

1 Synopsis

Name of Sponsor/ Company: CO.DON AG	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: co.don chondrosphere®	Volume:	
Name of Active Ingredient: Spheroids of human autologous matrix-associated chondrocytes	Page:	
Title of Study: Prospective non-interventional investigation to evaluate the long-term safety and linked efficacy of the three-dimensional autologous chondrocyte implantation product in paediatric patients from 15 to less than 18 years of age treated with the product		
Principal or co-ordinating investigator: For complete list of participating investigators refer to Appendix 16.1.4.		
Study centre(s): A total of 26 centres in Germany were involved in the study. Details are provided in Appendix 16.1.4.		
Publication:		
Studied period (years): Date of first signed Informed Consent Form (ICF)/ date of first enrolment: 7 May 2015 Date of last follow-up/ date of last completed: 29 November 2019	Phase of development: Post-marketing surveillance /Non-interventional study	
Objectives: The first objective of this study was to assess the long-term safety and linked effectiveness of the 3-dimensional autologous chondrocyte implantation (ACT3D-CS) product co.don chondrosphere® in paediatric patients from 15 to <18 years of age at the time of implantation. One special interest was the incidence of treatment failure rate as defined in the paediatric investigation plan (PIP). Further objectives included the evaluation of quality of life (QoL) and treatment satisfaction judged by both the physicians and the patients. An additional separate comparative analysis of pooled data from the Phase II and Phase III studies of patients aged from 18 to less than 35 years treated with of the ACT3D-CS product co.don chondrosphere® was performed with the objective to compare the treatment effect in this adult population vs the treatment outcome in the paediatric population (patients from 15 to <18 years of age) of this		

study. Details of this analysis are provided in Appendix 16.1.5.

Methodology:

This was a non-interventional, open-label, multicentre surveillance study in paediatric patients from 15 to <18 years of age having undergone matrix-associated autologous chondrocyte implantation (ACI-M) with co.don chondrosphere[®]. Data were collected by physicians from medical records and after a physical examination visit in a subpopulation of at least 30 patients. Magnetic resonance imaging (MRI) have been performed within a time window of ± 3 months from the physical examination in this subpopulation for the purpose of magnetic resonance observation of cartilage repair tissue (MOCART) analysis. Patients were asked to complete web-based questionnaires at home once during the study period.

Number of patients (planned and analysed): A minimum of 80 patients were planned to be included, of which at least 30 patients with physical examination visits, from approx. 40 centres. A total of 105 patients from 26 centres were enrolled into the paediatric study and have been analysed, with 94 physical examination visits and thereof 79 MRI examinations.

Study population:

Male or female patients aged ≥ 15 years but <18 years at the time of implantation, who had undergone treatment with co.don chondrosphere[®], with the treatment administered between 1 and 8 years before enrolment into the study.

Test product, dose and mode of administration, batch number:

The marketed product co.don chondrosphere[®] was used for ACI-M. Treatment decisions and treatment details were at the discretion of the physicians and in accordance with the Summary of Product Characteristics (SmPC) for co.don chondrosphere[®].

Duration of treatment:

Patients enrolled in this study had undergone ACI-M between 1 and 8 years before enrolment into the study.

Criteria for evaluation:

Effectiveness:

Effectiveness and other evaluations:

- Demographic data (age, sex, height, weight)
- Medical history relevant for the treatment in the course of this study
- Diagnosis (as a basis for treatment)
- Treatment with co.don chondrosphere[®] (ACI-M)
- Surgical re-treatment(s) after ACI-M on the treated knee and relationship to ACI-M
- Patient questionnaires (Knee Injury and Osteoarthritis Outcome Score (KOOS), International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, IKDC Current Health Assessment Form, Modified Lysholm Knee Scoring)
- Patient satisfaction with treatment
- Subpopulation: physical examination and assessment of MRI results (MOCART analysis)

Safety:

Safety was assessed by evaluation of:

- Adverse events (AEs)/adverse reactions (ARs) and serious adverse events (SAEs)/serious adverse reactions (SARs) during or after biopsy as well as during and/or after implantation

Statistical methods:

All variables were analysed in an exploratory manner using descriptive statistical methods: number of patients/events, mean, standard deviation (SD), minimum, lower quartile, median, upper quartile, and maximum for continuous variables, and frequency distribution tables with number and percentage for categorical data.

Primary endpoint:

Treatment failure rate up to the time of the non-interventional study, defined as physician's decision that surgical re-treatment of the treated lesion was required, with re-treatment defined as surgical treatment of the originally treated cartilage lesion involving either extensive debridement for lesion expansion, violation of the subchondral bone, or (repeated) autologous chondrocyte implantation (ACI).

SUMMARY – CONCLUSIONS

The full analysis set (FAS) comprised 105 patients and the physical examination subpopulation comprised 94 patients (88.7%).

Demographic Characteristics and Medical History (at the Time of Implantation)

The ratio of males to females in the study population was almost balanced at 55 (52.4%) and 50 (47.6%), respectively. The age of the patients at implantation ranged from a minimum of 15 years to a maximum of 17 years; the mean (SD) age was 16.2 (0.8) years. The mean (SD) BMI and height at implantation was 23.0 (3.4) kg/m² and 174.8 (9.98) cm, respectively.

At implantation, the epiphyseal growth plate was classified as closed in 61 (58.1%) and open in 28 (26.7%) patients. The status of the epiphysis was not documented in 16 patients (15.2%). Mean (SD) follow-up time, defined as the interval between the date of implantation and date of follow-up visit as documented by the physician in the eCRF, was 52.2 (20.3) months.

In most patients, the right knee was the involved knee (59 [56.2%] patients). The mean (SD) duration of symptoms was 22.7 (25.1) months and ranged from a minimum of 1 month to a maximum of 132 months. The mechanism of injury was classified as 'traumatic sudden onset' in 49 (46.7%) patients, 'gradual onset' in 40 (38.1%) patients, and 'non-traumatic sudden onset' in 16 (15.2%) patients. The activity during which the injury occurred was 'sports' in most patients (56 [53.3%]). Cartilage lesion caused by trauma was the most common diagnosis (54 [51.4%] patients). The next most common diagnoses were osteochondritis dissecans (OD; 42 [40.0%] patients), other (8 [7.6] patients) and avascular necrosis (1 [1.0%] patient). The mean (SD) defected area size was 4.07 (1.95) cm² and ranged from a minimum of 0.75 cm² to a maximum of 12.00 cm².

Treatment with co.don chondrosphere[®]

The time between documentation of data as part of this paediatric study and the ACI-M with co.don chondrosphere[®] ranged between 1 and 8 years (mean 52.2 months). Open implantation was performed in 80 patients (76.2%) and arthroscopic implantation in 25 patients (23.8%). The mean co.don chondrosphere[®] dose was 33.5 (± 18.9) spheroids/cm². Concurrent surgeries during biopsy were documented in 40 (38.1%) patients. Concurrent surgeries during implantation were documented in 41 (39.0%) patients.

EFFECTIVENESS RESULTS:

Treatment Failure (FAS)

Overall, 25 (23.8%) patients received at least one additional surgery after ACI-M. Most of these additional surgeries were performed in patients with a 'close' epiphysis status (15 [14.3%] patients). Of the 25 patients who received additional surgery, 5 (4.8%) patients met the study criteria for treatment failure, including 2 (1.9%) patients with a 'close' epiphysis status, 2 (1.9%) patient with 'not documented' epiphysis status, and 1 (1.0%) patient with an 'open' epiphysis status. Only these 5 cases were related to ACI-M with co.don chondrosphere® and thus, considered as treatment failures. The overall treatment failure rate was 0.048. The overall mean (SD) time up to treatment failure in the 'close' epiphysis status subgroup was 46.6 (17.3) months, in the 'not documented' epiphysis status subgroup was 18 (8.8%) and in the 'open' epiphysis status subgroup was 53.9 (SD not calculated, because this group consists of 1 patient only) months.

Minor surgical treatment as part of the maintenance of the original repair procedure such as shaving or trimming of hypertrophic repair tissue (Table 14.2.3.5; Listing 16.2.2.4.4)→ 5 patients (4.8%) (but only three patients related to ACI-M).

Physical examination (PE subpopulation of the FAS)

Physical examination data were available for 94 of 105 FAS patients who agreed to a follow-up visit. These 94 patients represented the PE subpopulation of the FAS. For patients in the PE subpopulation, the right knee was the most examined knee (52 [55.3%] patients). The musculature of the treated leg was 'equal' in 70 (74.5%) patients. Most patients had no evidence of effusion (86 [91.5%]); patella pressure pain was experienced by 10 (10.6%) patients and there were no signs of patella maltracking in most patients (86 [91.5%]). Meniscus sign was observed in 57 (60.6%) patients, of which 53 (93.0%) and 56 (98.2%) patients had negatives signs for medial meniscus (IM) and lateral meniscus (AM), respectively. The mean passive and active motion ranges of the affected knee were normal.

IKDC Knee Examination (PE subpopulation of the FAS)

In the overall PE subpopulation, the final IKDC evaluation group grade was A (normal) in 47 (50.0%) patients, B (nearly normal) in 32 (34.0%) patients, D (severely abnormal) in 7 (7.4%) patients, and missing in 8 (8.5%) patients. All 7 patients who were assessed as IKDC evaluation group grade D had a 'close' epiphysis status.

MRI examination (PE subpopulation of the FAS)

An MRI examination was performed in 79 (84.0%) patients in the PE subpopulation. Defect repair and filling was complete in 47 (59.5%) patients. An MRI within a time window of ± 3 months of physical examination could be used for MOCART-Analysis. The mean (SD) MOCART score derived from the MRI results was 74.4 (16.7) and ranged from a minimum of 30 to a maximum of 100.

Patient-reported Outcomes

Patient-reported outcome data were available for 92 of 105 FAS patients.

Knee Injury and Osteoarthritis Outcome Score (KOOS)

The mean (SD) KOOS total score in the overall FAS population at follow-up was 78.13 (16.52). The highest mean (SD) KOOS subscale score for the overall FAS population was observed for activities of daily living (ADL; 91.54 [12.60]) followed by pain (86.23 [16.52]), symptoms (81.68 [16.22]), sports (70.0 [23.97]), and quality of life (QoL; 61.21 [24.03]).

The mean KOOS total scores in the subgroups by epiphyseal growth plate status were: 83.2 \pm

14.1 (open, n=28), 75.5 ± 18.2 (closed, n=61), and 79.4 ± 12.1 (not documented, n=16). Mean (SD) sports subscale score was notably higher in patients with ‘open’ (80.21 [19.48]) versus ‘close’ (65.75 [25.69]) epiphysis status.

IKDC Current Health Assessment Form (SF-36)

In the overall FAS population, the best health status was observed for the domain ‘role emotional’ (mean [SD] score: 86.2 [28.0]), followed by ‘social functioning’ (mean [SD] score: 85.8 [21.4]), ‘role physical’ (mean [SD] score: 84.0 [29.3]), ‘physical functioning’ (mean [SD] score: 81.8 [18.9]), and ‘bodily pain’ (mean [SD] score: 76.9 [20.5]). The domains with the lowest mean (SD) scores were ‘mental health’ (mean [SD] score: 76.0 [19.8]), ‘general health’ (mean [SD] score: 72.8 [18.9]), and ‘vitality’ (mean [SD] score: 67.0 [21.0]).

In the ‘open’ epiphysis status subgroup, the mean (SD) IKDC physical component summary (PCS) and mental component summary (MCS) scores were 54.8 (6.1) and 49.9 (11.7), respectively. In the ‘close’ epiphysis status subgroup, the mean (SD) IKDC physical component summary (PCS) and mental component summary (MCS) scores were 49.8 (8.8) and 51.2 (11.5), respectively. In the ‘not documented’ epiphysis status subgroup, the mean (SD) IKDC physical component summary (PCS) and mental component summary (MCS) scores were 51.7 (7.8) and 56.0 (4.4), respectively.

IKDC Subjective Knee Evaluation

In the overall FAS population, the mean (SD) total IKDC score at follow-up was 77.4 (17.1). The mean (SD) total IKDC score was highest in patients in the ‘open’ epiphysis status subgroup (83.8 [15.4]) versus the ‘close’ (74.3 [17.7]) and ‘not documented’ (78.3 [14.9]) epiphysis status subgroups.

Modified Lysholm Knee Scoring

The mean (SD) modified Lysholm knee scale score for the overall FAS population at follow-up was 20.5 (3.5) and ranged from a minimum of 10 to a maximum of 24. The mean (SD) modified Lysholm knee scale score was 21.0 (3.6) in the subgroup with ‘open’ epiphysis status, 20.1 (3.8) in the subgroup with ‘close’ epiphysis status and 20.9 (1.6) in the subgroup with ‘not documented’ epiphysis status.

SAFETY RESULTS:

In the overall FAS population, a total of 26 AEs were reported, of which 9 had an open epiphysis, 13 had a closed epiphysis, and 4 were not documented. By patient, 15 (14.3%) patients reported AEs, thereof 11 (10.5%) patients experienced non-serious AEs, and 5 (4.8%) patients experienced SAEs. One patient experienced both AEs and SAEs. In 1 (1.0%) patient, the AE was associated with biopsy until implantation; 2 (1.9%) patients experienced AEs during implantation, and 14 (13.0%) patients experienced AEs after implantation. Most AEs occurred post implantation (14 [13.3%] patients) in the SOC ‘musculoskeletal and connective tissue disorders’ (10 [9.5%] patients). Within the ‘musculoskeletal and connective tissue disorders’ SOC, the most commonly experienced AEs by preferred term was ‘arthralgia’ (3 [2.9%] patients). Overall, 1 patient (1.0%) experienced one SAE between biopsy and implantation; this SAE was in the ‘musculoskeletal and connective tissue disorder’ SOC and was classified as ‘joint effusion’. One patient (1.0%) experienced SAEs during implantation, including ‘meniscus injury’ (SOC ‘injury, poisoning and procedural complications’) and ‘arthralgia’ and ‘joint effusion’ (SOC ‘musculoskeletal and connective tissue disorders’). Four patients (3.8 %) experienced at least one SAE post implantation; 2 (1.9%) patients experienced SAEs in the SOC ‘Injury, poisoning and procedural complications’ (including ‘graft delamination’, ‘joint dislocation’ in 1 patient each), and 2 (1.9%) patients experienced SAEs in the SOC ‘musculoskeletal and connective tissue disorders’ (including ‘chondropathy’, ‘joint swelling’, ‘loose body in joint’ and ‘osteochondrosis’ in 1 patient each). One SAE in the SOC

‘blood and lymphatic disorders’, namely ‘bone marrow oedema’ was observed in 1 (1.0%) patient, and ‘administration site infection’ was seen in 1 (1.0%) patient (SOC ‘infections and infestations’).

In total, 81 ARs were reported, of which 10 had an open epiphysis, 49 had a closed epiphysis, and 22 were not documented. By patient, 27 (25.7 %) patients experienced ARs, 22 (21.0%) patients experienced non-serious ARs and 8 (7.6%) experienced SARs. Two patients experienced both ARs and SARs. In 18 (17.1%) patients an AR was experienced after implantation; 14 (13.3%) patients experienced ARs between biopsy and implantation, and 9 (8.6%) patients experienced ARs during implantation. No serious ARs (SARs) were reported between biopsy and implantation or during implantation. Eight (7.6%) patients experienced at least one SAR post implantation. Five (4.8%) patients experienced SARs in the SOC ‘injury, poisoning and procedural complications’ (including ‘transplant failure’ in all 5 patients, and ‘graft loss’, ‘cartilage injury’ and ‘meniscus injury’ in 1 patient – the latter 2 SARs occurring in the same patient). Four (3.8%) patients experienced SARs in the SOC ‘musculoskeletal and connective tissue disorders’ (including ‘joint swelling in 2 (1.9%) patients, and ‘joint effusion’, loose body in joint’ and ‘osteochondrosis’ in one patient each). Three (2.9%) patients experienced ARs in the SOC ‘general disorders and administration site conditions’ including ‘pain’ in 2 (1.9%) patients and ‘implant site hypertrophy’ in 1(1.0) patient. One patient had a SAR in the SOC ‘infections and infestations’, namely ‘administration site infection’.

CONCLUSIONS:

Treatment of knee cartilage lesions in patients aged 15 to <18 years with co.don chondrosphere[®] was associated with a low treatment failure rate and positive patient reported outcomes in this study. No new or unexpected long-term safety signals were identified in this patient population.

Date of the report: 18 May 2020

