

The sound science
of cartilage regeneration

BSI  CARGEL®



BST-CarGel[®], naturally enhancing
the process of cartilage regeneration

BST-CarGel® Description

- BST-CarGel® is an easy to use, off-the-shelf product applied during a one-step cartilage repair procedure
- BST-CarGel® is easily prepared by combining two components — a chitosan solution and a buffer
- BST-CarGel® is mixed with fresh autologous whole blood just before its application to a lesion surgically-prepared by Bone Marrow Stimulation



BST-CarGel[®] Product Preparation



- 1 Draw exactly 0.3 mL from the ADD vial.



- 2 Inject the ADD solution in a drop-wise manner into the MIX vial.



- 3 Do not shake. Leave undisturbed for a minimum of 10 minutes.

Steps 1-3 can be done by a non-sterile nurse while the lesion is being surgically prepared.



- 4 Once the cartilage lesion is ready, draw 5 mL of fresh autologous blood.



- 5** Using a dispensing pin, slowly inject exactly 4.5 mL of blood into the MIX vial.



- 6** Immediately shake MIX vial vigorously for 10 seconds.



- 8** Administer the BST-CarGel®/blood mixture to the lesion in a drop-wise manner without overfilling.

Wait 15 minutes to allow implant to clot and maintain its integrity.



- 7** Using a second dispensing pin, draw 4 to 5 mL of the BST-CarGel®/blood mixture into a syringe.



Accessories Required but not Provided with BST-CarGel®

- one 1.0 mL sterile syringe with 0.1 mL graduations and a 26G sterile needle
- two 5.0 mL sterile syringes with 0.5 mL graduations
- two sterile dispensing pins vented with a 0.2 µm filter membrane
- one sterile phlebotomy needle
- one 18G sterile needle

Physiotherapy Program Summary

- standard knee immobilizer for the first 24 hours, and thereafter for 14 days at night and during all movement
- non-weight-bearing on the treated knee for 6-8 weeks
- frequent physiotherapy for 12 weeks, using typical modalities for joint health
- no high impact activities requiring pivoting or shifting for 12 months

Problems with Bone Marrow Stimulation

Certain aspects of standard Bone Marrow Stimulation impede the cartilage repair process:

- blood clot retraction by as much as 50% of original volume
- poor residency of the blood clot in the cartilage lesion
- insufficient quantity of blood components necessary to drive repair

BST-CarGel® Scientific Rationale

Increasing the quantity and improving the residency of the blood clot in the cartilage lesion by providing a more voluminous, adherent, and physically-stabilized blood clot should improve cartilage repair outcomes after Bone Marrow Stimulation.

BST-CarGel® is a first line cartilage repair option used in conjunction with Bone Marrow Stimulation during a one-step procedure. This bioscaffold, consisting of the biopolymer chitosan, is implanted with autologous whole blood into a prepared lesion where it physically stabilizes the resulting clot, regardless of lesion geometry and size, and modulates repair events.

The improved adhesivity that BST-CarGel® imparts to the clot ensures a prolonged activation of tissue repair processes by maintaining critical blood components above marrow access holes, thus enhancing marrow-derived repair.

BST-CarGel® treatment overcomes the major pitfall that surgeons face with standard Bone Marrow Stimulation, which is the quantity of the initial blood clot present in the cartilage lesion. The resulting outcomes from this enhanced treatment include a consistently greater volume of repair tissue with highly improved hyaline characteristics.



BST-CarGel® is a novel chitosan-based liquid bioscaffold that is mixed with fresh autologous whole blood prior to implantation in a debrided cartilage lesion that has been surgically prepared with Bone Marrow Stimulation.

BST-CarGel[®] Primary Mode of Action

The mode of action of BST-CarGel[®] is three-fold:

- 1 Acts as a scaffold to physically stabilize the blood clot in the cartilage lesion.
- 2 Impedes blood clot retraction while allowing for normal clotting to occur.
- 3 Adheres to the cartilage lesion surfaces.

Hoemann et al., Osteoarthritis Cartilage 2007
Hoemann et al., J Bone Joint Surg Am 2005

Enhanced Secondary Healing Events

Animal studies have provided extensive scientific evidence supporting the mode of action for BST-CarGel[®] as well as the downstream consequences of prolonging the residency of the BST-CarGel[®]/blood implant in the cartilage lesion. The traditional wound healing processes are enhanced by the BST-CarGel[®] during the early stages of repair:

- 1 Increased inflammatory and bone marrow-derived stromal cell recruitment.
- 2 Increased vascularization of the provisional repair tissue.
- 3 Increased intramembranous bone formation and subchondral bone remodeling.

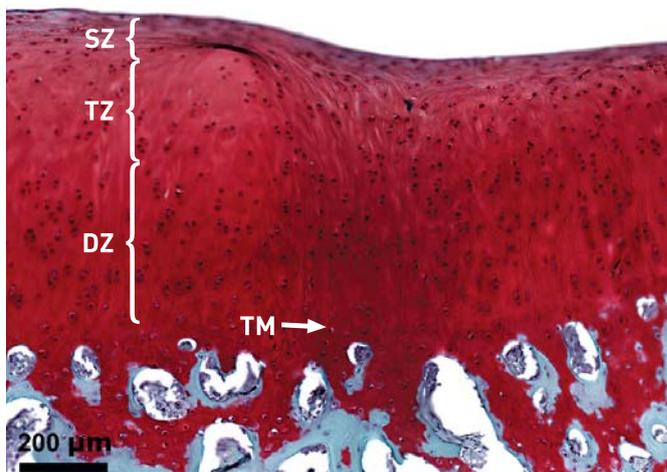
Chevrier et al., Osteoarthritis Cartilage 2007

These effects have been observed in multiple species following BST-CarGel[®] treatment including rabbits and sheep, demonstrating the efficacy of the treatment with the following outcomes:

- a greater lesion filling with a better integrated repair tissue
- an increase in glycosaminoglycan content in the repair tissue
- a more porous and vascularized subchondral bone
- a more cellular repair tissue with cells having a more chondrogenic phenotype
- an increase in collagen type II content in the repair tissue

Chevrier et al., Osteoarthritis Cartilage 2007
Hoemann et al., Osteoarthritis Cartilage 2007
Hoemann et al., J Bone Joint Surg Am 2005

BST-CarGel[®] Sheep Repair at 6 Months



Shive et al., Oper Tech Orthop 2006
Safranin-O/Fast Green Staining
SZ: Superficial Zone, TZ: Transitional Zone
DZ: Deep Zone, TM: Tidemark

BST-CarGel® International Clinical Trial



Clinical Sites

Canada

Halifax	Toronto
Calgary	Hamilton
New Westminster	London
Vancouver	Montreal
Winnipeg	Greenfield Park
Ottawa	Quebec City
Oakville	St-Eustache

Spain

Madrid
Barcelona
Gijon

South Korea

Seoul

BST-CarGel[®] International Clinical Trial Design

Representing the first of its kind in cartilage repair, this randomized clinical trial used state-of-the-art methodologies for endpoint measurements, including novel 3-dimensional quantitative magnetic resonance imaging (MRI).

- 1 Structural Co-Primary Endpoints at 12 Months**
- quantity of repair tissue as degree of lesion filling (% Fill) by quantitative MRI
 - quality of repair tissue by T2 mapping

- 2 Secondary Endpoints at 12 Months**
- clinical improvement by the Western Ontario and McMaster Universities Arthritis Index (WOMAC)
 - safety by the recording of adverse events

- 3 Tertiary Endpoint at 12 Months**
- quality of life by SF-36

Supportive Structural Data

- T2 stratification of repair tissue
- 2nd look and biopsy analysis
 - International Cartilage Repair Society (ICRS) macroscopic scoring during 2nd look arthroscopy
 - ICRS I & II histological scoring of biopsies (cellular, composition and structural parameters)
 - Polarized Light Microscopy (PLM) scoring of biopsies (collagen organization)

Patients – Baseline Characteristics

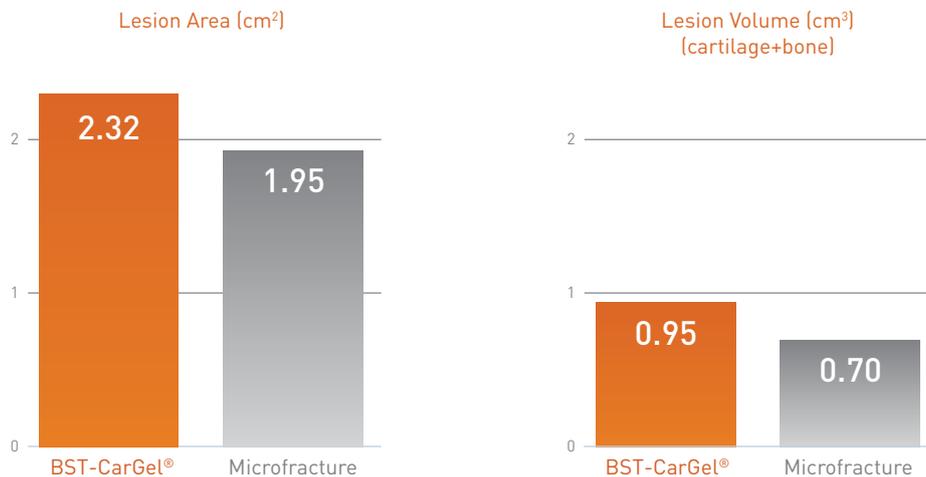
Baseline demographic characteristics of the 80 patients were similar in the two treatment groups, including **age, race, gender, BMI, smoking habits, and activity levels**. Compliance to the 12-week rehabilitation program was also equivalent between groups.

Similar Patient Characteristics for Both Groups

DEMOGRAPHICS (n=80)		BST-CarGel® (n=41)	Microfracture (n=39)
Age (years)	Mean (SD)	35.1 (9.63)	37.2 (10.62)
	Min, Max	20-52	18-55
Gender, n (%)	Male	23 (56.1%)	25 (64.1%)
	Female	18 (43.9%)	14 (35.9%)
BMI (kg/m ²)	Mean (SD)	27.0 (3.31)	25.2 (3.04)
Physiotherapy Compliance (sessions/12 weeks)	Mean (SD)	28.4 (7.4)	27.0 (7.6)

Lesions – Baseline Characteristics

BST-CarGel® generally had **larger** lesions by quantitative MRI. Lesion volume was a prespecified statistical covariate for endpoint analysis.



Maximum Lesion Area

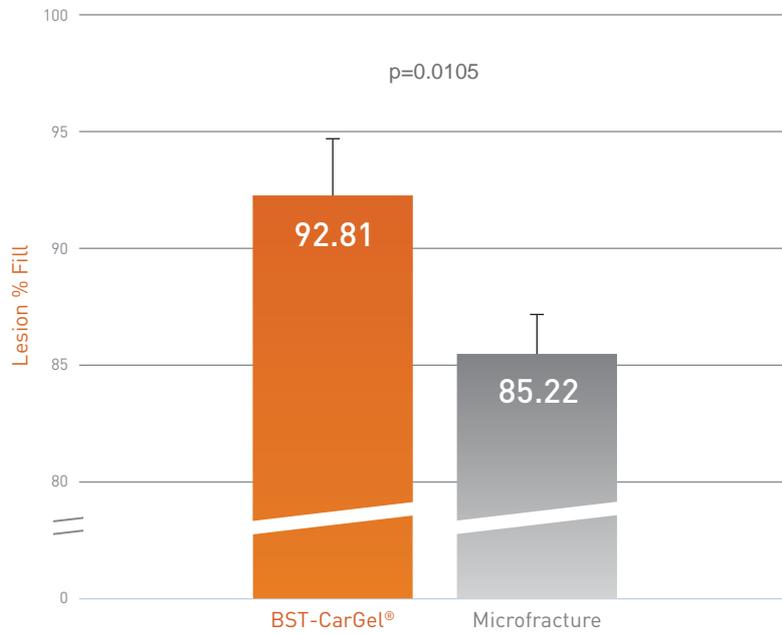
BST-CarGel®: 6.76 cm²

Microfracture: 4.45 cm²

BST-CarGel®: n=41, Microfracture: n=37

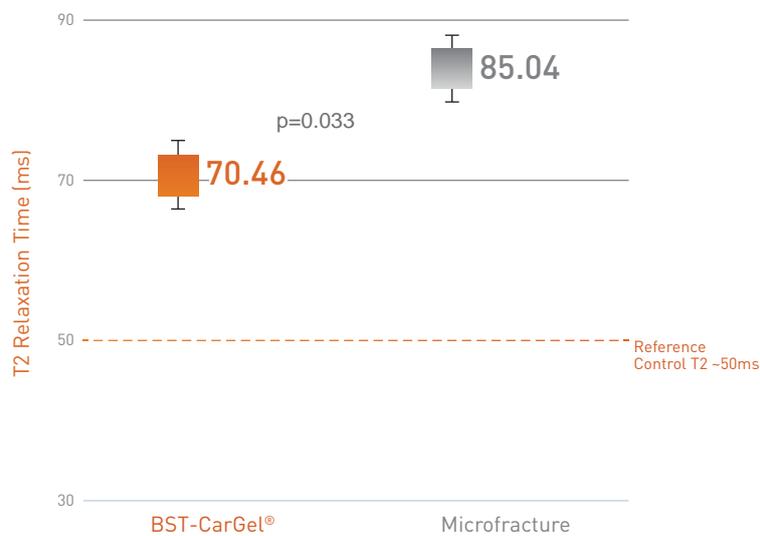
Co-Primary Endpoints Results: QUANTITY

First Co-Primary Endpoint Met
BST-CarGel® repair tissue quantity (Lesion % Fill) was significantly greater at 12 months post-operative by quantitative MRI.



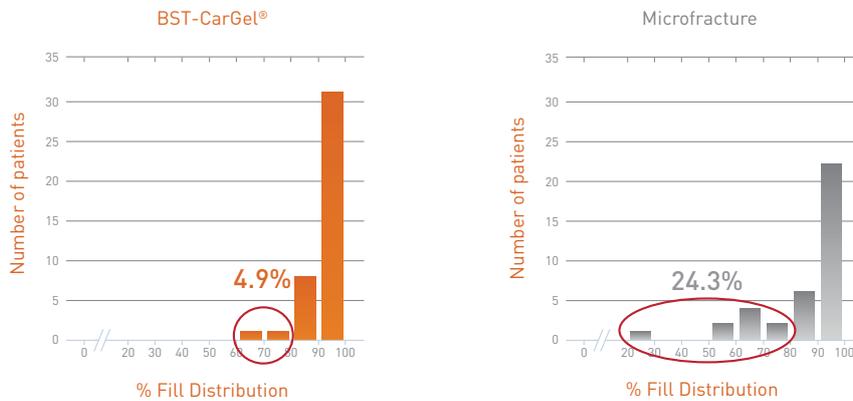
Co-Primary Endpoints Results: QUALITY

Second Co-Primary Endpoint Met
BST-CarGel® repair tissue quality is significantly closer to native cartilage at 12 months post-operative by T2 MRI.



More Consistent Cartilage Repair with BST-CarGel[®]

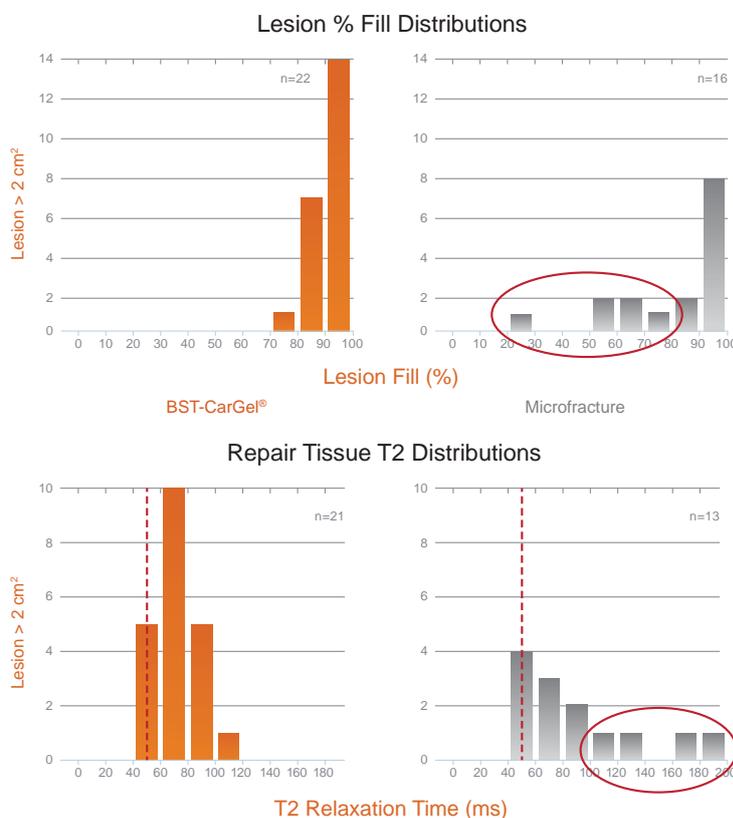
The Microfracture group had 5 times more failures (Lesion % Fill < 80%) than the BST-CarGel[®] group.



Size Doesn't Matter for BST-CarGel[®]

An analysis of structural outcomes was conducted where the lesion sizes were divided into two categories, above and below 2 cm².

Quantity and quality of repair tissue after BST-CarGel[®] treatment are not affected by the lesion size, especially > 2 cm².



The vertical dashed red line represents the control cartilage MRI T2 Value.

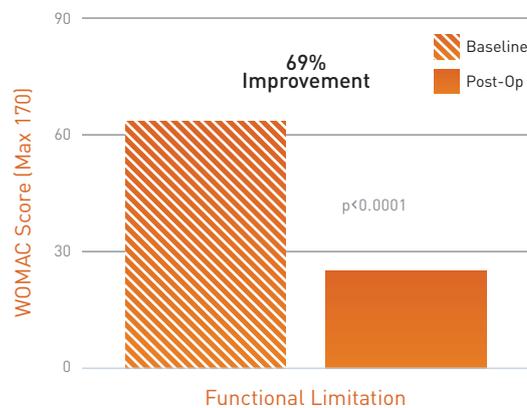
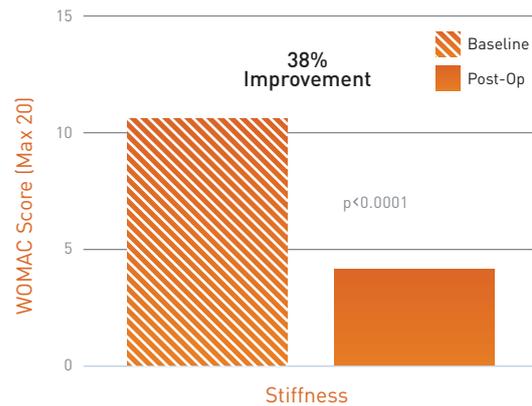
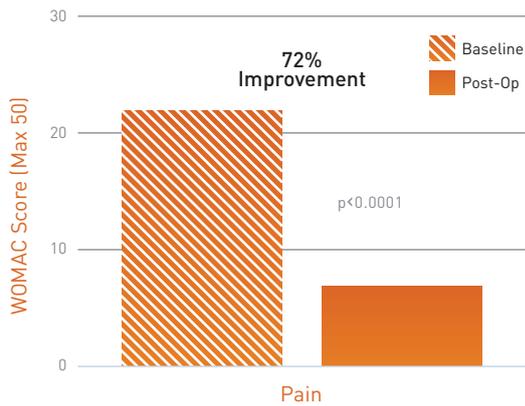
Repair Tissue QUANTITY
Treatment with BST-CarGel[®] leads to more consistent cartilage repair as seen in the histogram by a higher frequency of lesion fill (%) values above 80% than the Microfracture group in lesions > 2 cm².

Repair Tissue QUALITY
Treatment with BST-CarGel[®] leads to more consistent high quality tissue as seen in the histogram by a higher frequency of T2 MRI values closer to control cartilage than the Microfracture group in lesions > 2 cm².

Similar results were seen for lesions < 2 cm².

Clinical Benefits

BST-CarGel® treatment resulted in a significant clinical improvement at 12 months post-operative over baseline by WOMAC scores.



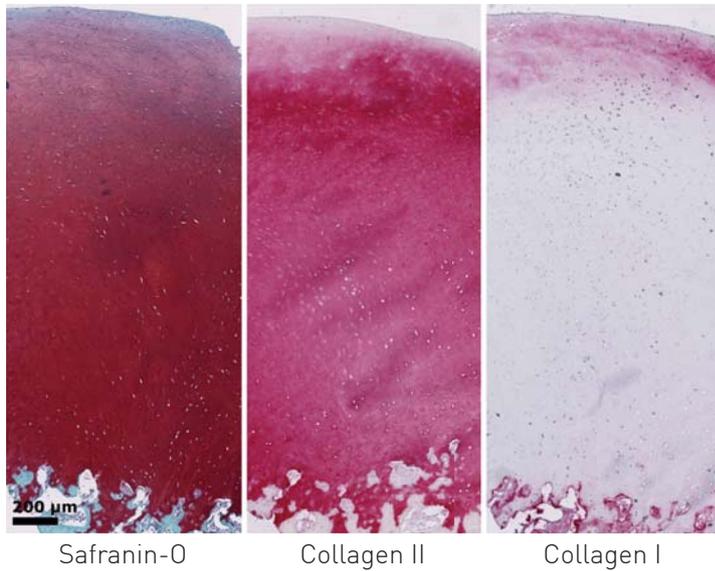
Both treatment groups showed equivalent clinical improvement at 12 months post-operative.

Safety

The safety of BST-CarGel® was comparable to Microfracture as measured by the recording of adverse events.

Biopsy Histology – Structural Parameters

BST-CarGel® treatment improves repair tissue structure at 13 months by ICRS histological scoring of biopsies.

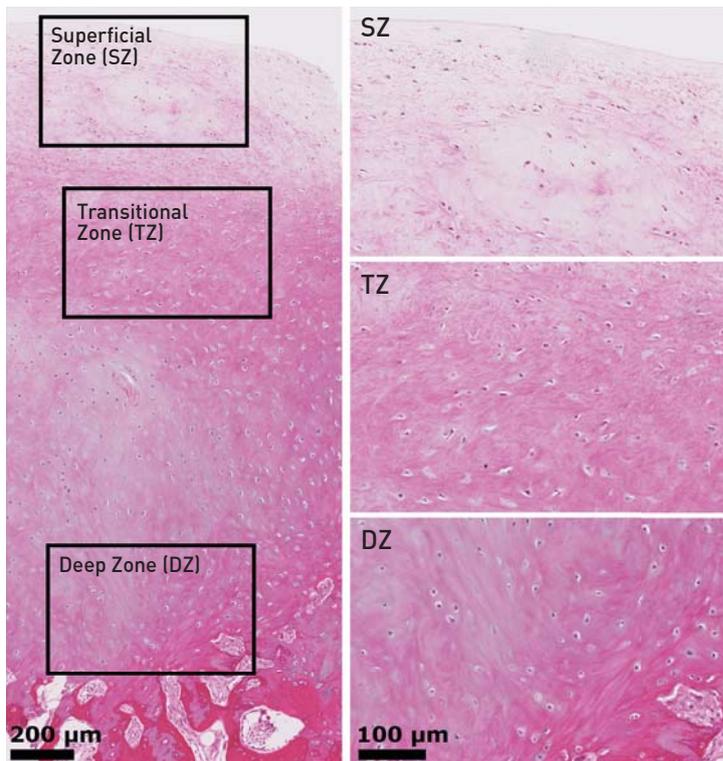


BST-CarGel® vs Microfracture	
Number of Improved ICRS Parameters	ICRS I, 4 of 6 ICRS II, 10 of 14
Superior Structure Parameters	Surface Architecture Superficial Zone Basal Integration Overall Assessment

BST-CarGel®: n=20
Microfracture: n=17

Biopsy Histology – Cellular Parameters

BST-CarGel® treatment improves repair tissue cellularity at 13 months by ICRS histological scoring of biopsies.



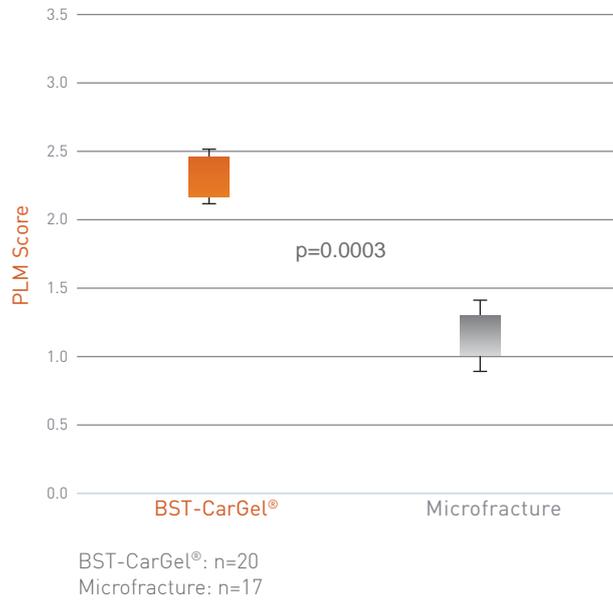
Hematoxylin/Eosin

BST-CarGel® vs Microfracture	
Number of Improved ICRS Parameters	ICRS I, 4 of 6 ICRS II, 10 of 14
Superior Cellular Parameters	Cell Viability Cell Distribution Cell Morphology

BST-CarGel®: n=20
Microfracture: n=17

Biopsy Collagen Organization

BST-CarGel® treatment improves collagen organization of repair tissue at 13 months by Polarized Light Microscopy (PLM) scoring.



BST-CarGel® Case Report

41-year-old male, BMI: 27
Chronic chondral lesion
Lesion size: 3.85 cm²



Cartilage lesion



After debridement



After Microfracture



Second look at 13 months



Quantitative MRI Results

Lesion % Fill: 97%

Average Repair Tissue T2: 58 ms



BST-CarGel[®] is a first line therapy
for most cartilage lesion sizes

Novel scaffold-based BST-CarGel[®] treatment
results in superior cartilage repair

Intended Use

BST-CarGel[®] is a medical device intended to promote hyaline cartilage regeneration when used in conjunction with the bone marrow stimulation technique for the repair of focal articular cartilage lesions.

Treatment with BST-CarGel[®] should be a one-time application administered through a mini-arthrotomy or by arthroscopic delivery performed by an orthopaedic surgeon properly trained in the technique.



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