Non-interventional Study Protocol

Study No. cod16 HS17 paediatric

Title	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 until December 2011.
Protocol version	1.0
Date of last version of protocol	9th October 2014
Active substance	Spheroids of human autologous matrix-associated chondrocytes
Medicinal product	co.don chondrosphere®
Product reference	German approval no. PEI.A.11507.01.1
PIP procedure number	EMEA-001264-PIP01-12
Marketing authorization holder(s)	co.don® AG Warthestr.21 D-14513 Teltow
Joint PASS	No
Research question and objectives	Evaluation of the long-term safety and linked efficacy of co.don chondrosphere® implantation in paediatric patients
Country(-ies) of study	Germany
Author	René Haußmann

Protocol authorization form

Title: **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 until December 2011.**

Study number: **cod16 HS 17 paed**

Version: 1.0 **Date:** 9th October 2014

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2 LIST OF ABBREVIATIONS

2D	Two-dimensional
3D	Three-dimensional
ACI	Autologous chondrocyte implantation
ACI-M	Matrix-associated autologous chondrocyte implantation
ACT	Autologous chondrocyte transplantation
ACT3D	Autologous chondrocyte transplantation with a 3-dimensional chondrocyte product
ADR	Adverse drug reaction
AE	Adverse event
BMI	Body Mass Index
eCRF	Electronic case report form
CRO	Contract research organization
EC	European Commission
EDC	Electronic data capture
e.g.	for example (Exempli gratia)
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GVP	Good Pharmacovigilance Practice
ICH	International Conference on Harmonization
ICRS	International Cartilage Repair Society
IKDC	International Knee Documentation Committee
KOOS	Knee injury and Osteoarthritis Outcome Score
MedDRA	Medical dictionary for regulatory activities
MOCART	Magnetic Resonance Observation of Cartilage Repair Tissue
MRI	Magnetic Resonance Imaging
NaCl	Sodium Chloride
NSAID	Non-steroidal anti-inflammatory drug
PASS	Post-authorization safety study
PEI	Paul-Ehrlich-Institute
PDCO	Paediatric Committee of the EMA
PIP	Paediatric Investigation Plan
QoL	Quality of Life
QPPV	Qualified Person for Pharmacovigilance (EU)
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SPC	Summary of product characteristics
SUSAR	Suspected unexpected serious adverse reaction

3 RESPONSIBLE PARTIES

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4 ABSTRACT

Title 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 until December 2011 (cod16 HS 17 paediatric; version: 1.0; date: 9th October 2014)

Rationale and background: co.don chondrosphere® is produced from human autologous chondrocyte-spheroids and is used for transplantation into cartilage defects of joints. co.don chondrosphere® is available on the German market since 2004. In 2012 co.don has applied for centralized Marketing Authorisation to the European Medicines Agency (EMA). Following Directive 2006/1901 the development auf co.don chondrosphere® in paediatric population was discussed with the paediatric committee (PDCO) and a paediatric investigation plan (PIP) was developed and determined by the PDCO. In the context of a PIP, the company is now gathering further safety and linked efficacy data of paediatric patients who have been treated with co.don chondrosphere® until 2011. Initial data show good clinical results and document the safety of using co.don chondrosphere® to treat patients below the age of 18 years of age [P1].

Research question and objectives: The overall research goal is to assess the long-term safety and linked efficacy of the three-dimensional autologous chondrocyte implantation product co.don chondrosphere® (ACI-M) in paediatric patients from 15 to less than 18 years of age at the time of implantation. Primary safety parameter is treatment failure rate defined by PDCO [P1].

Study design: This is a company-sponsored national, open-label, multicentre, non-interventional study in a cohort of adolescence outpatients combining retrospective data collection and current evaluation of health status by physical examination and validated patient and physician's questionnaires.

Population: At least 80 adult male or female patients having co.don chondrosphere® implantation in the knee joint at the age of 15 to less than 18 years until the year 2011 will be enrolled by their treating physicians. A subgroup of 30 patients will undergo physical examination.

Inclusion criteria

Patients who meet the following criteria can be considered for inclusion into the study:

- Male or female patients being at least 15 but less than 18 years of age at the time of implantation
- Treatment with co.don chondrosphere® until December 2011
- Treatment was conducted max. 8 years before enrolment
- Written informed consent has been obtained.

Exclusion criteria

There are no specific exclusion criteria in this non-interventional study.

Study duration for patients: It is planned that at least 80 study participants will complete a web-based questionnaire at one time point between approximately 3 (until December 2011) and eight years after treatment.

Dosage, treatment regimen, route of administration: not applicable. Patients were treated until December 2011 with standard procedure for ACI-M at each site.

Variables: Documented variables include demography, information on ACT3D, incidence of treatment failure, patient reported outcomes, current health status, quality of life, MRI, if applicable, and adverse events.

Data sources: The participating physician will collect demographic and clinical characteristics from medical records and data from physical examination including MRI from a subgroup of patients will be evaluated. Additionally, patients are asked to complete a standardized web-based data collection form comprising the validated questionnaires KOOS (knee injury and osteoarthritis outcome score), modified Lysholm Knee Scoring and the IKDC subjective knee evaluation form.

Study size: About 80 patients who were transplanted until December 2011 will be contacted by participating physicians, of theses 80 patients all should be complete the questionnaires. From a subgroup of at least 30 patients a physical examination of the treated knee and an assessment of the chondral structure by MRI are requested.

Data analysis: Statistical analyses will be exploratory using descriptive statistics. The primary endpoint is the treatment failure rate up to the time point of survey of the non-interventional study.

Milestones:

Start of data collection:	Q1 / 2015
End of data collection:	Q4 / 2015
Data base lock:	Q2 / 2016
Final report of study results:	Q4 / 2016

5 AMENDMENTS AND UPDATES

None.

6 MILESTONES

Table 1 Key study milestones and planned dates of completion

Milestone	Date
Start of data collection[a]	Q1 / 2015
End of data collection[b]	Q4 / 2015
Database lock	Q2 / 2016
Final report of study results	Q4 / 2016

[a] The date from which information on the first study subject is first recorded in the study dataset.
[b] Date from which the analytical data set is completely available.

No study progress reports and no interim reports are planned.

7 RATIONALE AND BACKGROUND

co.don chondrosphere® are spheroids of human autologous matrix-associated chondrocytes for implantation suspended in isotonic sodium chloride solution and is used for implantation into cartilage defects of joints. The spheroids are spherical aggregates of *ex vivo* expanded human autologous chondrocytes with self-synthesized extracellular matrix.

co.don chondrosphere® is a 3-dimensional chondrocyte product (ACT3D) which is intended exclusive for use in a matrix-associated autologous chondrocyte implantation (ACI-M). ACI-M is an established two-step procedure for the treatment of full-thickness cartilage defects of the knee. Cartilage harvest from the affected knee joint by biopsy represents the first step of this procedure and is essential for further in vitro expansion of autologous chondrocytes by co.don®. In a second step the autologues chondrocytes are implanted in the affected knee by an experencied surgeon.

Articular chondral and osteochondral injuries in joints are common in people below the age of 35 years being active in sports. Symptomatic lesions left untreated may lead to chronic pain and functional disability [1]. In children and adolescents the main causes for cartilage defects in the knee include acute traumatic injuries. Non-operative measures, i.e. physical measures and pharmacologic treatment of small lesions in young children are reasonable treatment options. In contrast, a relatively large lesion in an adolescent approaching maturity and with closed epiphysis, may require surgical intervention such as ACT3D [P1].

Another indication for ACT3D is Osteochondritis dissecans (OCD). OCD is an acquired idiopathic lesion of subchondral bone resulting in delamination and sequestration with or without articular cartilage involvement and instability [2]. OCD is a relatively rare lesion amongst the population as a whole, with a prevalence of between 0.01% and 0.06% [3] and often presents in children and adolescents in connection with competitive sports activities [4].

Patients less than 18 years of age with closed epiphyseal growth plate are biologically adults as far as treatment of their joints is concerned [5]. In general, the cartilage regeneration capacity of young adults (below age of 30 years) using ACT is higher than observed in older patients [6]. A differentiation of young adults above and below 18 years of age is transposing a legal age limit into an artificial medical age limit.

From the beginning of marketing of co.don chondrosphere® in Germany in 2004 until 04/2012 more than 3250 patients were treated with co.don chondrosphere®. Most of them were treated at the knee joint (about 94%). Several "young" patients have been treated with the spheroids. 473 patients had an age of between 18 and 30. 158 patients were under 18 years of age at the time of treatment. These are approximately 5% of the total number of treated patients. According to the current SmPC [Annex 1] administration of co.don chondrosphere® is indicated for adults and adolescents with closed epiphyseal growth plate.
The administration to patients with open epiphyseal growth plate has to be considered as off-label use.

To date clinical data in paediatric patients treated with co.don chondrosphere® are available from one retrospective case series with 29 adolescents (including 6 patients with closed epiphyseal growth plate) and 4 case studies including further adolescent patients (in total 36 patients). The ACT3D was judged by the physicians as being "suitable" for all patients during each time interval. These clinical results strongly indicate that particularly observations obtained in the younger age groups between 14 and 18 years of age at the time point of transplantation can be extrapolated to the adolescent patient group. [P1].

In 2012 co.don has applied for EU marketing authorisation of co.don chondrosphere® to the European Medicines Agency (EMA). In the context of a paediatric investigation plan (PIP) [P1] the company is now gathering further data on young people who have already been treated with co.don chondrosphere®.

Out of >3000 patients treated with co.don chondrosphere® until the end of 2011, about 80 patients meet the inclusion criteria as defined in the PIP [P1].

The main considerations regarding the treatment of cartilage defects in adolescents are possible special features of the young patients, such as reaction to physical stress or different expectations for long term quality of life [P1]. To investigate these aspects a survey of all identified patients (80 patients) treated at the age of 15 to less than 18 years will be used to collect patient reported outcomes as well as data regarding their physical status and chondroidal structure of the knee joint for a subgroup of 30 patients that undergo physical examination including MRI, if applicable.

Background on questionnaires, scoring scales and techniques used in this study

Patients participating in this study will be asked to complete a web-based data collection form composed of - among other questions - the validated questionnaires KOOS, IKDC Subjective Knee Evaluation Form and modified Lysholm Scoring. Self-completed questionnaires have the obvious practical advantage of quick and easy completion in any setting without the need for clinical staff to be in attendance.

KOOS

The KOOS (Knee injury and Osteoarthritis Outcome Score) was developed in the 1990s as an instrument to assess the patient's opinion about their knee and associated problems. Since the first publication in 1998, the psychometric properties of the KOOS have been assessed in more than twenty individual studies from all over the world in patients from 13-79 years of age. Furthermore, KOOS has been evaluated and compared to other instruments in several reviews [7-14].

KOOS consists of 5 subscales: Pain, other Symptoms, Function in daily living (ADL), Function in sport and recreation (Sport/Rec) and knee related Quality of life (QOL). The previous week is the time period considered as the week before answering the KOOS. Standardized answer options are given (5 Likert boxes) and each question is assigned a score from 0 to 4. A normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) is calculated for each subscale.

KOOS is a self-explanatory, patient-administered questionnaire.

IKDC and IKDC Subjective Knee Evaluation Form

The International Knee Documentation Committee (IKDC) was established to unify the assessment of outcomes by developing a standardized international knee form. The original IKDC form included only the minimum essential criteria necessary to evaluate results [15], while the new IKDC Subjective Knee Evaluation Form (Subjective Knee Form), is well tested and found to be a valid and reliable instrument [16,17] that can be used to assess symptoms, function, and sports activity in patients with a variety of knee disorders.

The IKDC Subjective Knee Form consists of 18 questions in the domains of symptoms, functioning during activity of daily living and sports, current function of the knee, and participation in work and sports.

Modified Lysholm Knee Scoring

The Lysholm score, which measure the patient's perceptions of function [18], is commonly used to document outcomes after ACI. The Lysholm score is based on eight domains: limp, locking, pain, stair-climbing, support, instability, swelling, and squatting.
By removing the swelling item and using unweighted scores, a modified version of the Lysholm Knee Scoring according to Smith et al. (2008) has been recommended as an outcome measure for knee chondral damage. The scores range from 0 to 24.

MRI and MOCART score

Magnetic resonance imaging (MRI) is generally the imaging technique of choice for cartilage surfaces [19]. The main advantages of MRI for cartilage imaging are not only its non-invasiveness, but also its reproducibility and accuracy by using standardized imaging protocols.

The MOCART scoring systems (Magnetic Resonance Observation of Cartilage Repair Tissue) includes nine variables for the accurate description of cartilage repair tissue with high correlation to the clinical and arthroscopic outcome of the procedures [20]. Available MRI results in the current study will be evaluated by the participating physicians according to the MOCART scoring system.

8 RESEARCH QUESTION AND OBJECTIVES

Objectives

The objective of this study is to assess the long-term safety and linked efficacy of the three-dimensional autologous chondrocyte implantation product co.don chondrosphere® in paediatric patients from 15 to less than 18 years of age at time of implantation. One special interest is the incidence of treatment failure rate as defined in the PIP [P1]. Further objectives are the evaluation of quality of life and treatment satisfaction judged by both, physicians and patients.

9 RESEARCH METHODS

Study design

9.1.1 Overall study design and rationale for the chosen design

This is a non-interventional, open-label, multicentre surveillance study in patients having undergone ACI-M until December 2011with co.don chondrosphere® at the age of 15 to less than 18 years of age and treatment is conducted max. 8 years before enrolment.

A developed Paediatric Investigational Plan (PIP) is a prerequisite for European Marketing Authorisation application of the drug product. After approving of the PIP by the responsible institution, the Paediatric Committee (PDCO), this PIP has to be fulfilled in order to maintain the EU-Marketing Authorisation. If changes from the agreed paediatric investigational plan arise co.don has to apply for modification of the PIP. Therefore, this investigation uses a combination of retrospective data collection, patient reported outcomes (survey) and collection of follow-up data to assess long-term outcomes of patients treated in the past.

9.1.2 Primary endpoint

Primary endpoint (as defined in the PIP):

- Treatment failure rate up to the time point 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 that involved either extensive debridement for lesion expansion, or violation of the subchondral bone, or ACI

9.1.3 Secondary endpoint(s)

Secondary endpoints with times of assessment (as defined in the PIP):

For all patients:

- Incidence of surgical treatments to the knee treated with co.don chondrosphere®, defined as minor surgical treatment of repair tissue as part of the maintenance of the original repair procedure, such as shaving or trimming of hypertrophic repair tissue.
- Pain, knee function as measured by the knee injury and osteoarthritis outcome score (KOOS)
- quality of life as measured by the knee injury and osteoarthritis outcome score (KOOS) and IKDC Subjective Knee evaluation Form

- Global patient assessment of treated knee measured by IKDC Subjective Knee Evaluation Form and modified Lysholm Knee Scoring
- Average time to treatment failure (based on date physician decided that surgical retreatment of the treated lesion was required)

For patients that undergo physical examination and MR Imaging:

- MOCART Score derived from MRI
- Final Evaluation of IKDC Knee Examination Form

Setting

9.1.4 Site selection

Investigational sites will be chosen based on ACI-M treatments performed in the respective study population: Participating sites should have performed at least 1 ACI-M´s in the target population between 2007 and 2011.

9.1.5 Study population

According to analyses of co.don® AG approx. 80 patients are eligible to criteria of paediatric investigation plan and will be contacted. Aim is that at least 80 adult male or female patients having co.don chondrosphere® implantation in the knee joint at the age of 15 to less than 18 years between 1 and 8 years prior start of enrolment will be enrolled by their treating physicians. A physical examination of the treated knee including MRI results is requested from a subgroup of 30 patients.

9.1.5.1 Inclusion criteria

Patients who meet the following criteria can be considered for inclusion into the investigation:

- Male or female patients being at least 15 but less than 18 years of age at the time of implantation
- Treatment with co.don chondrosphere® until December 2011
- Treatment is conducted max. 8 years before enrolment
- Written informed consent has been obtained.

9.1.5.2 Exclusion criteria

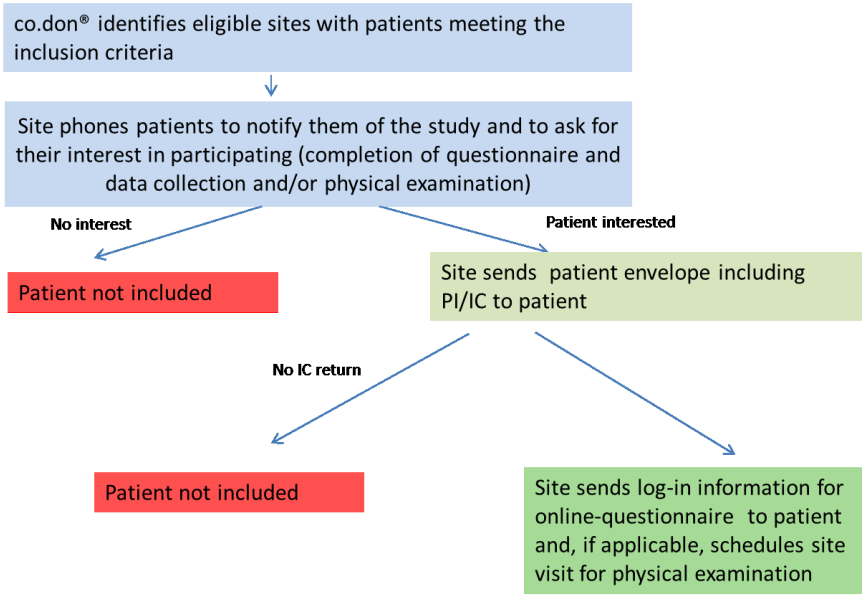
There are no specific exclusion criteria in this non-interventional study.

9.1.5.3 Patient recruitment

Participating sites will be identified by co.don® AG. Patients will first be contacted from their physician by phone and informed about the purpose of the study. If interested, patients will receive a letter containing the Patient Information Sheet/Informed Consent Form to be signed, dated and sent back to the site in case of participation. Patients can provide their email contact on the Informed Consent Form to receive individual log-in data for a web-based data collection tool via the site.

From a subgroup of at least 30 patients a physical examination of the treated knee and an assessment of the chondral structure by MRI are requested.

Study scheme patient recruitment



9.1.5.4 Discontinuation criteria

There are no specific discontinuation criteria in this non-interventional study. Patients have the right to withdraw their consent at any time, without prejudice to their medical care and they are not obliged to state their reasons.

9.1.6 Study duration

The study is planned to consist of a setup period of 4 months, a data collection period of 12 months and an analysis period of 3 months. Data collection is expected to start in January 2015.

- Study participants will complete an online study survey between approximately 3 and 8 years after treatment
- Patients in the physical examination subgroup (30 patients) must have at least one study visit

9.1.7 Visits

There will be no fixed study visit schedule. Data collected by the physicians will be either derived from the medical records or documented using the Examination Form at patient visit after patients have given their informed consent.

In addition patients are requested to complete a web-based questionnaire at home once during the study.

If patient gives consent, a follow-up visit will be arranged to perform physical examinations.

A MRI within a time window of ± 3 month of physical examination could be used for MOCART-Analysis.

Variables

9.1.8 Variables recorded by the physician

The following variables shall be recorded by the participating physicians:

9.1.8.1 Inclusion

- Confirmation that inclusion criteria are met and signed and dated informed consent has been obtained

9.1.8.2 Demographic data at the time of implantation

- Age
- Sex
- Height/Weight/BMI
- Relevant concomitant diseases

9.1.8.3 Anamnesis

- 2000 IKDC/ICRS -Knee History Form
- 2000 IKDC Surgical Documentation Form
- Epiphysis open/closed/not documented

9.1.8.4 Treatment with co.don chondrosphere®

- Date of biopsy
- Date of implantation
- Kind of treatment for implantation: arthroscopic/open surgery
- Amount of spheroids
- Further interventions during implantation (according to ICRS knee history registration - previous surgery)
- Duration of hospitalisation
- Adverse Events between biopsy and implantation:
    - Event term
    - Start and stop date
    - Course
    - Causal relationship with drug product, co.don chondrosphere®, and surgery (biopsy/implantation)
    - Seriousness
    - Severity
    - Further information, e.g. Status, measures
- Adverse Events during and after implantation:
    - Event term
    - Start and stop date
    - Course
    - Causal relationship with drug product, co.don chondrosphere®, and surgery (biopsy/implantation)

  - Seriousness
  - Severity
  - Further information, e.g. Status, measures
- Surgical re-treatments after ACI-M implantation at the treated knee and relationship to ACI-M:
  - Surgical re-treatment of the treated cartilage lesion involving either
    - Extensive debridement for lesion expansion
    - Violation of the subchondral bone
    - ACI
    - Other
  - Minor surgical treatment as part of the maintenance of the original repair procedure such as shaving or trimming of hypertrophic repair tissue
- Satisfaction with the treatment with co.don chondrosphere®

9.1.8.5 Variables for physical examination subgroup

- 2000 IKDC Knee Examination Form
- Result of physical examination of the treated knee (musculature, effusion, pain)
- Results from MRI according to MOCART scoring scale, if available

9.1.9 Variables recorded by the patient

- Age, present
- Height/weight, present
- Intake of analgesics during last 4 weeks week
- Surgical treatments after ACI-M at the treated knee
- Which physician would have been contacted in case of adverse events?
- Satisfaction with the treatment with co.don chondrosphere®
- Validated questionnaire *KOOS*
- Validated questionnaire *IKDC Subjective Knee Evaluation Form*
- Validated questionnaire *mod. Lysholm Knee Scoring*

9.1.10 Adverse events / adverse drug reactions

All adverse events from the date of biopsy until date of study documentation will be recorded by the physician as described in Section 11. As described in the safety plan the categorization into AE/SAE/ADR/SADR/SUSAR will be performed by Syneed. Categorization will be "reportable" events, which will immediately reported to co.don® AG for further processing, and "Other", which will be collected until analysis for study report.

Reportable event fulfils the following criteria minimally:

a. The event is a serious event acc. to definition of seriousness
b. The causality of the event to the treatment is possible, probable or certain (classification of event as drug reaction)
c. The event is acute or ongoing (not resolved)

Data sources

The participating physician will collect demographic and clinical characteristics from medical records from all patients and for 30 patients by physical examinations during a study visit.

The occurrence of adverse events will be assessed by the physician based on patient reported outcomes, patient files and physical examinations, if applicable.

All data collected during this study will be entered into an eCRF by the participating physician and patients will complete a web-based questionnaire.

Study size

About 80 patients who were transplanted until December 2011 will be contacted. From a subgroup of 30 patients a physical examination of the treated knee and an assessment of the chondral structure by MRI is requested.

Data management

The contract research organization (CRO) will be responsible for setup and management of an electronic data capture (EDC) system and analysis of data collected during the study.

eCRFs and patient questionnaires will be part of the same EDC system, which allows documentation of data in a standardized way. All entries in the eCRF will be checked for plausibility as defined in the data management plan and data validation worksheet.

Each patient will be identified by a unique central patient identification number. Only the patient's physician will be able to identify the patient based on the patient identification number. CRO and sponsor will exclusively handle pseudonymized data.

The participating physician is responsible for ensuring that data are properly recorded in each patient's eCRF only after the respective informed consent has been received. Data will be entered in the eCRFs in a timely manner on an ongoing basis (see special requirements for SAEs, section 11).

Patients will be provided with their log-in data by email. The e-mail address will be given on the Informed Consent Form by the patient. By creating an eCRF for one patient the physician will be able to send an email with the log-in data to the patient using the physician's regular Email software. The patient's contact data will thus not be saved in the EDC system and will not be available to the CRO or sponsor.

Adverse events will be coded by syneed medidata using the MedDRA coding system (latest version at study start).

Data analysis

All variables will be analysed in an exploratory manner with appropriate descriptive statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by sample statistics (i.e. mean, standard deviation, minimum, median, quartiles and maximum).

An additional subgroup analysis for patients with closed epiphyseal growth plate, patients with open epiphyseal growth plate, and patients with this information being missing, respectively, is planned.

Data will be compared to the results for adult data of patients from 18 to less than 35 years of age.

Statistical analyses will be performed using validated statistical software (e.g. SAS®, SAS Institute Inc.).

All statistical details including calculated variables and proposed format and content of tables will be detailed in the statistical analysis plan (SAP). The SAP will be finalized before study database lock. The analysis will be performed in accordance with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology [R5].

Quality control

9.1.11 Data quality

Before study start clinical monitors authorized by co.don will train all sites on the background of the study, ethical and regulatory obligations, and the use of the EDC system.

Interim monitoring visits will be performed for source data verification and to check compliance of the site with AE reporting procedures. It is planned that monitoring for 10% of patients in a minimum of 3 sites will be performed.

All data will be recorded in a standardized, validated EDC system complying with international quality standards (e.g. FDA Guidance for Industry Title 21 CFR Part 11). After data entry, data will be validated. Detailed information on checks for completeness, accuracy, plausibility and validity will be given in the data management plan. The same plan will specify measures for handling of missing data and permissible clarifications.

National and international data protection laws as well as regulations on observational non-interventional studies will be followed. Electronic records used for patient documentation will be validated.

9.1.12 Storage of records and archiving

co.don will make sure that all relevant documents of this study including eCRFs and other patient records will be stored after the end or termination of the study for at least 10 years. Other instructions for storage of medical records will remain unaffected.

The participating physicians have to archive documents at their sites according to local requirements, considering possible audits and inspections from the sponsor and/or local authorities.

9.1.13 Limitations of the research methods

1. No scientific rationale is given for a separate investigation of patients aged 15 – 17 years. There is no physical difference between the knee of a patient on the last day of his 17th and the first day of his 18th year. This age limit is artificial from a medical point of view. The age limit of 18 years is a legal age limit.
2. No statistical calculations for patient number.
3. In a retrospective data collection sponsored by co.don® AG 29 adolescent patients treated with co.don chondrosphere® were analysed. (data submitted in course of PIP). The population included patients with open, closed and unknown epiphysis status.

   Out of 29 adolescent patients, only 6 adolescents with a closed epiphysis could be identified. The data of these 6 patients supported the German marketing permission acc. to §4b German Drug Law (AMG).

The results of patients with open and unknown epiphysis status are not relevant.

The EMA granted a waiver (no need for the treatment in this population) until closed epiphysis. Reason is lack of significant therapeutic benefit. In the German product information (SmPC and package leaflet) for co.don chondrosphere® an open epiphysis is currently indicated as a contraindication.

4. Results from this study are prone to selection bias (e.g. by restriction to outpatients) and confounding factors prevailing in patients in a real-world setting (e.g. by indication, concurrent disease and concomitant drugs). It is acknowledged that such biases are present in any observational study. These limitations of the study-design are inherent and result from the non-interventional character and the fact of voluntary participation of physicians and patients.

   Information bias may stem from inability of the patients to report details of interim surgical interventions or failure to recall surgical interventions since initial biopsy procurement.

9.1.14 Other relevant limitations

The sponsor analysed how many adolescents with eligible inclusion criteria were treated with co.don chondrosphere®. There are about 80 patients in about 40 centres at start of data collection in Q1 2015. According to the PDCO's requirements regarding the planned data collection 80 patients with a time of approx. 3-8 years between treatment and enrolment have to be included. That means that all of the available patients have to be included in the planned data collection to fulfil the requirements of the authority. Therefore the sponsor has doubt that the necessary number of 80 patients could be contacted and enrolled.

10 PROTECTION OF HUMAN SUBJECTS

Independent ethics committee requirements and authority notifications

In Germany, the counsel of an independent ethics committee (IEC) is recommended for non-interventional studies and will be performed prior to commencing the study.

Notification of the competent authority (in this case Paul-Ehrlich-Institute, PEI) and German health insurers' central associations (GKV), the National Association of Private Health Insurance Funds (PKV) and the German central association of panel doctors (KBV) will be performed in accordance with the German drug law (AMG §63g and §67(6)).

As the study is conducted in the context of a PIP, the protocol will be submitted to the European Medicines Agency's PDCO for approval prior to commencing the study.

Regulatory and ethical principals

The non-interventional investigation will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (Helsinki, 1964, including all amendments).

The study will comply with the definition of the non-interventional (observational) study provided in Article 2(c) of Directive 2001/20/EC and provisions made in the EU Guideline on Good Pharmacovigilance Practices (GVP), Module VIII – Post-Authorization Safety Studies [R2].

In addition, the local representative of the Sponsor and participating physicians will follow relevant national legislation.

Informed consent and patient information

Before documentation of any data, the physician must inform the patient about their participation in the study and obtain an informed consent signed and dated by the patient.

Patient insurance

A patient insurance will not be provided as the study is non-interventional by nature and any investigations are conducted according to current medical practice. There will be no additional risks for the patient beyond those of regular therapy with marketed medication.

Data privacy

According to the European Commission directive 95/46/EC, processing of personal data is legitimate for scientific purposes if adequate safeguards are provided and followed. co.don® as well as all participating physicians ensure adherence to applicable data privacy protection regulations. Data are transferred in encoded (pseudonymized) form only. Study findings stored on a computer will be stored in accordance with local data protection laws. Patient names will not be supplied to the sponsor or CRO. If the patient name appears on any document, it must be obliterated before a copy of the document is supplied to the sponsor or CRO. The physician will maintain a list to enable patients' records to be identified in case of queries and quality checks of CRO.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Definitions

As stated in the ICH-E2A guideline [R7], an ***adverse event*** is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An ***adverse drug reaction*** (ADR) with regard to a marketed medicinal product is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.

A ***serious adverse event (***SAE*)* is any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

A ***serious adverse drug reaction*** (SADR) is any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect with a probable causality to the applied drug product.

Collection and reporting

In accordance with the EMA GVP Guideline Module VI [R1], non-interventional studies are considered organised data collection systems where adverse events are actively sought (solicited reports).

Participating physicians are required to document adverse events which occurred from the date of biopsy until the date of data collection. All AEs, whether serious or not, must be documented on the AE Report Form of the eCRF. Serious adverse events related to co.don chondrosphere® and are "ongoing" at date of data collection must be reported immediately, i.e. within 24 hours of knowledge of the event, to co.don. In this case the respective information of the SAE can be printed out of the eCRF, signed by the physician and faxed to co.don® AG . When additional information about an SAE becomes available, physicians must report the new information (by fax or email) to co.don within 24 hours of knowledge of the new information. Follow-up information will also be recorded by the investigators in the respective eCRF. AEs/SAEs will be expedited by co.don to Competent Health Authorities according to local regulations.

SAEs reported by the patient in the survey, e.g. re-operation performed, will be followed-up by the designated CRO through the participating physician.

For each AE, the physician must assess and document the seriousness, intensity, duration, causal relationship to co.don chondrosphere® and/or ACI, action taken and outcome of the event.

The causal relationship will be classified as follows:

- certain:
  Event or laboratory test abnormality, with plausible time relationship to drug intake, cannot be explained by disease or other drugs, response to withdrawal plausible (pharmacologically, pathologically), event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacologic phenomenon) or rechallenge satisfactory, if necessary
- probable:
  when there are good reasons and sufficient documentation to assume a causal relationship in the sense of plausible, conceivable, likely;
- possible:
  when there is sufficient information to accept the possibility of a causal relationship in the sense of not impossible and not unlikely, although the connection is uncertain or doubtful, e.g., due to missing data or insufficient evidence;
- unlikely

  Reasonable coincidence with administration of the treatment.

  AE has not been reported as a side effect of the treatment.

  AE persists after discontinuation of treatment or dose reduction.

  AE may be caused by other reasons.
- unrelated:
  when there is sufficient information to accept a lack of a causal relationship in the sense of impossible and improbable;
- unassessable:
  when the causal relationship is not assessable for whatever reason, e.g. due to insufficient evidence, conflicting data or poor documentation.

The intensity will be classified according to the following criteria:

- mild: the AEs causes awareness of sign and symptoms, but is easily managed;
- moderate: the AEs causes discomfort sufficient to interfere with normal activities;
- severe: the AEs is incapacitating leading to inability to perform normal activities;
- unassessable: in some cases an AE could be „All or Nothing“ and cannot be assessed.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study protocol and the final study report will be included in regulatory communications in line with the paediatric investigation plan, development safety update report, and other regulatory requirements. The study protocol is part of the PIP for co.don chondrosphere® that was agreed with the PDCO of the European Medicines Agency EMA.

The study will be registered in the ENCePP electronic register of studies [R3] and on the publicly available database clinicaltrials.gov

The final study report will be prepared following GVP Module VIII [R2]. The report will be made available according to scheduled timeline as outlined in Section 6.

At the end of study, a report will be provided to the PEI within 12 months after completion of data collection as required by AMG §63g.

Current guidelines for good pharmacoepidemiology practices emphasize that there is an ethical obligation to disseminate findings of potential scientific or public health importance such as results concerning the safety of a marketed medication [R8]. co.don will publish results of this study in the scientific literature (following the usual rules for scientific publication including those for authorship such as established by the International Committee of Medical Journal Editors [R6]) or will communicate the results via appropriate scientific venues.

13 REFERENCES

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Proprietary reports and regulatory documents

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Annex 1 List of stand-alone documents

Number	Date	Title
1	01.04.2014	Summary of Product Characteristics co.don chondrosphere®