ChondroMimetic® Osteochondral Scaffold

**ChondroMimetic is an all arthroscopic, single-surgery, cost-effective solution for osteochondral defect repair backed by 8 years of clinical evidence**

- All arthroscopic instrumentation, fully sterile kit, compatible with existing surgical techniques
- Single surgery procedure, not requiring cell harvesting and expansion
- Cost effective, projected to be 10% of the cost of other cell-based therapies
- Strong clinical evidence; backed by a longitudinal 8-year clinical study
Study Highlights

- Single-centre study of 15 patients (7 female, 8 male) followed over 8 years; average age at time of surgery of 32.7 years (range 18.7 to 47.9)

- Long-term durability of cartilage regeneration confirmed by advanced MRI analysis
  - Quantitative MRI using 3D reconstruction demonstrated 95% defect fill
  - T2 mapping demonstrated structural quality nearly identical to native cartilage

- Improvement in patient clinical outcomes:
  - Modified Cincinnati Rating – measures functional and clinical status after knee surgery
    Improvement from 64.4 pre-op to 80.9 after 8-years\(^1\); graded “excellent”

  - Knee injury and Osteoarthritis Outcome Score (KOOS)\(^2\)
    Better / equal to expensive two-stage cartilage repair technologies; graded “excellent”

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1. Highly statistically significant change (p=0.0065)
2. Clinical measure of symptoms, pain, activities of daily living, sports and recreation, and knee-related quality of life
“Based on our first-hand clinical experience with ChondroMimetic, and these new results confirming the sustainability of both cartilage regeneration and the improvement in patient outcomes, it is my firm belief that this scaffold has an important place in the treatment of focal chondral lesions as an alternative to microfracture.”

Professor László Hangody, MD, PhD, DSc
Uzsoki Hospital, Budapest, Hungary
Inventor of the Mosaicplasty Osteochondral Autograft Technique

“The long-term quantitative MRI data of cartilage repair volume and tissue quality in patients who were treated with ChondroMimetic are extremely attractive. This is consistent with the previously performed animal studies which showed a 25% improvement in cartilage repair over controls.”

Dr. Alan Getgood, Mphil, MD FRCS (Tr & Orth)
Fowler Kennedy Sport Medicine Clinic, London, Ontario, Canada
ChondroMimetic® Clinical Study Update Summary

Original Study
- Single centre study to confirm the safety and early outcomes with ChondroMimetic® in the treatment of osteochondral defects of the knee
- 6-Month clinical trial enrolled 17 patients in 2009-2010
- 6-Month results demonstrated safety and improved clinical outcomes
- MRI data analysed in 2017 indicated early improved structural defect repair

Extension Study
- 15 patients assessed in 2017 for prospective 8-year extension study
- Study to assess long-term sustained cartilage defect repair
- Full data analysis completed February, 2018
Study Key Measures

3D quantitative MRI analysis
  • Repair tissue morphology to measure % fill of defect
  • T2 mapping to assess the structure and quality of cartilage

Clinical and functional outcome scores
  • Modified Cincinnati Rating System
    Scoring of occupational / athletic activities, symptoms, & functional limitations in sports and daily life
  • Knee injury and Osteoarthritis Outcome Score (KOOS)
    Patient-relevant evaluation of knee injuries and posttraumatic osteoarthritis of Pain, Symptoms, Activities of daily living (ADL), Function in sport and recreation (Sports), and quality of life (QoL)

Refer to summary study design and methods in the appendix
Repair Tissue Morphology: Defect Fill at 8 Years Follow-up

10 Day Post-operative Volume:
Baseline

8 Year Post-operative Volume:
Cartilage Repair Fill (%)

Near complete filling of defect across all patients

Average Cartilage Fill (%): 95.1
Structural Quality (T2 Mapping): T2 Values at 8 Years Follow-up

Regenerated cartilage nearly indistinguishable from native cartilage at 8 years

ChondroMimetic T2 values compare favorably to microfracture and alternative therapy in similar MRI assessment in published study (graph below)

ChondroMimetic at 8-years: 52.5 ms

Native cartilage control: 52.3 ms

Data represents means±SD;
N=14, 11, 9 and 14 for 10 Days, 3 months, 6 months and 8 years respectively
Clinical Study Case Report 1 at 8 Years Follow-up

Study Subject 02, Female, 39 yrs old, 28 BMI, primary repair (2 implants)

- 2 ChondroMimetic implants
- Hyper-intense peri-implant boundaries
- Lack of cartilaginous repair tissue
- Iso-intense peri-implant boundaries
- Cartilaginous repair tissue
- Previous bone defect filled with bony repair tissue
- Previous cartilage defect filled with cartilaginous repair tissue

2D MRI

10 Days Post-op

6 months Post-op

8 yrs, 4 mos Post-op
Clinical Study Case Report 2 at 8 Years Follow-up

Study Subject 03, Female, 29 yrs old, 28 BMI, backfill (5 implants)

- 5 ChondroMimetic implants
- Hyper-intense peri-implant boundaries
- Lack of cartilaginous repair tissue

10 Days Post-op

- Bone integration
- Cartilaginous repair tissue

6 months Post-op

- Previous bone defect filled with bony repair tissue
- Previous cartilage defect filled with cartilaginous repair tissue

8 yrs, 3 mos Post-op
Modified Cincinnati Knee Rating Scores

- Improved 64.4 pre-op to 80.9 at 8 years
- Highly statistically significant (p=0.0065)
- 8-year overall grading of ‘excellent’

Longitudinal Modified Cincinnati Scores

Data represents means ± SE

N=17 for 1, 3 and 6 months; n=15 for 8 years
KOOS Scores, Literature Comparison
Single-Surgery ChondroMimetic vs Two-Stage Cell Therapies

- Subscales for ChondroMimetic generally superior at 8 years than cell-based technologies at 1.5 - 2 years
- ChondroMimetic is expected to be 10% of the cost of two-stage cell therapies, implying favorable health-economic benefits

ChondroMimetic® KOOS scores equal to or better than well known cell-based technologies

Data represents means ± SE
ChondroMimetic 8-year, n=15
CCI 18-month data from Saris AJSM 2008, n=44
MACI 2-year data from Saris AJSM 2014, n=72
Sports & Recreation subscale not reported in Saris 2008
Conclusions and Next Steps

• Study confirms sustained long-term regeneration of cartilage and improved clinical symptoms:
  • 3D MRI data shows long-term cartilage durability and sub-chondral bone remodeling
  • T2 data shows improvements in cartilage quality from 6 months to 8 years
  • T2 data shows cartilage quality nearly identical to surrounding native cartilage at 8 years
  • Modified Cincinnati Score significantly improved from baseline, with 8-year overall grading of ‘excellent’
  • KOOS scores equal to / better than cell-based therapies

• Regulatory approval targeted for second half of 2018
  • Submission process started with notified body for CE Mark
  • Staged data submission to begin this quarter
Appendix

Study Design and Methods
ChondroMimetic 6-Month Clinical Study Design

- Open label, prospective single to confirm the safety and early outcomes with ChondroMimetic in the treatment of osteochondral defects of the knee
- February 2009 - October 2010
- GCP-Compliant, single center, Uzsoki Hospital, Traumatology department, Prof. Laszlo Hangody, Budapest, Hungary
- 17 Subjects
  - 15 mosaicplasty backfill defects
  - 2 primary cartilage defects
- Assessments at 6 months
  - Visual Analogue Scale (VAS) for pain
  - Modified Cincinnati Rating System
  - Bandi Score
  - MRI (MOCART)
  - Optional osteochondral biopsy
ChondroMimetic Clinical Extension Study Design

• Extension study to determine the long-term (8 years) outcomes of the original patients
• Major protocol modifications include 3D MRI, T2 analysis, and KOOS questionnaire
• New data to demonstrate long-term durability of clinical outcomes and structural repair

• Open label, prospective extension study to confirm the safety and long-term outcomes with ChondroMimetic in the treatment of osteochondral defects of the knee
• June 2017 - October 2017
• GCP-Compliant (NAMSA-monitored), single center, Uzsoki Hospital, Traumatology department, Prof. Laszlo Hangody, Budapest, Hungary
• 15 of 17 Subjects who completed 6 month protocol
  • 13 mosaicplasty backfill defects
  • 2 primary cartilage defects
• Assessments at single follow-up visit
  • Modified Cincinnati Rating System
  • Knee injury and Osteoarthritis Outcome Score (KOOS)
  • MRI: Repair tissue quantity (Quantitative morphological analysis), Quality (T2 relaxation time) and subjective scoring (MOCART)
Advanced 3D Quantitative MRI Analysis

To assess sustainability, completeness of bone and cartilage defect filling, and cartilage quality, applied to both 6-Month and 8-Year data sets

**T2 Mapping**
- Technique to evaluate knee cartilage
- Assesses the 3D structure of cartilage
- Used in research studies to detect disease- and treatment-related changes to cartilage

**Repair Tissue Morphology**
- Technique to quantify the % fill of both cartilage and bone
- Used to provide quantitative and statistical analysis of completeness of bone and cartilage defect filling

To assess sustainability, completeness of bone and cartilage defect filling, and cartilage quality, applied to both 6-Month and 8-Year data sets

<table>
<thead>
<tr>
<th>Normal</th>
<th>Degenerative</th>
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![Images of normal and degenerative cartilage](image)

![Diagram showing Time of Surgery and After Healing/Remodelling](image)
Atlas-based Segmentation

1. Automatic (unsupervised) definition of the different anatomical knee regions based on programmed atlas.
2. Confirmation or correction and lesion identification by radiologist
3. 3-D Reconstruction and analysis of ROIs (lesion, Fill, control) from segmentation

*Courtesy of Qmetrics Technologies, Rochester, NY*
Key Clinical Outcomes Measures

**Modified Cincinnati Knee Rating System**

- Developed for scoring of occupational and athletic activities, symptoms, and functional limitations in sports and daily life.
- 11 components including measurements of physical examination, instrumented knee stability, testing and radiographic findings.

**Knee injury and Osteoarthritis Outcome Score (KOOS)**

- Developed to assess patient-relevant evaluation of knee injuries and posttraumatic osteoarthritis.
- 5 dimensions scored:
  - Pain
  - Symptoms
  - Activities of daily living (ADL)
  - Function in sport and recreation (Sports)
  - Knee-related quality of life (QoL)

* Lysholm et al, Acta Orthopaedica, 2007