

CONDROTIDE®

an innovative
intra-articular
treatment

Polynucleotides for
intra-articular injection

Polinucleotidi per
infiltrazioni intra-articolari

Where innovation
is a tradition

MASTELLI
Bio-Pharmaceutical Company Italy

Since 1952



Polynucleotides - PN

POLYNUCLEOTIDES are a DNA fraction extracted from fish for human consumption by using Mastelli's peculiar methods

POLYNUCLEOTIDES

- ✓ *They exert a trophic and metabolic effect on cells*
- ✓ *Efficiently treat damaged, senescent and atrophic tissues in vitro and in vivo models*



Polynucleotides - PN

Polynucleotides characteristics:

- Extracted from fish: natural origin
- Perform a regenerative effect
- Have a proven effect on wound healing
- For acute, chronic and surgical wounds
- High safety and tolerability
- Perform a trophic and metabolic action on fibroblasts
- Thanks to its regenerative effect, PN effectively treat damaged, senescent and atrophic tissues both in *in vitro* and *in vivo* models



PN Mechanism of Action

Polynucleotides are natural DNA fractions, they are able to promote the physiological cellular regeneration and trophism.

Polynucleotides are able to reduce inflammatory cytokines.

The result is an increase of trophism and tissue regeneration.

In vitro study demonstrated a significant increase of production of cartilage extracellular matrix protein ECM, including Aggrecan and Collagen II.



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Polynucleotides

**Polynucleotide gel acts as a lubricant
and helps to normalize the viscosity of the synovial fluid.**

Indications:

Painful joint diseases caused by degenerative or post-traumatic conditions or by modification of a joint.



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Polynucleotides

Advantages:

Polynucleotides can significantly reduce pain intensity associated with arthrosis thus globally improving the quality of life.

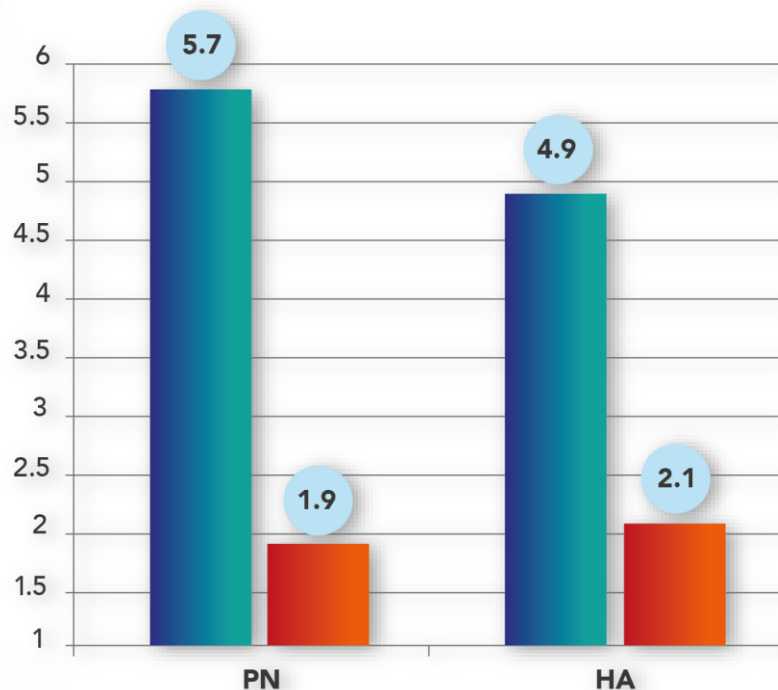
1. **Pain relief**
2. Improved **quality of life**
3. Reduced intake of **NSAIDs**
4. Improved **trophism of the cartilage**



1. Pain relief

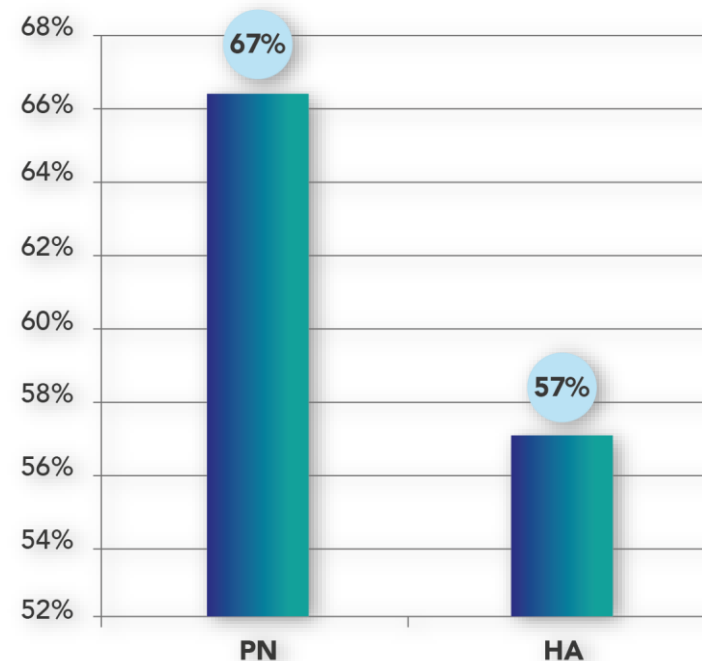
Reduction in VAS scoring:

- CONDROTIDE from 5.7 to 1.9
- HA from 4.9 to 2.1



% of VAS scoring reduced by:

- 67% in patients treated with CONDROTIDE
- 57% in patients treated with HA

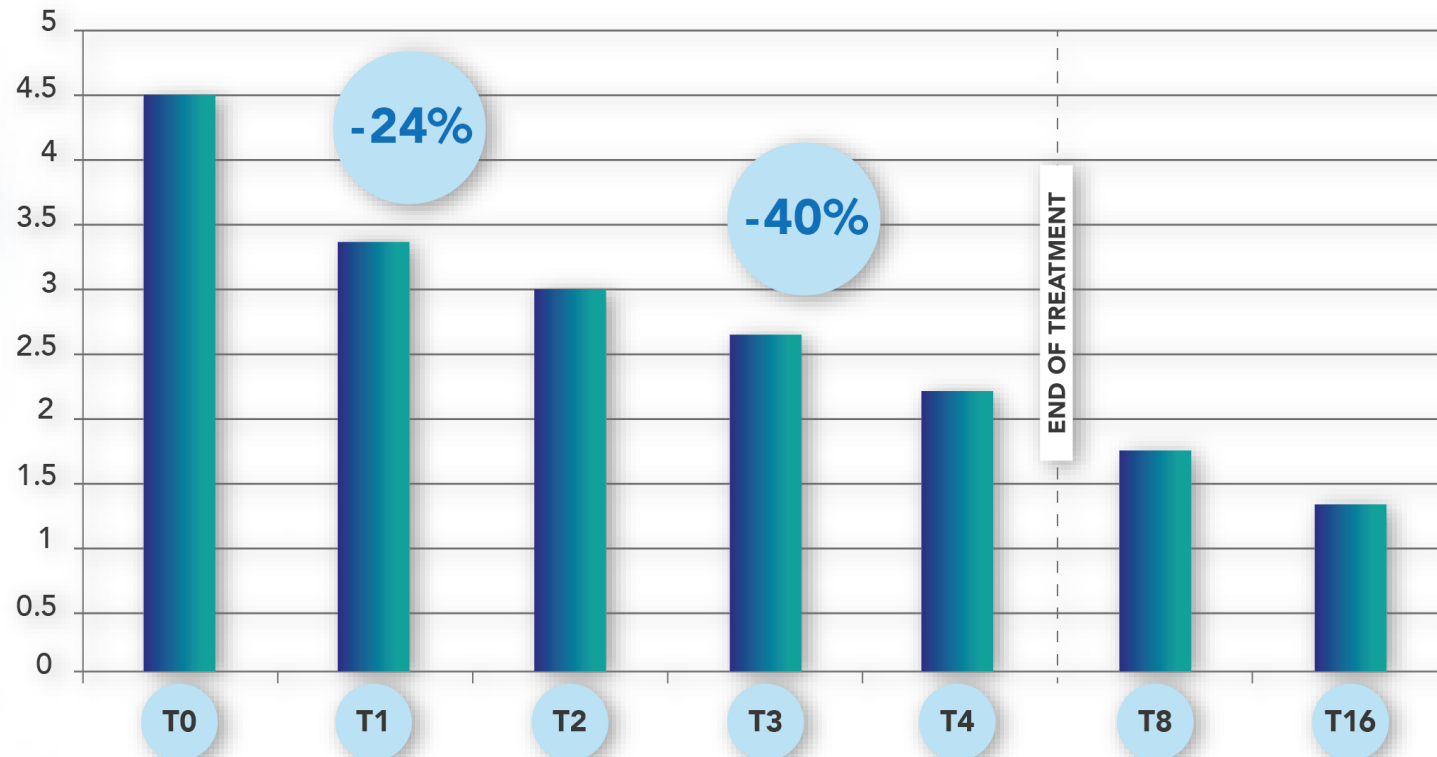


Knee Surg Sports Traumatol Arthrosc 2010; 18: 901-7



1. Pain relief

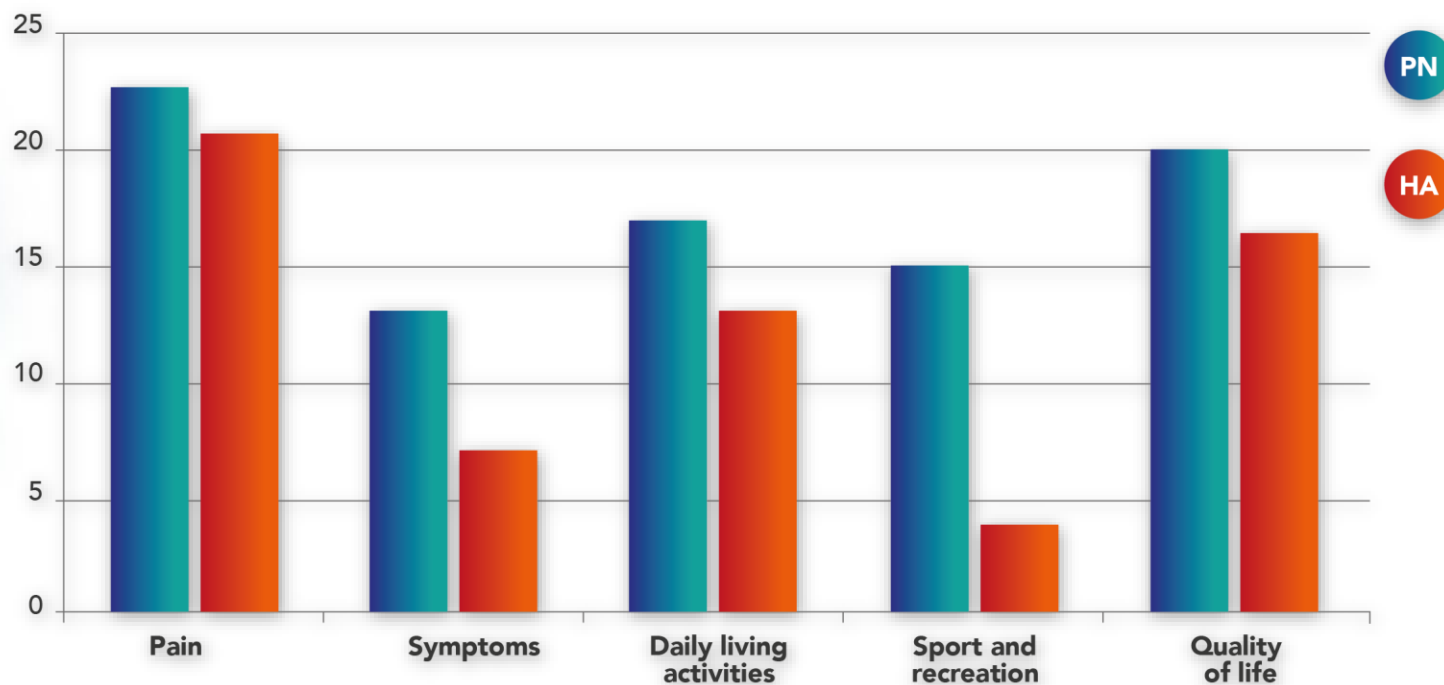
VAS pain score



Knee Surg Sports Traumatol Arthrosc 2010; 18: 901-7



2. Improved quality of life

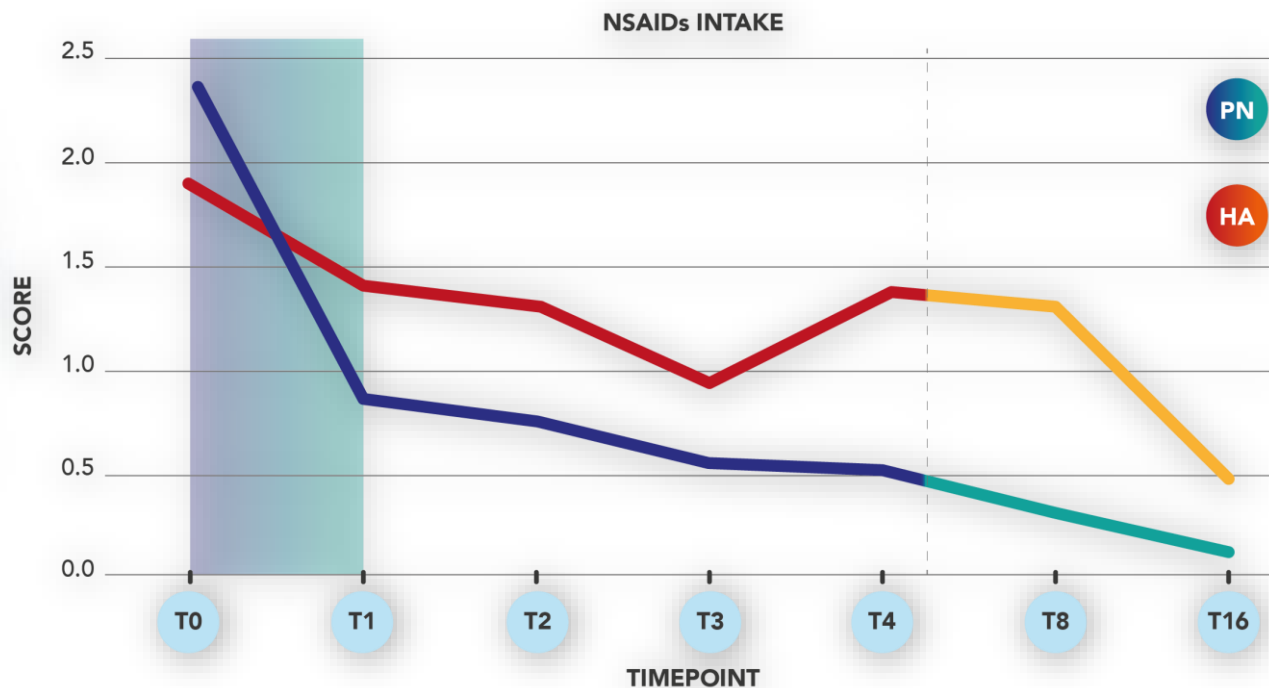


VAS Increase in KOOS score (score difference after 16 weeks as compared to initial scoring) in patients treated with Polynucleotides (PN) vs Hyaluronic acid (HA)

Knee Surg Sports Traumatol Arthrosc 2010; 18: 901-7



3. Reduced NSAIDs intake



Patients treated with CONDROTIDE showed:

- a reduced consumption of NSAIDs at the end of the trial as compared to initial scoring
- a reduced consumption of NSAIDs if compared with patients treated with HA

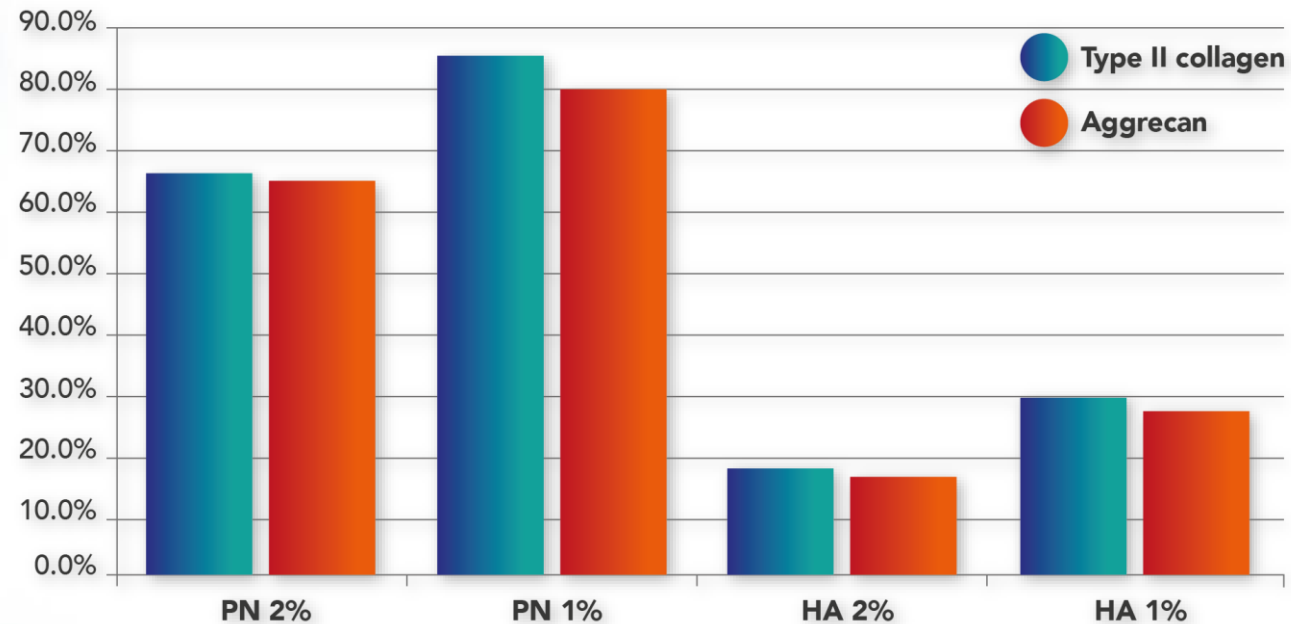
Knee Surg Sports Traumatol Arthrosc 2010; 18: 901-7



4. Improved trophism of the cartilage

The treatment with PN increased the production of the extracellular matrix: Collagen II and Aggrecan.

They both decreased with HA (evaluation after 30 days)



Gennero L., et al. Protective effects of polydeoxyribonucleotides on cartilage degradation in experimental cultures. Cell. Biochem. Funct. 2013 Apr;31(3):214-27



CONDROTIDE®

Polynucleotides

Product description:

- 40 mg/2 ml polynucleotides (of fish origin)
- 2 ml solution
- Sterile, non-pyrogenic, pre-filled glass syringe for single use
- International patent: EP 2358373



CONDROTIDE®

Polynucleotides – 3 Clinical Trials

1. Vanelli R, Costa P, Rossi P, Benazzo F.

Efficacy of intra-articular Polynucleotides in the treatment of knee osteoarthritis: a randomized, double-blind clinical trial.

Knee Surg Sports Traumatol Arthrosc. 2010;18: 901-907

Knee: Condrotide® vs Synovial®

60 patients - Policlinico San Matteo - Pavia

2. Giarratana LS, Marelli BM, Crapanzano C, De Martinis SE, Gala L, Ferraro M, Marelli N, Albisetti W.

A randomized double-blind clinical trial on the treatment of knee osteoarthritis: The efficacy of polynucleotides compared to standard hyaluronian Viscosupplementation.

The Knee. 2014;2:661-668

Knee: Condrotide® vs Hyalubrix®

75 patients - Istituto Ortopedico Gaetano Pini - Milan

3. Saggini R, Di Stefano A, Capogrosso F, Carniel R, Haidar Hassan K, Bellomo RG.

Viscosupplementation with Hyaluronic Acid or Polynucleotides: Results and Hypothesis for Condro-synchronization.

J Clin Trials 2014; 4(6)

Shoulder: Condrotide® vs Synovial One®

165 patients - Università di Chieti - Chieti



CONDROTIDE®

Polynucleotides – 3 Clinical Trials

1. Vanelli R, Costa P, Rossi P, Benazzo F.

Efficacy of intra-articular Polynucleotides in the treatment of knee osteoarthritis: a randomized, double-blind clinical trial *Knee Surg Sports Traumatol Arthrosc.* 2010;18: 901- 907

- Randomized, double-blind clinical trial enrolling 60 patients
- 30-Polynucleotides (PN)
- 30-Hyaluronic acid SYNOVIAL (HA)
- 16 weeks
- Policlinico San Matteo Pavia - Italy

ENDPOINT:

- Pain reduction in the knee (VAS scale 0-10 cm)
- Evaluation of the Knee Osteoarthritis Outcome Score (KOOS)
- NSAIDs intake



CONDROTIDE®

Polynucleotides – 3 Clinical Trials

1. Vanelli R, Costa P, Rossi P, Benazzo F.

Efficacy of intra-articular Polynucleotides in the treatment of knee osteoarthritis: a randomized, double-blind clinical trial *Knee Surg Sports Traumatol Arthrosc.* 2010;18: 901- 907

RESULTS:

1. **Reduced PAIN:** VAS score decreased:

- ✓ PN from 5.7 to 1.9
- ✓ HA from 4.9 to 2.1
- ✓ **With a statistically significant difference after 16 weeks**

2. In both cases KOOS scores increased testifying an **improvement in knee functionality**
A greater efficacy of PN as compared to HA was also found
Patients treated with PN were administered less NSAIDs

No significant adverse events were reported with both treatments



CONDROTIDE®

Polynucleotides – 3 Clinical Trials

1. Vanelli R, Costa P, Rossi P, Benazzo F.

Efficacy of intra-articular Polynucleotides in the treatment of knee osteoarthritis: a randomized, double-blind clinical trial *Knee Surg Sports Traumatol Arthrosc.* 2010;18: 901- 907

CONCLUSIONS:

« Results suggest that infiltrations with the polynucleotide gel are able to substantially reduce the intensity of pain due to arthrosis, thus globally improving the quality of life »

« Therefore, the treatment with polynucleotides can be considered as an alternative to hyaluronic acid for symptomatic arthrosis and that gel could be useful to extend the range of therapeutic options available in this field »



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Polynucleotides – 3 Clinical Trials

2. Giarratana LS, Marelli BM, Crapanzano C, De Martinis SE, Gala L, Ferraro M, Marelli N, Albisetti W.

**A randomized double-blind clinical trial on the treatment of knee osteoarthritis:
The efficacy of polynucleotides compared to standard hyaluronian viscosupplementation.
The Knee. 2014;21: 661-668**

- Randomized, double-blind clinical trial enrolling 72 patients
- 36-Polynucleotides (PN)
- 36-Hyaluronic acid HYALUBRIX (HA)
- 6 months follow-up
- Istituto Ortopedico Gaetano Pini (Milan)
- Intra-articular polynucleotides infiltrations vs hyaluronic acid infiltrations in the treatment of knee osteoarthritis

ENDPOINT:

- Pain reduction in the knee (VAS scale 0-10 cm)
- Evaluation of the Knee Osteoarthritis Outcome Score (KOOS)
- NSAIDs intake



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Polynucleotides – 3 Clinical Trials

2. Giarratana LS, Marelli BM, Crapanzano C, De Martinis SE, Gala L, Ferraro M, Marelli N, Albisetti W.

**A randomized double-blind clinical trial on the treatment of knee osteoarthritis:
The efficacy of polynucleotides compared to standard hyaluronian viscosupplementation.
The Knee. 2014;21: 661-668**

RESULTS:

The pain reduction and the increase of KOOS scores as compared to basic values were statistically significant in both cases

CONCLUSIONS:

Condrotide is effective like Hyalubrix in reducing the symptoms of knee osteoarthritis.

The treatment with polynucleotides was proven to reduce painful symptoms faster and can be considered as a valid alternative to the use of hyaluronic acid, avoiding the adverse events associated with NSAIDs and intra-articular corticosteroids



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Polynucleotides – 3 Clinical Trials

3. Saggini R, Di Stefano A, Capogrosso F, Carniel R, Haidar Hassan K, Bellomo RG.
Viscosupplementation with Hyaluronic Acid or Polynucleotides: Results and Hypothesis
for Condro-synchronization.
J Clin Trials 2014; 4(6)

- Randomized clinical trial
- **165 patients**
- **Painful shoulder (rotator cuff syndrome)**
- Group A: Polynucleotides (PN)
- Group B: Synovial one (HA)
- Group C: control (lidocaine 2%)
- 4 infiltrations
- 16 weeks
- University of Chieti



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Polynucleotides – 3 Clinical Trials

3. Saggini R, Di Stefano A, Capogrosso F, Carniel R, Haidar Hassan K, Bellomo RG.
Viscosupplementation with Hyaluronic Acid or Polynucleotides: Results and Hypothesis for Condro-synchronization.
J Clin Trials 2014; 4(6)

ENDPOINT:

- Pain reduction of the shoulder (VAS 0-10 cm)
- Evaluation of the functionality of the shoulder and resulting quality of life (Constant Murley Score top score 100)
- Evaluation of shoulder Range of Motion (ROM)



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Polynucleotides – 3 Clinical Trials

3. Saggini R, Di Stefano A, Capogrosso F, Carniel R, Haidar Hassan K, Bellomo RG.
Viscosupplementation with Hyaluronic Acid or Polynucleotides: Results and Hypothesis for Condro-synchronization.
J Clin Trials 2014; 4(6)

RESULTS:

Reduced PAIN: VAS score decreased:

- PN from 8.03 to 1.9
- HA from 7.72 to 2.0

2. In both cases **the functionality of the shoulder improved in the short and medium term** The polynucleotides were experimented for the first time in the shoulder and were well tolerated

No significant adverse events were reported with both treatments



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Polynucleotides – an In Vitro Study

Gennero L, Denysenko T, Calisti GF, Vercelli A, Vercelli CM, Amedeo S, Mioletti S, Parino E, Montanaro M, Melcarne A, Juenemann C, De Vivo E, Longo A, Cavallo G, De Siena R

Protective effects of polydeoxyribonucleotides on cartilage degradation in experimental cultures

Cell Biochemistry and Function 2013; 31(3): 214-27



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Polynucleotides - an *in vitro* study

Gennero L, Denysenko T, Calisti GF, Vercelli A, Vercelli CM, Amedeo S, Mioletti S, Parino E, Montanaro M, Melcarne A, Juenemann C, De Vivo E, Longo A, Cavallo G, De Siena R

Protective effects of polydeoxyribonucleotides on cartilage degradation in experimental cultures

Cell Biochemistry and Function 2013; 31(3): 214-27

An *in vitro* study carried out using explants of human nasal cartilage

A model developed to study the cartilage and the surrounding microenvironment

Evaluation of the action of the treatment with

- Polynucleotides and Hyaluronic acid (1% and 2%)

Evaluations:

- Survival and mortality of chondrocytes
- Degree of degradation of Glycosaminoglycans (GAGs)
- Deposition of extracellular matrix (ECM: type II collagen and aggrecan)



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Polynucleotides - an in vitro study

Gennero L, Denysenko T, Calisti GF, Vercelli A, Vercelli CM, Amedeo S, Mioletti S, Parino E, Montanaro M, Melcarne A, Juenemann C, De Vivo E, Longo A, Cavallo G, De Siena R

Protective effects of polydeoxyribonucleotides on cartilage degradation in experimental cultures

Cell Biochemistry and Function 2013; 31(3): 214-27

Human chondrocytes extracted from nasal cartilage were treated with PN and showed:

- Longer cell survival
- Increased deposition of extracellular matrix, aggrecan and type II collagen, in particular
- Reduced GAGs degradation in the cartilage explants
- Highlighting a PN trophic and metabolic effect on cartilage



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Polynucleotides - an in vitro study

Gennero L, Denysenko T, Calisti GF, Vercelli A, Vercelli CM, Amedeo S, Mioletti S, Parino E, Montanaro M, Melcarne A, Juenemann C, De Vivo E, Longo A, Cavallo G, De Siena R

Protective effects of polydeoxyribonucleotides on cartilage degradation in experimental cultures

Cell Biochemistry and Function 2013; 31(3): 214-27

CONCLUSIONS:

« Chondrocytes treated with PN showed a physiological deposition of extracellular matrix. PDRN were capable of inhibiting proteoglycan degradation in cartilage explants.

The activity of matrix metalloproteinases 2 and 9 was reduced in all the samples treated with PDRN.

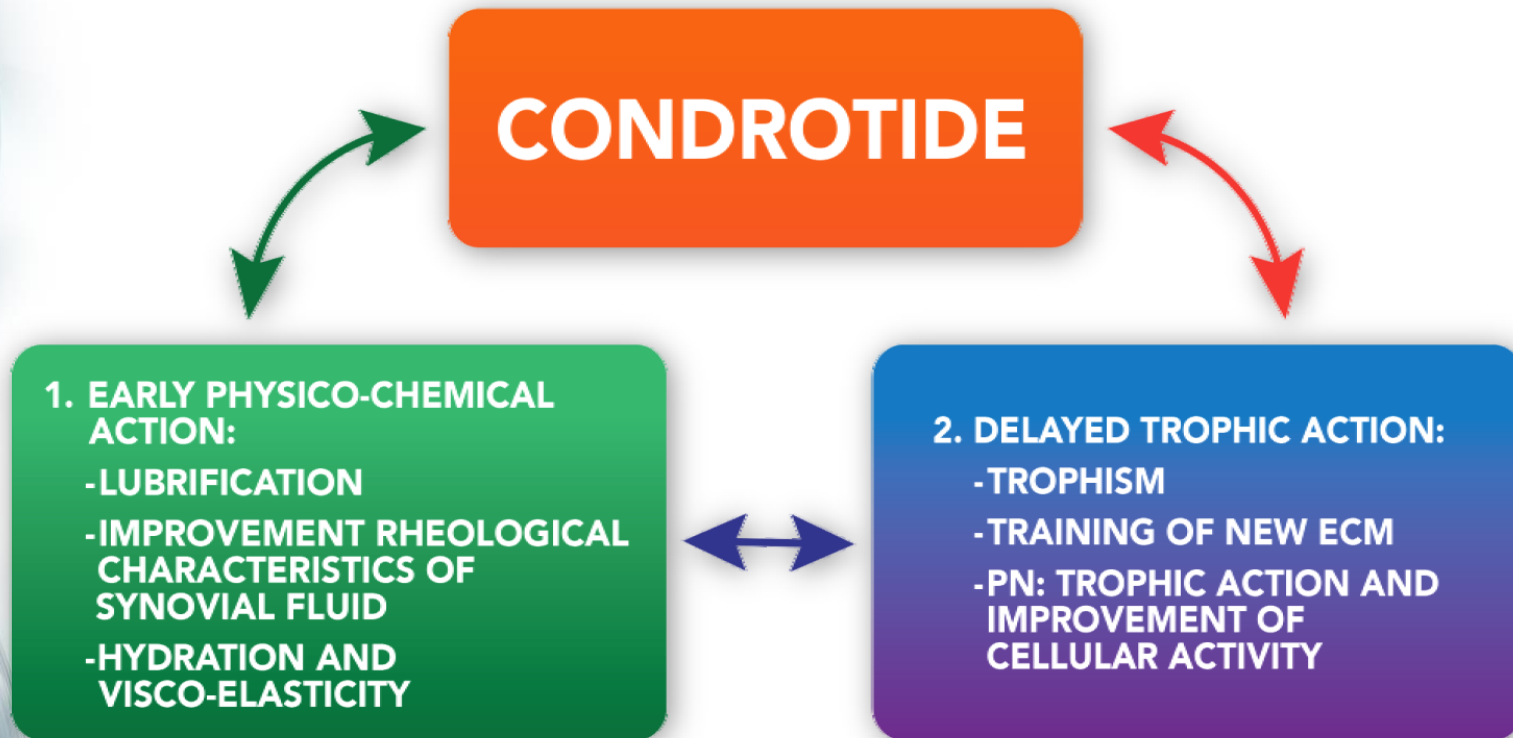
Our results show that PDRN are suitable for a long term in vitro cartilage culture and have therapeutic effects on chondrocytes protecting the cartilage.



CONDROTIDE®

Polynucleotides

Double action for a complete efficacy



CONDROTIDE®

Polynucleotides

INDICATIONS

- Painful joint diseases caused by degenerative or post- traumatic conditions or by modification of a joint
- This product helps to restore the rheological and physiological conditions of the joints
- It reduces pain
- It protects the joints
- It performs trophic action on the joint cartilage improving cellular activity



CONDROTIDE®

Polynucleotides

SAFETY

- Class III MEDICAL DEVICE CE 0373
- Highly purified polynucleotides of natural origin (fish)
- Biocompatible
- High tolerability



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Polynucleotides

DOSAGE

- One intra-articular infiltration once a week of 2.0 ml of product for 3-5 weeks
- The following protocol is also suggested:
one infiltration every 15-21 days (for 3-5 times)



CONDROTIDE®

Polynucleotides

INDICATIONS

- The only alternative to Hyaluronic acid
- Beneficial, safe, effective and innovative for intra-articular treatments
- Trophic effect on the cartilage (Gennero et al. 2014)
- Natural
- 3 clinical trials
- Publication of numerous clinical and experimental studies supporting the findings (see the following references)
- High tolerability



References - CONDROTIDE®

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2. Vanelli R, Costa P, Rossi SM, Benazzo F. Efficacy of intra-articular polynucleotides in the treatment of knee osteoarthritis: a randomized, double-blind clinical trial. Knee Surg Sports Traumatol Arthrosc. 2010;18(7):901-7
3. Vanelli R, Costa P, Rossi SM, Benazzo F. Efficacia dei polinucleotidi intra-articolari nel trattamento dell'artrosi del ginocchio: uno studio clinico randomizzato e in doppio cieco. Il giornale della terapia infiltrativa
4. Giarratana LS, Marelli BM, Crapanzano C, De Martinis SE, Gala L, Ferraro M, Marelli N, Albisetti W. A randomized double-blind clinical trial on the treatment of knee osteoarthritis: the efficacy of polynucleotides compared to standard hyaluronan viscosupplementation. The Knee. 2014;21(3):661-8
5. Gennero L, Denysenko T, Calisti GF, Vercelli A, Vercelli CM, Amedeo S, Mioletti S, Parino E, Montanaro M, Melcarne A, Juenemann C, De Vivo E, Longo A, Cavallo G, de Siena R. Protective effects of polydeoxyribonucleotides on cartilage degradation in experimental cultures. Cell Biochemistry and Function 2013; 31:214-227
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9. Saggini R, Di Stefano A, Capogrosso F, Carniel R, Haidar Hassan K, Bellomo RG. Viscosupplementation with Hyaluronic Acid or Polynucleotides: Results and Hypothesis for Condro-synchronization. J Clin Trials 2014; 4(6)
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14. Notarnicola A, Moretti L, Moretti B. Infiltrazione intra-articolare di polinucleotidi nel trattamento della gonartrosi: caso clinico. Minerva Ortop. Traumatol. 2011;62(Suppl. 2 al N.6):13-19
15. Cerino A. Terapia intra-articolare con lunghe catene di polinucleotidi (Condrotide) in un paziente affetto da artrosi del ginocchio. Risultati clinici a 4 mesi. Minerva Ortop. Traumatol. 2011;62(Suppl. 2 al N.6):21-5
16. Maserà F R. Efficacia dei polinucleotidi (Condrotide) nella gonartrosi. Minerva Ortop. Traumatol. 2011;62(Suppl. 2 al N.6):27-30



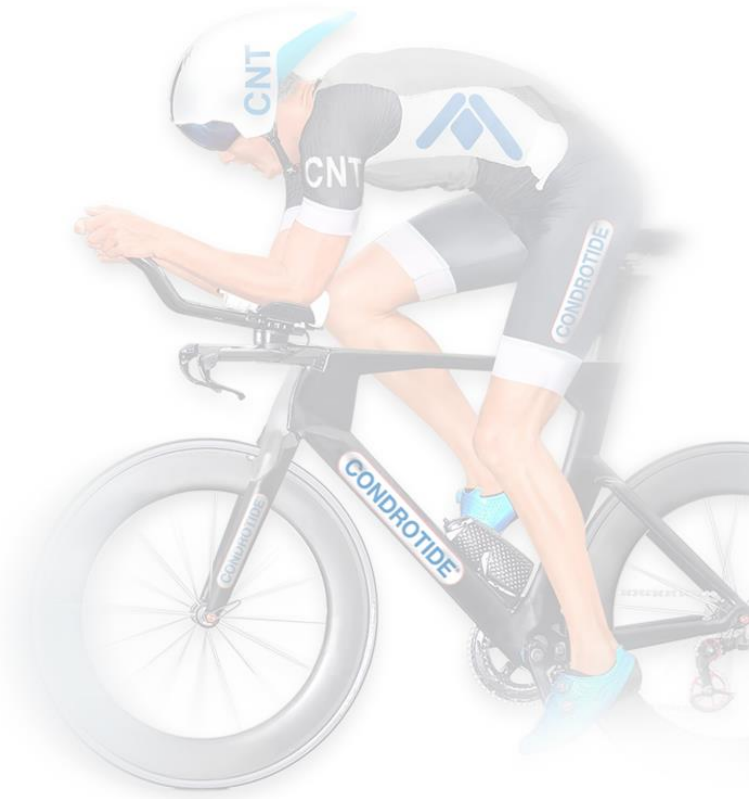
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19. Tropea S. Trattamento intra-articolare di gonartrosi con polinucleotidi: caso clinico. *Minerva Ortop. Traumatol.* 2011;62(Suppl.2 al N.6):41-3
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Future developments

1. Box containing 3 pre-filled syringes of Condrotide
2. Food supplement under study
3. New product for intra-articular infiltrations combining PN + HA.
Currently under development:
 - Ongoing randomized, double-blind clinical trial with PN + HA vs hyaluronic acid
 - 100 patients
 - Istituto Ortopedico Rizzoli - Bologna, Italy



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