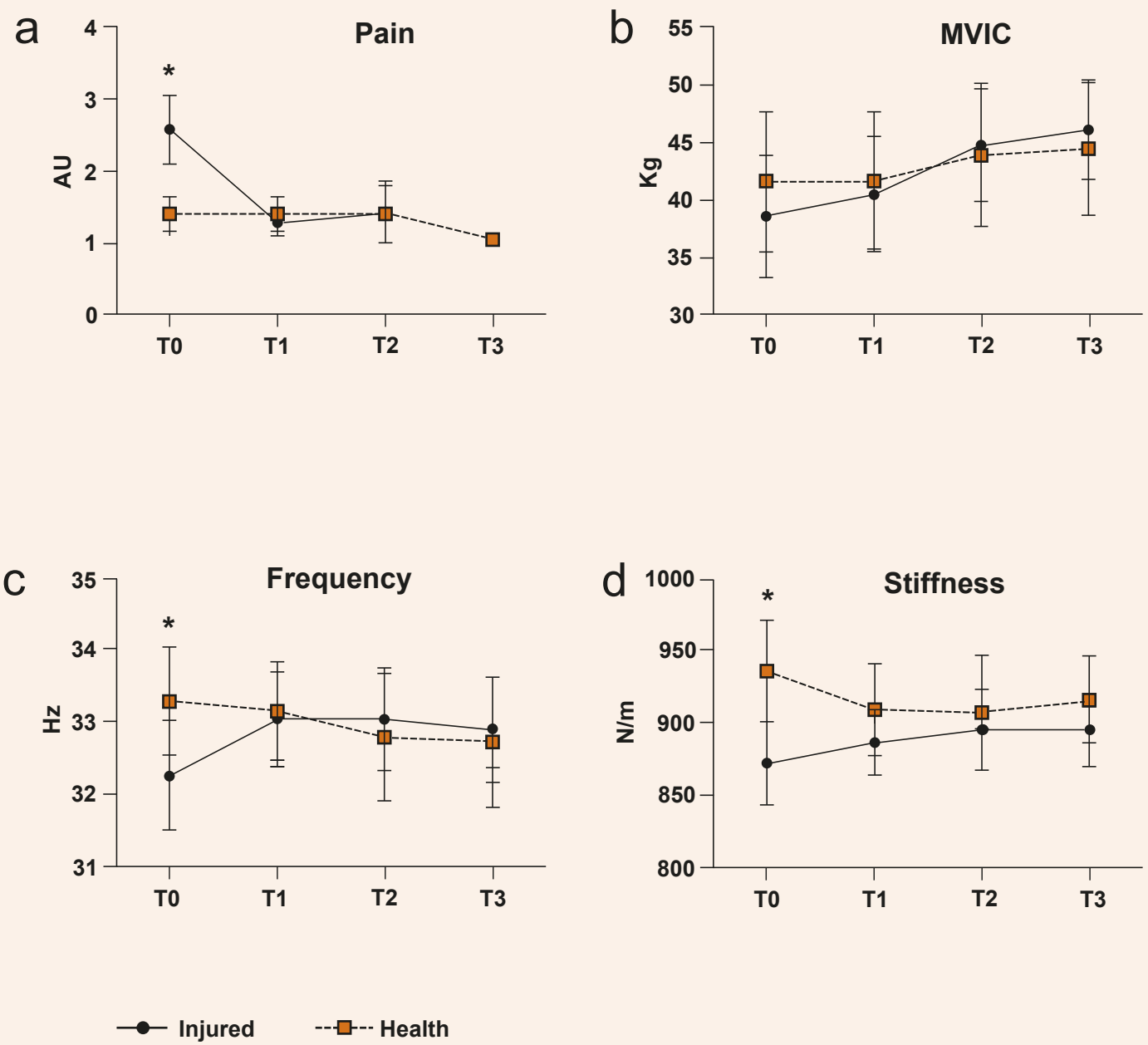
- **Clinical assestment**
- **Viscoelastometric, functional & pain evaluation (prior to injections)**
- **Biological specimens**
- **HA injections**



Biosynchronisation

Synchronous reduction of capsular, tendon and cartilage degradation processes
At 15 days after the first infiltration there is a significant and rapid synchronous reduction of pro-inflammatory and degenerative markers, according to the Biosynchronisation concept.





Functional improvement

At 15 days after the first infiltration, the clinical-symptomatological parameters clearly indicate a significant functional improvement regarding pain, joint discomfort and systemic repetitive motion frequency capacity.

Conclusions

The protocol of three infiltrations of Regenflex T&M has proven, with clinical and biochemical data, to be effective in the treatment of Achilles tendinopathies with a marked clinical and functional improvement and full recovery of the physiological structure of the tendon.

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