CLINICAL TRIALS OVERVIEW OF AVAILABLE DATA

Clinical trials (Phase II and Phase III) conducted with M-ACI with spheroid technology

CODON
HUMAN CELL EXPERTS

PHASE II: Efficacy and safety study for different doses of M-ACI with spheroid technology[1]

Reference	Summary
Hoburg A, Niemeyer P, Laute V, Zinser W, John T, Becher C, Izadpanah K, Diehl P, Kolombe T, Fay J, Siebold R, Fickert S. *Safety and Efficacy of Matrix-Associated Autologous Chondrocyte Implantation With Spheroids for Patellofemoral or Tibiofemoral Defects: A 5-Year Follow-up of a Phase 2, Dose-Confirmation Trial*. Orthopaedic Journal of Sports Medicine. Jan 2022. doi:10.1177/23259671211053380	ACI using spheroids was safe and effective for defect sizes up to 10 cm² and showed maintenance of efficacy up to 5 years for all 3 doses that were investigated. The different defect locations (patella, trochlea, weightbearing part of the femoral condyles) and defect sizes showed comparable clinical improvement. Overall treatment failure rate until 5 years was 4%. Most treatment-related adverse events occurred within the first 12 months after implantation, with most frequent adverse reactions being joint effusion (n=71), arthralgia (n=14), and joint swelling (n=9).
Eschen C, Kaps C, Widuchowski W, Fickert S, Zinser W, Niemeyer P, Roel G. *Clinical outcome is significantly better with spheroid-based autologous chondrocyte implantation manufactured with more stringent cell culture criteria.* Osteoarthritis and Cartilage 2020. doi: 10.1016/j.ocarto.2020.100033	Cultivation time impacts clinical outcome. Shorter cultivation yields higher KOOS scores and responder rate; i.e. new specifications for Spherox in phase III 87.5% responders (ΔKOOS > 8 points) vs. 75% for all ACT3D after 12 months. Total ACI group with spheroid technology vs. MF shows non-inferiority; ACI subgroup with Spherox specifications vs. MF shows superiority.
Niemeyer P, Laute V, Zinser W, John T, Becher C, Diehl P, Kolombe T, Fay J, Siebold R, Fickert S. *Safety and efficacy of matrix-associated autologous chondrocyte implantation with spheroid technology is independent of spheroid dose after 4 years*. KSST 2020. Apr;28(4):1130-1143. doi: 10.1007/s00167-019-05786-8; PubMed PMID: 31897548	Significant improvement of KOOS across all treatment groups. No dose dependence. No difference between defect sizes. Comparable safety profile for all dose groups. SOC most often affected: musculoskeletal and connective tissue disorders.
Hoburg A, Löer I, Körsmeier K, Siebold R, Niemeyer P, Fickert S, Ruhnau K. *Matrix-Associated Autologous Chondrocyte Implantation Is an Effective Treatment at Midterm Follow-up in Adolescents and Young Adults.* Orthop J Sports Med. 2019 Apr 25;7(4). doi: 10.1177/2325967119841077. PubMed PMID: 31041335; PubMed Central PMCID: PMC6484242	Comparison of adolescents (range: 15 to 17 years) with young adults treated in phase II (range: 19 to 34 years). Comparable results with respect to all considered scores after minimum of 4 years. Low number of treatment failures in both groups (3% in adolescent and 5% in adult group).
Niemeyer P, Laute V, Zinser W, Becher C, Diehl P, Kolombe T, Fay J, Siebold R, Fickert S. *Clinical outcome and success rates of ACI for cartilage defects of the patella: a subgroup analysis from a controlled randomized clinical phase II trial (CODIS study)*. Arch Orthop Trauma Surg. 2020 Jun;140(6):717-725. doi: 10.1007/s00402-019-03264-x. PubMed PMID: 31451902	Non-inferiority of treatment of patella vs. femoral condyle proven. Similar improvement of all scores across the whole study period. Lasting results up to 5 years post treatment.
Becher C, Laute V, Fickert S, Zinser W, Niemeyer P, John T, Diehl P, Kolombe T, Siebold R, Fay J. *Safety of three different product doses in autologous chondrocyte implantation: results of a prospective, randomised, controlled trial.* J Orthop Surg Res. 2017 May 12;12(1):71. doi: 10.1186/s13018-017-0570-7. PubMed PMID: 28499391; PubMed Central PMCID: PMC5429514	Comparison of dose groups in phase II up to 3 years. No relevant dose difference in number of adverse events, affected patients, treatment-related adverse reactions, serious and severe adverse events. Most affected SOC: musculoskeletal and connective tissue disorders. Most common adverse reaction: arthralgia.
Niemeyer P, Laute V, John T, Becher C, Diehl P, Kolombe T, Fay J, Siebold R, Niks M, Fickert S, Zinser W. *The Effect of Cell Dose on the Early Magnetic Resonance Morphological Outcomes of Autologous Cell Implantation for Articular Cartilage Defects in the Knee: A Randomized Clinical Trial.* Am J Sports Med. 2016 Aug;44(8):2005-14. doi: 10.1177/0363546516646092. Epub 2016 May 20. PubMed PMID: 27206690	No statistically significant difference in MOCART scores between dose groups after 1 year. No dose dependence of adverse events. No correlation between structural (MOCART) and patient-reported end point (KOOS).

PHASE III: Comparator study of M-ACI with spheroid technology and microfracture[2]

Hoburg A, Niemeyer P, Laute V, Zinser W, Becher C, Kolombe T, Fay J, Pietsch S, Kuźma T, Widuchowski W, Fickert S. *Sustained superiority in KOOS subscores after matrix-associated chondrocyte implantation using spheroids compared to microfracture.* Knee Surg Sports Traumatol Arthrosc. 2022 Oct 21. doi: 10.1007/s00167-022-07194-x. Epub ahead of print. PMID: 36269383	Non-inferiority of M-ACI with spheroid technology vs. microfracture confirmed even after 5 years for overall KOOS and KOOS subscores. Superiority of M-ACI with spheroid technology shown for subscores „Quality of Life", „Activities of Daily Living" and „Sports and Recreation". Safety and efficacy proven after 5 years.
Hoburg A, Niemeyer P, Laute V, Zinser W, Becher C, Kolombe T, Fay J, Pietsch S, Kuźma T, Widuchowski W, Fickert S. *Matrix-Associated Autologous Chondrocyte Implantation with Spheroid Technology Is Superior to Arthroscopic Microfracture at 36 Months Regarding Activities of Daily Living and Sporting Activities after Treatment.* Cartilage 2020 Jan 1. doi: 10.1177/1947603519897290. PubMed PMID: 31893951	Non-inferiority of M-ACI with spheroid technology vs. microfracture proven for overall KOOS and KOOS subscores. Superiority of M-ACI with spheroid technology shown for subscores „Activities of Daily Living" and „Sport and Recreation" at 3 years. Comparable safety profile. Treatment failure rate (need for reoperation) for microfracture (4 of 49); none in M-ACI with spheroid technology.
Niemeyer P, Laute V, Zinser W, Becher C, Kolombe T, Fay J, Pietsch S, Kuźma T, Widuchowski W, Fickert S. *A Prospective, Randomized, Open-Label, Multicenter, Phase III Noninferiority Trial to Compare the Clinical Efficacy of Matrix-Associated Autologous Chondrocyte Implantation With Spheroid Technology Versus Arthroscopic Microfracture for Cartilage Defects of the Knee.* Orthop J Sports Med. 2019 Jul 10;7(7). doi: 10.1177/2325967119854442. eCollection 2019 Jul. PubMed PMID: 31317047; PubMed Central PMCID: PMC6620731	Non-inferiority of M-ACI with spheroid technology vs. microfracture shown. At 24 months superiority in KOOS subscore „Activities of Daily Living" for M-ACI with spheroid technology. Histologic analysis did not reveal significant differences between treatments but slightly better outcome of M-ACI with spheroid technology. Comparable safety profile.

(1) Prospective, randomised, open label, multicentre Phase II clinical trial to investigate the efficacy and safety of the treatment of large defects (4-10 cm²) with 3 different doses of the autologous chondrocyte transplantation product co.don chondrosphere® (ACT3D-CS) in subjects with cartilage defects of the knee. EudraCT Number: 2009-016816-20

(2) Prospective, randomised, open label, multicentre Phase III clinical trial to compare the efficacy and safety of the treatment with the autologous chondrocyte transplantation product co.don chondrosphere® (ACT3D-CS) with microfracture in subjects with cartilage defects of the knee with a defect size between 1 and 4 cm². EudraCT Number: 2009-016466-82