Clinical Trial – Final Report Including Follow-up

Prospective, randomised, open-label, multicentre Phase II clinical trial to investigate the efficacy and safety of the treatment of large defects (4–10 cm^2) with 3 different doses of the autologous chondrocyte implantation product chondrosphere® (ACT3D-CS) in subjects with cartilage defects of the knee

Investigational product:	Spherox (ACT3D-CS/chondrosphere)
Indication	Cartilage defects of the knee
Sponsor	**CO.DON AG** Warthestraße 21 14513 Teltow, Germany Telephone: +49 (0)3328 - 4346-0 Telefax: +49 (0)3328 - 4346-43 Web site: www.codon.de
Protocol no.:	cod16HS14
EudraCT no.:	2009-016816-20
Phase of development:	II
Study period:	Beginning of study: 21st. November 2010 (first patient's consent) End of study: 31st. March 2018 (database lock for 5-year follow-up period)

Sponsor's contact person:	Sponsor's signatory:
xxx VP, Global Scientific Portfolio Development	xxx Director of Clinical Research
Telephone: +49 (0) 30 - 240 352 xxx Telefax: +49 (0) 30 - 240 352 309 E-mail: xxx@codon.de	Telephone: +49 (0) 30 - 240 352 xxx Telefax: +49 (0) 30 - 240 352 309 E-mail: xxx@codon.de

This clinical trial, including archiving of relevant documents, was conducted in compliance with Good Clinical Practice (GCP) and with all applicable laws and regulations.

2. SYNOPSIS

Name of Sponsor/Company: CO.DON AG Warthestr. 21 14513 Teltow, Germany	Individual Study Table Referring to Part of the Dossier Volume Page	*(For National Authority Use only)*
Name of Finished Product: Spherox/ACT3D-CS/chondrosphere		
Name of Active Ingredient: Spheroids of human autologous matrix-associated chondrocytes		

Study title

Prospective, randomised, open-label, multicentre Phase II clinical trial to investigate the efficacy and safety of the treatment of large defects (4–10 cm^2) with 3 different doses of the autologous chondrocyte implantation product chondrosphere® (ACT3D-CS) in subjects with cartilage defects of the knee

Indication

Cartilage defects of the knee

Co-ordinating Investigator

xxx

Study centres

- Orthopädisch-Unfallchirurgisches Zentrum, Universitätsmedizin Mannheim, Theodor-Kutzer-Ufer 1-3. 68167 Mannheim
- DRK Kliniken Westend, Klinik für Unfallchirurgie und Orthopädie, Spandauer Damm 130, 14050 Berlin
- St. Vinzenz-Hospital, Orthopädie und Unfallchirurgie, Dr.-Otto-Seidel-Str. 31-33, 46535 Dinslaken
- Orthopädische Klinik der Medizinischen Hochschule Annastift, Anna-von-Borries-Str. 1-7, 30625 Hannover
- Lubinus Clinicum Kiel, Unfall- und arthroskopische Chirurgie, Sporttraumatologie, Steenbeker Weg 25, 24106 Kiel
- DRK Krankenhaus Luckenwalde, Unfall- und Wiederherstellungschirurgie, Saarstr. 1, 14943 Luckenwalde
- Orthopädiezentrum München Ost, Orthopädie und Unfallchirurgie, Kellerstr. 8, 85567 Grafing
- Gelenk- und Wirbelsäulenzentrum Steglitz, Kieler Str. 1, 12163 Berlin
- Internationales Zentrum für Hüft-, Knie, Fußchirurgie (HKF) in der ATOS Klinik, Bismarkstr. 9-15, 69115 Heidelberg
- Department Orthopädie und Traumatilogie, Universitätsklinikum der Albert-Ludwigs-Universität Freiburg, Hugstetter Str. 55, 79106 Freiburg

Test substance

Product ACT3D-CS = autologous chondrocyte product chondrosphere, administered at one of three dose levels according to the extent of the defect: 3–7 ***OR*** 10–30 ***OR*** 40–70 spheroids/cm^2.

[Note: In order to fulfil requirements for the name of the drug product for marketing authorisation, CO.DON AG submitted the name “Spherox” to the Name Review Group. In April 2017 the name was accepted. The product was originally named co.don chondrosphere in the study protocol and the relevant study documents. In this report the term “chondrosphere” is retained.]

Duration of the study for each patient

From screening to implantation: ca. 2–3 months

From implantation to Visit 4 (final analysis): 12 months

From implantation to last follow-up visit: 5 years.

Objectives

Assessment of the short-term and long-term efficacy and safety of 3 different doses of the three-dimensional autologous chondrocyte implantation product Spherox/chondrosphere for the treatment of cartilage defects (4–10 cm^2) of knee joints.

Methods

Autologous chondrocyte implantation (ACT) is based on the harvesting of the patient's own chondrocytes isolated from healthy cartilage, their culture *in vitro* and their subsequent implantation into the cartilage defect. chondrosphere is cultured and implanted as three-dimensional spheroids (Spherox/chondrosphere).

Number of subjects planned and analysed

Planned: 75 patients (25 per treatment group), with approximately 100 patients screened.

Analysed: 75 patients in final assessment (12 months after implantation of chondrosphere).

Criteria for evaluation

Primary efficacy variable: Change of overall KOOS (Knee Injury and Osteoarthritis Outcome Score) from baseline (Day 0) to final assessment at Visit 4 (12 months after implantation), determined for each dose group and between the dose groups. This is performed with the intention-to-treat population. Further assessments are at Visit 1 (6 weeks), Visit 2 (3 months) and Visit 3 (6 months) and follow-up Visits 5–9 (18, 24, 36, 48 and 60 months) after implantation.

Secondary efficacy variables include related changes in KOOS (e.g. for different time intervals), magnetic-resonance assessment variables, MOCART (magnetic resonance observation of cartilage repair tissue; after 3, 12, 18, 24, 36, 48 and 60 months), Bern score, Lysholm score, and International Cartilage Repair Society rating (histological and immunochemical scoring after re-biopsy 12 months after implantation).

Safety variables are adverse events, vital signs including electrocardiography, physical examination, concomitant pain medication and laboratory values.

Health-economic variables were recorded but are not evaluated in the present report.

Statistical methods

The primary analysis was performed according to a prospectively defined hierarchical scheme: First the primary efficacy variable at final assessment was compared with its baseline value for the high-dose group, next the same comparison was made for the medium-dose group and next the same for the low-dose group. Finally, an exploratory between-group comparison was performed.

Secondary analyses were performed, at descriptive level, in an analogous manner where the structure of the variable allowed this; in other cases, appropriate descriptive statistics were provided.

Safety was analysed by tabulation of adverse events (numbers of reports and numbers/percentages of patients affected) and by presenting descriptive statistics for vital signs, body weight and body mass index, and standard laboratory variables.

Results: Demography, baseline and treatment compliance

The dose groups were well balanced in respect of size, and demography and disease background; minor imbalances (patients' sex; smoking habit) were not considered relevant. The analysis population comprised 75 patients (22 women, 53 men) aged 34 ± 9 years. Medical history at baseline was unremarkable except for a greater number of patients with a history or presence of 'infections and infestations' in the medium-dose group. Defect sizes ranged from 2 to 10 cm^2. Primary defect locations were mostly the patella (47/75) or the femur (28/75); the tibia was not represented. Any additional defects were treated, and their results recorded, if they were at the same location. ICRS (International Cartilage & Joint Preservation Repair Society) grades were mostly III C or IV A, and were fairly evenly distributed between the treatment groups.

Apart from the administration of lower doses than envisaged to seven several patients in the high-dose group, compliance with study treatment and with the subsequent rehabilitation measures was good.

Results: Efficacy

In the primary analysis, the primary variable 'overall KOOS' for the intention-to-treat population showed a statistically significant improvement, compared with baseline, in all three within-group analyses (for the high-, medium- and low-dose group respectively $p = 0.0005$, <0.0001 and 0.0002 was assessed one year after study treatment. The corresponding difference remained highly significant thereafter (0.0054, <0.0001 and 0.0002 respectively after two years and without notable further change after three, four and five years). For 'all dose groups' the mean overall KOOS rose in the first year after treatment from 57.0 to 73.4 on a scale from 0 (worst) to 100 (best) and continued to rise slightly, reaching 74.6 after 18 months, 73.8 after two years, 77.0 after three years, 77.1 after four years and 76.9 after five years. Changes within each dose group were of similar magnitude, and the between-group (pairwise) analyses did not reveal any statistically significant differences between the dose groups. The 18-month, 2-year, 3-year, 4-year and 5-year analyses showed approximately stable values, with a continued improvement in overall KOOS in the low- and medium-dose groups and a small decrease in the high-dose group up to two years after treatment and stable values in the third, fourth and fifth years.

At the 12-month (final) assessment, KOOS subscores also generally showed strong within-group improvements – mostly with $p < 0.05$ – while between-group comparisons did not show any significant difference. The strongest overall improvements after 12 months were for 'knee-related quality of life', 'function in sport and recreation' and 'pain', improving by 23, 17 and 16 points respectively (likewise on a scale from 0–100), with 'function in daily living' improving by 12 and 'other symptoms' by 13 points. All these within-group comparisons gave $p < 0.05$. Corresponding comparisons in which the reference point was Day 0′ (day before implantation) rather than baseline gave a result similar to the corresponding comparisons based on Day 0. At the 24-month assessment, the corresponding results were hardly changed: 'knee-related quality of life' had improved by 25 points, while the other subscores remained unchanged. The overall KOOS and the subscores 'function in sport and recreation' as well as 'knee-related quality of life' continued to improve slightly between the 24- and 36-month visits (3–7 percentage points) and remained constant thereafter. For the subscores 'pain', 'other symptoms' and 'function in daily living' no further improvement was seen, but stable values were reported at the 36-month, 48-month and 60-month assessments.

All KOOS-related variables showed an initial worsening of the patient's condition after implantation (possible exception: 'pain' because of analgesic medication), with a lowest value at Visit 1 (6 weeks after implantation), and a subsequent rise indicating a small improvement at Visit 2 (3 months after implantation), a further improvement in almost all cases between Visits 3 (6 months) and 4 (12 months). The 18-month and 24-month analyses (Visits 5 and 6) revealed generally stable means of the subscores for the three dose groups; small decreases noted in the subscores for the high-dose group against the background of high scatter (standard deviations) did not appear clinically or otherwise relevant. The 36-month (Visit 7) and 48-month (Visit 8) assessments revealed small improvements in most of the KOOS-related variables, which were maintained at the 60-month assessment (Visit 9).

MOCART could not be assessed before study treatment, but initial values – in view of the patients' clinical condition – can be regarded as having been close to the value 0. From the 3-month visit (Visit 2) to the 12-month visit (Visit 4) MOCART showed improvements, with a slight dose dependence, and a further improvement was seen thereafter, though without dose dependence. The mean MOCART total scores – on a scale from 0 (worst) to 100 (best) – at 3 months (Visit 2) were

59.8, 64.5 and 64.7 for the low-dose, medium-dose and high-dose group respectively, and 62.9 for 'all patients'; at 12 months (Visit 4) these were 74.1, 74.5 and 68.8 for the respective dose groups and 72.4 for 'all patients'. [At Visit 4, several MOCART items ('Surface of the repair tissue', 'Structure of the repair tissue', 'Signal intensity of the repair tissue', 'Subchondral bone' and 'Effusion/Synovitis') showed a more rapid response with the medium and high chondrosphere doses than with the low dose, implying a potential dose relationship.] At 18, 24, 36, 48 and 60 months after study treatment (Visits 5–9) the improvement was maintained: respective dose-group scores at Visit 6 were 72.2, 76.0 and 71.2, and 73.3 overall, while at Visit 7 these were 72.8, 79.6, 72.6 and 75.2 overall, at Visit 8 73.9, 78.0, 74.3 and 75.5 overall, and at Visit 9 75.0, 76.4, 73.6 and 75.1 overall.

In the IKDC (International Knee Documentation Committee) Knee Examination Form overall score, 35 patients showed improvement, 33 showed no change and 4 showed worsening at Visit 4 (12 months) compared with baseline. At Visit 6 (24 months) very similar results were found: improvement in 34 patients, no change in 35 patients, worsening in 4 patients. At Visit 7 (36 months) corresponding totals were 37, 33 and 3 patients, at Visit 8 (48 months) they were 36, 33 and 4 patients, and Visit 9 (60 months) they were also 36, 33 and 4 patients. In each dose group the result was similar at Visit 4 (12 months); at Visit 6 (24 months) levels were comparable, with very slight improvements in the low- and medium-dose groups and a very slight worsening compared with Visit 4 (12 months) in the high-dose group; no noteworthy further change occurred up to Visits 7–9 (36–60 months). Subscores, and also results from the IKDC Current Health Assessment Form, the IKDC subjective knee evaluation form and the modified Lysholm score, revealed several differences with $p < 0.05$ for within-group comparisons between Visit 4 (12 months) and baseline (pre-arthroscopy visit), but without any clear general trend regarding differences between the dose groups. The scores remained largely constant from Visit 4 (12 months) to Visit 9 (60 months).

Arthroscopic assessment of cartilage repair at Visit 4 (12 months) for a subset of eight patients gave the result 'normal' or 'nearly normal' in six cases and 'abnormal' in two; none were 'severely abnormal'.

Results: Safety

There were no fatal adverse events in this trial; four life-threatening events (one cerebrovascular accident and three in connection with a bicycle accident) occurred between 3 and 4 years after study treatment and were assessed as being unrelated to the study treatment. In the first year after treatment, two serious adverse events (convulsions and arthralgia) were judged unrelated to the study treatment. Five serious adverse events possibly or probably related to the treatment were as follows: two episodes of osteochondral injury (osteochondrosis and osteonecrosis in the same patient (high-dose group, probably related) in the second year, cartilage hypertrophy and arthralgia (low-dose group, probably related) in the third year and extraskeletal ossification (high-dose group, probably related) in the fourth year.

Furthermore, serious adverse events unrelated to the treatment, or unlikely to be related to it, were recorded as follows: in the first year 2 events (convulsions, chondromalacia); in the second year, 7 (syncope, chondropathy, haemorrhoids, uterine cysts, osteoarthritis, chondrocalcinosis, umbilical hernia, meniscus injury); in the third year, 2 (chondropathy, bladder cancer); in the fourth year, 8 (cerebrovascular accident, skull fracture, optic nerve injury and subdural haematoma, anal prolapse, intervertebral disc protrusion, chondropathy, patella fracture); in the fifth year, 3 (angina pectoris, myocarditis, chondromalacia, cartilage graft).

Two adverse events led to the withdrawal of patients from the study.

In summary, adverse events were as follows (numbers of patients are shown, except in the bottom block; m = months):

Dose group:	**Low** *N* = 25		**Medium** *N* = 25		**High** *N* = 25		**All** *N* = 75	
Time after treatment:	12m	60m	12m	60m	12m	60m	12m	60m
Any adverse event	19	23	22	24	22	23	63	70
Any treatment-related adverse event	16	17	22	24	21	22	59	63
Any adverse event leading to withdrawal	–	–	–	–	1	2	1	2

Any severe adverse event	–	3	1	3	1	6	2	12
Any life-threatening adverse event	–	1	–	–	–	1	–	2
Any serious adverse event	1	7	–	5	1	8	2	20
Number of events	47	106	41	93	52	149	140	348
Number of treatment-related events	26	37	30	46	29	44	85	127

Most of the patients in all dose groups reported at least one adverse event. At the 12-month assessment the numbers of reports had no clear relationship with dose level (see table above). At the 24-month, 36-month, 48-month and 60-month assessments there were rather more adverse events in the high-dose group; however, the incidence of treatment-related adverse events was not greater in this group compared with the other groups. Adverse events in the System Organ Class (SOC) 'musculoskeletal and connective-tissue disorders' were the most frequent, especially joint effusion; this is regarded as being related to the surgical procedure. Almost all cases of joint effusion occurred within the first year after study treatment. Adverse events in other SOCs were less frequent, most occurring only once. No dose relationship could be observed regarding onset, duration or severity of adverse events.

The laboratory measurements (haematology and clinical chemistry), the assessments of vital signs, the electrocardiography, the measurements of body weight and the recorded concomitant medications gave no indication of any unwanted effect of the trial treatment, while the patients' use of pain medication at Visit 2 (12 weeks after implantation) and thereafter was consistent with a long-term advantage of the treatment in all treatment groups.

Conclusions

The within-group efficacy analyses showed a clear improvement in the patients' condition in each dose group from baseline to the 12-month post-treatment examination. This improvement was maintained over the follow-up period, which extended over a total of 5 years following the implantation procedure Between-group comparisons did not show any dose-dependent difference between the effects of the various doses of chondrosphere administered. In the second year after study treatment, most efficacy variables showed a maintenance of the improvement attained in the first year in the low-dose and medium-dose groups, while there was a slight worsening in overall KOOS 24 months after treatment compared with the 12-month assessment in the high-dose group only; this worsening was of doubtful clinical significance and in the context of the high scatter of results may have no relevance. In the third year of the study most efficacy variables showed a small improvement compared with at the 24-month follow-up examination. Thus, the results of the 36-month analysis supported those of the earlier analyses. The per-protocol analysis supported the results of the intention-to-treat analysis at all time points (12, 24 and 36 months after implantation), despite the inevitable steady reduction in the size of the per-protocol population. The results of the 48-month and 60-month analyses supported those of the 36-month analysis.

The adverse event 'joint effusion' was frequent in all dose groups and included one possibly and one probably treatment-related severe event. In the first two years of the study one patient suffered from osteochondrosis and osteonecrosis, which were considered probably treatment-related; in the third year two patients also experienced chondropathy, one considered unrelated and one unlikely to the related to the study treatment. An episode of cartilage hypertrophy with arthralgia and a case of extraskeletal ossification in the affected joint during (respectively) the third and fourth years after treatment were considered to be probably treatment-related. Other safety analyses, including the follow-up assessments over 5 years, showed no unwanted effects of the study treatment.

The study thus provides a strong indication that the chondrosphere is efficacious for large cartilage defects (4–10 cm^2) at various locations in the knee (femur, patella) in the short and long term. A significant and sustained improvement in overall KOOS and each of the KOOS subscores was seen, for all dose groups and overall, between baseline and the 12-month post-treatment examination, and the improvement was maintained stably over the five-year observation period. The standard dose specification frame of 10–70 spheroids/cm^2 is supported by the results of this study.

DATE OF REPORT: October 12th. 2018