20 May 2021
EMA/384141/2021
Committee for Medicinal Products for Human Use (CHMP)

Extension of indication variation assessment report

Invented name: Spherox

International non-proprietary name: spheroids of human autologous matrix-associated chondrocytes

Procedure No. EMEA/H/C/002736/II/0020

Marketing authorisation holder (MAH) CO.DON AG

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, CO.DON AG submitted to the European Medicines Agency on 20 November 2020 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of the indication to include treatment of adolescents with closed epiphyseal growth plate in the affected joint; consequently, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordingly.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/0161/2018) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (P/0161/2018) was completed.

On 24 July 2020, the PDCO issued an opinion on compliance for the PIP (P/0161/2018).

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH sought Scientific Advice from CAT/CHMP.

During the development program, the Applicant received Scientific Advice from the CHMP on 30/01/2009 and 02/09/2009. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the original MAA dossier. Additional advice related to quality was provided on 27/06 2019.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CAT was:

Rapporteur: Lisbeth Barkholt

Timetable	Actual dates
Submission date	20 November 2020
Start of procedure:	26 December 2020
CAT Rapporteur Assessment Report	19 February 2021
PRAC members comments	n/a
CAT and CHMP members comments	09 March 2021
Updated CAT Rapporteur(s) (Joint) Assessment Report	15 March 2021
CAT Request for Supplementary Information (RSI)	19 March 2021
CAT Rapporteur Assessment Report	29 April 2021
CAT and CHMP members comments	n/a
Updated CAT Rapporteur Assessment Report	n/a
CAT Opinion	12 May 2021
CHMP Opinion	20 May 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Articular cartilage injuries affect many people each year (in the USA alone more than one million people per year (Melero-Martin & Al-Rubeai, 2007) and in Germany 285,601 people (number of arthroscopic operations of cartilage defects and meniscal operations from 2008; Deutsches Statistisches Bundesamt") and are therefore a common orthopaedic problem. Consequences of cartilage defects are reduced function of the joint and pain.

The principle of implantation of autologous chondrocyte products such as chondrosphere is based on taking samples of the patient's own healthy cartilage. The chondrocytes isolated from the cartilage biopsy are cultured in vitro and subsequently transplanted into the cartilage defect in order to integrate them into the host tissue and into the defect by de novo synthesis of hyaline matrix components

On 10-Jul-2017 a marketing authorisation was granted by the European Commission (EC) for the medicinal product under the brand name "Spherox" for the European market. As by 2020, Spherox is the only matrix-associated autologous chondrocyte product available in the EU. The approved indication is:

Repair of symptomatic articular cartilage defects of the femoral condyle and the patella of the knee (International Cartilage Regeneration & Joint Preservation Society [ICRS] grade III or IV) with defect sizes up to 10 cm2 in adults.

The current variation seeks to expand this indication to include paediatric patients with a closed growth plate as follows:

Repair of symptomatic articular cartilage defects of the femoral condyle and the patella of the knee (International Cartilage Regeneration & Joint Preservation Society [ICRS] grade III or IV) with defect sizes up to 10 cm2 in adults ***and adolescents with closed epiphyseal growth plate in the affected joint.***

2.1.2. About the product

The medicinal product Spherox consists of spheroids of human autologous matrix-associated chondrocytes as active substances suspended in 0.9% NaCl suspension. The product is used to treat and repair cartilage defects in the knee.

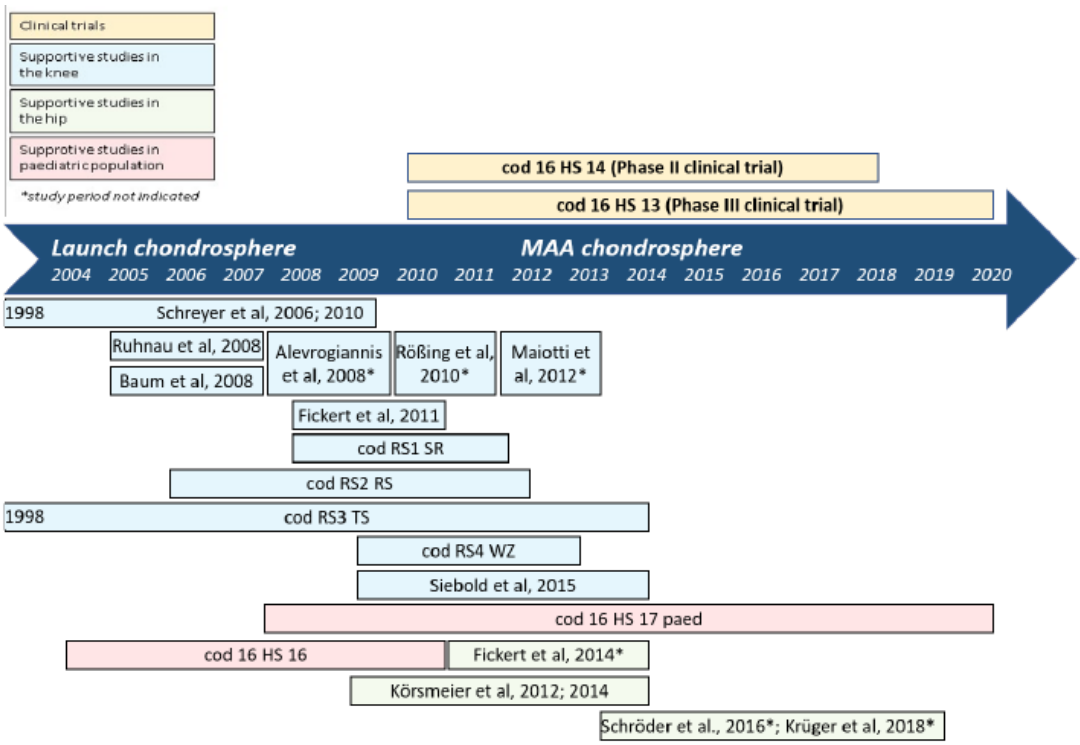
Spherox is administered to patients by intraarticular implantation.

Posology: 10-70 spheroids are applied per square centimetre defect.

The number of spheroids to be implanted is calculated individually by the physician depending on the estimated defect size (10-70 spheroids/cm^2) at the time of biopsy procurement. The implants are delivered either in a syringe or an application system, so called co.fix with a stem length 150 mm containing 60 spheroids. The drug substance is prepared by isolation of autologous chondrocytes from patient's cartilage biopsy and the expansion of cells in a monolayer culture. After the expansion step, chondrocytes are transferred to coated culture plates, where they cannot adhere to the surface, but start to form cell aggregates, spheroids. For harvesting, the spheroids are washed and transferred into 0.9% NaCl solution.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

A summary schematic of the overall development program is provided below.



During the development program, the Applicant received Scientific Advice from the CHMP on 30/01/2009 and 02/09/2009. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the original MAA dossier. Additional advice related to quality was provided on 27/06 2019.

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0253/2012 on the agreement of a paediatric investigation plan (PIP).

At the time of the initial submission, there were 2 non-interventional studies, cod 16 HS 16 (2012) and (cod 16 HS 17 paed) that assessed the long-term safety and corresponding efficacy of chondrosphere in the *paediatric populatio*n (aged 14 to less than 18 years).

Study cod 16 HS 16 was a non-interventional, multicentre (8 centres in Germany), retrospective data collection from 29 children/adolescent patients having knee joint cartilage defect who were followed up to seven years from the Spherox transplantation.

Only **study cod 16 HS 17 paed** is part of the agreed PIP (EMEA-C-001264-PIP01-12-M02).

The completion of this study was deferred to June 2020.

The initial submission included an interim report from this study, dated 15 September 2016, using a data cut-off date of 31 January 2016. At this cut-off date, the FAS dataset comprised 29 patients. As there was a considerable overlap reported of 12 patients between studies cod 16 HS 16 and cod 16 HS17 paed, the additional informative value of study cod 16 HS 16 was considered to be limited. Consequently, at the time of the MAA, the 29 FAS patients (with only 12 patients with verified closed epiphyseal growth plate) in study cod16HS17 were not considered sufficient for granting a paediatric indication.

With the final results of this study cod 16 HS 17 paed included in this variation, the MAH seeks a modification of the approved indication. On 24 July 2020, CO.DON AG received a Positive Opinion of the PDCO on compliance with the PIP (P/0161/2018).

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which is considered acceptable.

In summary, for the initial MAA, the non-clinical testing strategy was concentrated mainly on pharmacodynamics for proof of concept, to demonstrate that the spheroids in chondrosphere show the characteristics necessary to repair the treated cartilage defect. These pharmacodynamic aspects were assessed in in vitro as well as in vivo investigations. Several safety-relevant aspects were also addressed. In accordance with the Guideline on cell-based medicinal products (CBMP) (EMEA/CHMP/410869/2006), no pharmacokinetic studies were conducted. No toxicological reactions have reportedly been observed with chondrosphere/Spherox. However, possible toxicological risks during manufacturing and application have been taken into account in the development of chondrosphere and have been evaluated in a risk analysis. In accordance with the Guideline on CBMP (EMEA/CHMP/410869/2006), the tumorigenic potential of chondrosphere has also been assessed in the IMA.

2.2.1. Ecotoxicity/environmental risk assessment

Spherox does not contain genetically modified organisms (GMOs). It is composed of spheroids, spherical aggregates of *ex vivo* expanded human autologous cells with self-synthesized extracellular matrix. It belongs to the group of biological medicinal products which according to the EMA guideline EMEA/CHMP/SWP/4447/00, is exempted from the obligation to perform environmental risk studies. The excipient, isotonic sodium chloride solution, an electrolyte, is exempted as well.

The product is provided as individual treatment dose (10–70 spheroids/cm² defect) and applied by intraarticular injection. The spheroids administered to the patient are likely to remain in the implantation site. No biodistribution or excretion is expected. Therefore, the product is not released to the environment. The use of Spherox is unlikely to result in any risk to the environment.

2.2.2. Conclusion on the non-clinical aspects

No new clinical data have been submitted in this application, which is considered acceptable.

The new/extended indication is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

Pivotal clinical trials cod 16 HS 14 and cod 16 HS 13 previously conducted in adults (and submitted at the time of the original MAA, see table below) were performed in accordance with GCP as claimed by the MAH. The initial MAA also included the retrospective data collection cod 16 HS 16. Furthermore, the non-interventional study (cod 16 HS 17 paed) in paediatric patients was performed, essential documents were archived in compliance with GCP and Good Pharmacovigilance Practices (GVP).

- Tabular overview of clinical studies

Reference	Clinical investigation details					
	Pro-spective	Retro-spective	Controlled	Number of patients in chondrosphere group	Number of patients in group treated by other methods	Follow-up time (months)
Pivotal clinical investigations						
Phase II clinical trial cod 16 HS 14	X			75		12-month final assessment 24-, 36-, 48- and 60-month follow-up reports
Phase III clinical trial cod 16 HS 13	X		X	52	50 (MF)	12-month interim analysis and 24- final assessment, as well as 36- and 48- months follow-up reports
Supportive clinical investigations (not further described herein)						
Paediatric investigations						
Clinical studies in the paediatric population						
co.don Retrospective Data Collection 2012 (cod 16 HS 16)		X		29		Up to 57
cod 16 HS 17 paed (2020)	X	X		105		Mean 52.2 (12.5 – 94.1)
Total number of studies / patients	**9**	**8**	**1**	**605***	**100**	

* Potential overlap between various supportive studies was identified. CO.DON AG has confirmed that at least 492 individuals were treated with chondrosphere in all investigations.
+ chondrotransplant = chondrocyte suspension (ACT product) manufactured by CO.DON AG until 2004. During transplantation into defect chondrocyte suspension was covered with periosteal flap.

2.3.2. Pharmacokinetics

No pharmacokinetic studies have been conducted. This is in accordance with the Guideline on CBMP (EMEA/CHMP/410869/2006), which states that conventional ADME studies are not relevant for human cell-based products.

2.3.3. Pharmacodynamics

No clinical studies with a primary pharmacodynamic objective have been performed. In previous clinical trials Phase II (cod 16HS14) and Phase III (cod 16HS13) macroscopic, histological, immunohistochemical as well as MRI/MOCART assessments were performed.

MRI/MOCART data were provided for cod 16 HS 17 paed. See Clinical Efficacy.

2.3.4. Discussion on clinical pharmacology

Spherox is used to treat and repair cartilage defects in the knee. It is applied in a re-transplantation procedure using a 3-dimensional autologous chondrocyte transplantation (ACT3D) in the donor's cartilage defect. The recommended posology is that 10–70 spheroids are applied per square centimetre defect.

The recommended dose for adults and adolescents with a closed epiphyseal growth plate is the same.

No new clinical pharmacology studies relevant for the current application have been conducted.

MRI/MOCART data are discussed in the Clinical Efficacy section.

2.3.5. Conclusions on clinical pharmacology

No new clinical pharmacology studies relevant for the current application have been conducted and this is considered acceptable.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No new dose-response studies were conducted. The recommended dose for adults and adolescents with a closed epiphyseal growth plate is the same.

2.4.2. Main study(ies)

Cod16HS17paed 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

Methods

This was a non-interventional, open-label, pro-and retrospective, multicentre surveillance study conducted in patients who had undergone ACI-M with co.don chondrosphere and who were at least 15 years of age but less than 18 years of age at the time of implantation/treatment with co.don chondrosphere. In addition, treatment had to be administered a maximum of 8 years before enrolment in the non-interventional study.

There was no fixed study visit schedule.

Data collected by the physicians were either derived from the **medical records** or documented using the **specific examination form** provided for this study, completed at routine visit(s) after patients had submitted their signed and dated informed consent.

In addition, patients were requested to complete a **web-based questionnaire** at home once during the course of the study.

The chondroidal structure of the knee joint was assessed in a **subgroup** of patients undergoing physical examination including MRI, if applicable. If a patient entered the subgroup, i.e. agreed to such a follow-up examination, a follow-up visit was arranged to perform physical examinations. A voluntary MRI examination within a time window of ±3 months from the physical examination was performed for the purpose of an MRI observation of cartilage repair tissue (MOCART) analysis.

Figure: Patient recruitment scheme

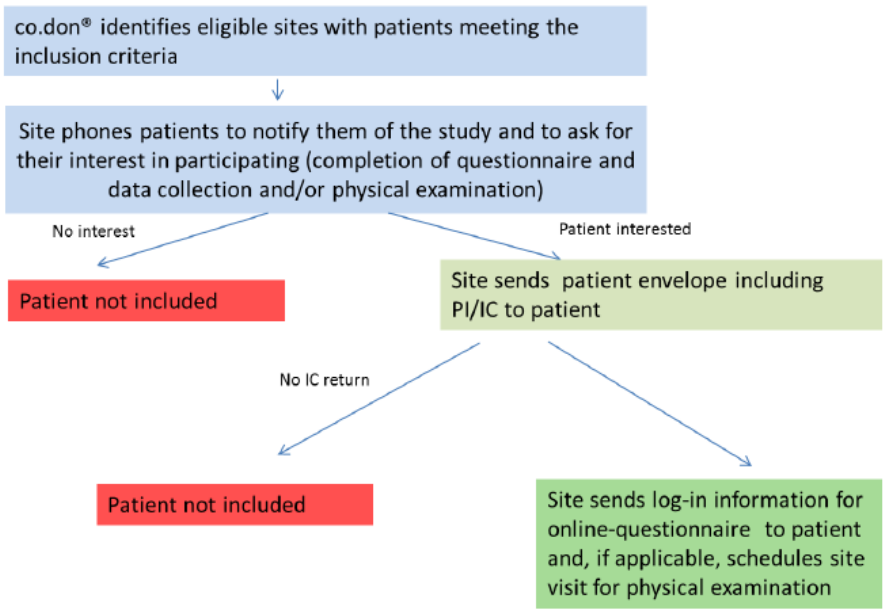


Table: Study schedule

Assessment	By physician examination form	By patients web-based questionnaire	Final examination by physician (subgroup only)
Demographic data at implantation	●		
Demographic data actual date		●	
Anamnesis			
- IKDC/ICRS -Knee History Form	●		
- IKDC Surgical Documentation Form	●		
Treatment with co.don chondrosphere®	●		
Re-treatments after ACI-M implantation	●	●	
Physical examination of the treated knee - IKDC - Knee Examination Form			●
MRI			●
Patient IKDC Subjective Knee Evaluation Form		●	
Patient IKDC Current Health Assessment Form		●	
Patient questionnaire KOOS		●	
Patient mod. Lysholm Knee Scoring		●	
Satisfaction with the treatment with co.don chondrosphere®	●	●	
Adverse Events/Reactions	●		

ACI-M: Matrix-associated autologous chondrocyte implantation; ICRS: International Cartilage Regeneration & Joint Preservation Society; IKDC: International Knee Documentation Committee; KOOS: Knee Injury and Osteoarthritis Score

Study participants

Inclusion criteria:

- Male or female patients aged ≥15 years but <18 years at the time of implantation
- Treatment with co.don chondrosphere
- Treatment was conducted **between 1 and a maximum of 8 years** before enrolment
- Written informed consent had been obtained

Exclusion criteria:

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

Patients could withdraw at any time.

Treatments

Patients enrolled in this study had undergone ACI-M (1 to 8 years before enrolment) with the product co.don chondrosphere.

Concomitant medication was not recorded except for the intake of analgesics during the last 4 weeks of the day of physical examination. Any other relevant concomitant medication was documented only in the

context of (serious) adverse event/reaction ((S)AE/(S)AR) reporting on the AE report form of the electronic case report form (eCRF).

Objectives

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.

Outcomes/endpoints

Primary: Treatment failure rate up to the time point of the survey

(defined as: *Physician's decision that surgical re-treatment of the treated lesion was required, 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*.)

Other variables collected for evaluation of effectiveness:

- 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 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.

After obtaining signed informed consent, all adverse events and adverse drug reactions captured in the patient records were to be recorded in the eCRF.

Sample size

The population was determined by the number of available patients treated with co.don chondrosphere who met the inclusion criteria of the study. Approximately 80 patients were planned to be evaluated including a subgroup of at least 30 patients who had a physical examination of the treated knee as well as an MRI scan.

Randomisation

Not applicable.

Blinding (masking)

Not applicable.

Statistical methods

Study cod16HS17paed was part of the pediatric investigation plan (PIP). According to the PIP the study had three objectives (see above). Therefore, the evaluation of the study comprised three analyses:

1. To assess the long-term safety and linked effectiveness of the ACT3D-CS) product in paediatric patients from 15 to <18 years of age at the time of implantation, especially incidence of treatment failure rate.

2. To compare the treatment effect in Phase II and Phase III studies of patients aged from 18 to less than 35 years (adults) treated with the ACT3D-CS product and the treatment effect in patients from 15 to <18 years of age (adolescents) in this study.

3. To compare the treatment effect in Phase II and Phase III studies of patients aged from 18 to less than 35 years (adults) treated with of the ACT3D-CS product and the treatment effect in patients from 15 to <18 years of age by EGP (epiphyseal growth plate) status in this study.

In this section, the statistical methods for objective 1 are presented. The statistical methods for objective 2 and 3 are described in the section "Analysis performed across trials (pooled analyses and meta-analysis)" below.

Statistical methods for objective 1 (long-term safety and linked effectiveness)

The analysis for objective 1 analyzed the primary endpoint "Treatment failure rate up to the time point of the survey" in this non-interventional, un-controlled cohort study with a single measurement time point.

Design. The treatment effect (effectiveness) and safety was evaluated in a non-interventional, open-label, multi-centre study with a single visit without baseline in pediatric patients, who had been treated with SPHEROX between 1 and 8 years before.

Statistics. All variables were analysed in an exploratory manner using descriptive statistical methods: Summary statistics included number of patients/events (N), mean, SD, minimum (Min), lower quartile (Q1), median, upper quartile (Q3), and maximum (Max) for continuous variables, and frequency distribution tables with number (N) and percentage for categorical data. The incidence of AEs were presented by MedDRA system organ class (SOC) and preferred term (PT) in frequency distribution tables with number and percentage.

Data analysis was purely descriptive. No statistical tests were planned.

Multiple testing procedure. Not applicable.

Endpoints. The primary effectiveness endpoint was "Treatment failure rate up to the time point of survey", ie treatment failure in the non-interventional study is defined as the 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.

Secondary effectiveness endpoints included in the FAS: 1) Incidence of surgical treatments to the knee treated with co.don chondrosphere, 2) Pain, knee function as measured by the KOOS, 3) QoL as measured by the KOOS and 4) IKDC Subjective Knee Evaluation Form, 5) Global patient assessment of treated knee measured by IKDC Subjective Knee Evaluation Form and 6) modified Lysholm Knee Scoring, 7) Average time to treatment failure (only in patients that undergo physical examinations).

Analysis sets.

PIP-FAS (Pediatric Investigation Plan, Full Analysis Set): The data included all patients who gave their informed consent and were enrolled by their treating physicians following ACI-M with co.don chondrosphere® in the knee joint at the age of 15 to <18 years between 1 and 8 years prior to their enrolment. All analyses (including safety analyses) were based on the PIP-FAS.

PIP-FAS-PE, PID-FAS-PRO, PIP-FAS-MRI: The data included a subpopulation of the PIP-FAS which had data available from physical examination (PE) data of the affected knee (physical examination), patient reported outcomes (PRO) data or Magnetic Resonance Imaging (MRI) data. Additional effectiveness analyses were performed in these subpopulations.

Missing data. Missing data have generally not been replaced (except 'Derived Variables'). In frequency tables of categorical data, a category 'missing data' was provided whenever there are patients with missing entries for the respective variable.

Sensitivity analysis. Not available.

Interim analyses. All patients who were included in the study population by 31 January 2016 were included in the interim analysis (N(PIP-FAS)=29, N(PIP-FAS-PE)=23). Additional analyses at other timepoints were performed in this study for objectives 2 and 3 (see below).

Subgroup analysis. Additional effectiveness analyses were performed in these subpopulations:

- Subpopulation "Physical Examination (PE)": The subpopulation 'Physical Examination (PE)' comprised patients with a physical examination of the treated knee and (optional) an assessment of the chondral structure by MRI (see PIP-FAS-PE above).
- Subgroups by Status of Epiphysis (epiphyseal growth plate, EGP):
    - Patients with closed epiphyseal growth plate (PIP-FAS-EGP-CLOSED)
    - Patients with open epiphyseal growth plate (PIP-FAS-EGP-OPEN)
    - Patients with missing information on epiphyseal growth plate status (PIP-FAS-EGP-MISS)

Stratification. Not applicable.

Amendments and changes. Changes versus the Observational Plan (version 1.0, dated 09 October 2014):

- An interim analysis on all patients who had been included into the study population by 31 January 2016 was stipulated in the final SAP (version 1.4, dated, 18 April 2016)
- The IKDC Current Health Assessment Form (SF-36) was used in this study and calculation of subscale and summary scores was described in the final SAP (version 1.4, dated, 18 April 2016)

Changes in the Statistical Analysis Plan (SAP, Final 2.0 on 12 December 2019) and SAP (Final 3.0 on 26 March 2020) relative to the original SAP (version Final 1.4 on 18 April 2016):

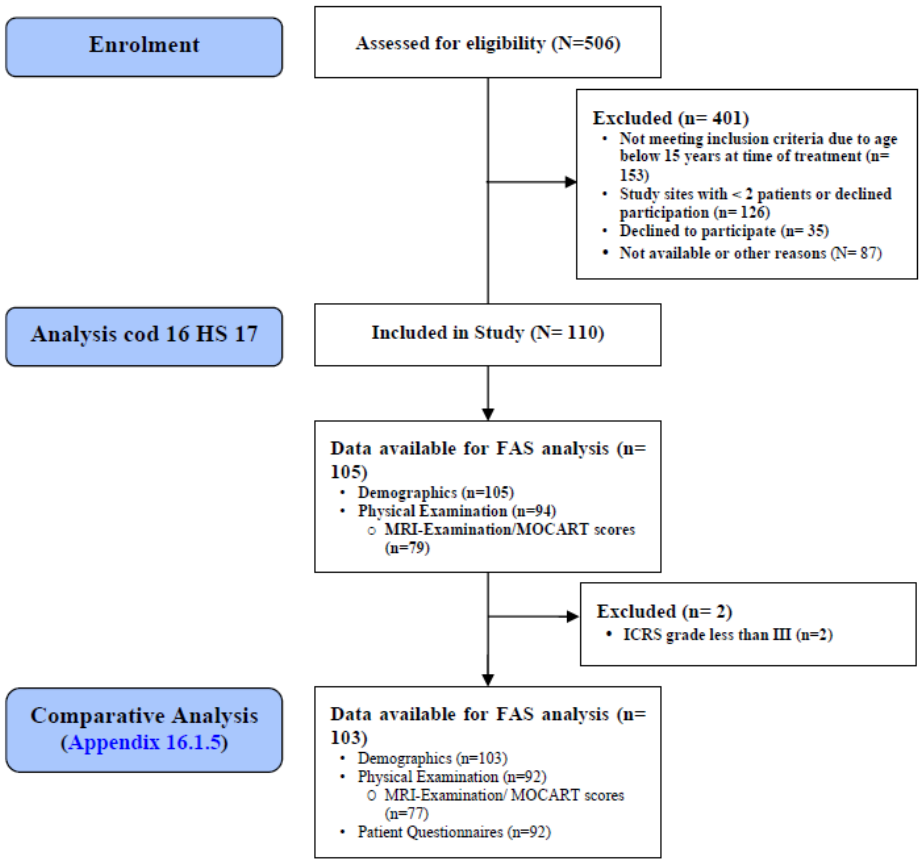
- **Final 2.0:**
    - Change of Study Title to match protocol change
    - End of Study Date
    - Additional comparative analysis of the cod 16 HS 17 study data with a set of pooled data of an adult population from Phase II and Phase III studies (See Addendum in Appendix 16.1.5)
    - Mock-ups of tables and subject data listings (Mock-ups removed from SAP)
    - Change of SAP template
- **Final 3.0:**
    - Time to follow-up to be included in descriptive statistics
    - Change of additional comparative analysis of the cod16HS17 study data with a set of pooled data of an adult population from Phase II and Phase III studies.

A Statistical Analysis Plan – Extension (Version No.: Final 1.0) describing analyses in subgroups of epiphysis as well as cod16HS13:MF was finalized on 2020-05-06 (see section "Analysis preformed across trials"). **Governance**: The data of the database lock was not provided. The Statistical Analysis Plan (SAP, Final 3.0) was finalized on 2020-03-26 with an extension (Final 1.0) added on 2020-05-06.

Results

Participant flow

Figure: Patient disposition



Recruitment

Study initiation date: 07 May 2015

Study completion date (LPLV): 29 November 2019

Conduct of the study

Changes versus the Observational Plan (version 1.0, dated 09 October 2014):

- An interim analysis on all patients who had been included into the study population by 31 January 2016 was stipulated in the final SAP (version 1.4, dated, 18 April 2016)
- The IKDC Current Health Assessment Form (SF-36) was used in this study and calculation of subscale and summary scores was described in the final SAP (version 1.4, dated, 18 April 2016)

There were two amendments to the study protocol as follows:

- Amendment 1, dated 18th October 2016, introduced changes to responsible persons and their addresses, alteration of study milestones and a decision to conduct an interim analysis
- Amendment 2, dated 16th March 2018, adjustment the study milestones, removed references to '2011 and December 2011', from closure of the epiphysis in the title and other areas of the text', adjustment the name of the company conducting the safety analysis, and the date was changed from 2007 and 2011' to '2007 and 2017' under site selection

Analysis of protocol deviations/violation was neither planned nor performed due to the non-interventional nature of the study. However, 5 of the 110 patients included in the study were not included in FAS:

Patient [redacted]: Implantation date was >8 years before signing the informed consent form

Patient [redacted]: No ICF available

Patient [redacted]: Patient was older than 18 years at the time of implantation

Patient [redacted]: Implantation date was <1 year before signing the informed consent form

Patient [redacted]: Implantation date was <1 year before signing the informed consent form

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

Changes in the statistical and analytical plan:

See statistical methods section above.

Baseline data

Table: Demographic characteristics

Characteristic	Statistics / Category	Total (N=105) n (%)*
Sex	Female	50 (47.6)
	Male	55 (52.4)
Age (years) at implantation	n	105
	Mean	16.2
	SD	0.8
	Median	16.0
	Range (Q1, Q3)	(16.0, 17.0)
	Range (Min, Max)	(15.0, 17.0)
Height (cm) at implantation	n	105
	Mean	174.8
	SD	10.0
	Median	175.0
	Range (Q1, Q3)	(168.0, 181.0)
	Range (Min, Max)	(140.0, 195.0)
Weight (kg) at implantation	n	105
	Mean	70.4
	SD	13.00
	Median	70.0
	Range (Q1, Q3)	(62.0, 76.0)
	Range (Min, Max)	(45.0, 121.0)
BMI score (kg/cm^2) at implantation	n	105
	Mean	23.0
	SD	3.4
	Median	22.5
	Range (Q1, Q3)	(20.8, 24.7)
	Range (Min, Max)	(15.7, 34.6)
BMI score (kg/cm^2) at present time	n	92
	Mean	24.3
	SD	3.8
	Median	23.9
	Range (Q1, Q3)	(21.5, 26.3)
	Range (Min, Max)	(18.2, 35.1)

N = total number of patients in treatment group; n = number of patients in subgroup for a specific parameter
* Percentages are related to the total number of patients in the FAS
BMI data are not available for all patients in the FAS.
Source: Table 14.1.2

Table: History of Injured Knee and Previous Surgery (IKDC/ICRS – Knee History Form)

Characteristic	Category / Statistics	Total (N=105) n (%)*
Involved knee	Right	59 (56.2)
	Left	46 (43.8)
Contralateral knee	Normal	88 (83.8)
	Nearly normal	6 (5.7)
	Abnormal	11 (10.5)
	Severely abnormal	0 (0.0)
Duration of symptoms (months)	N	105
	Mean	22.7
	SD	25.1
	Median	14.0
	Range (Q1, Q3)	(4.0, 30.0)
	Range (Min, Max)	(1.0, 132.0)
Mechanism of injury	Gradual onset	40 (38.1)
	Non-traumatic sudden onset	16 (15.2)
	Traumatic sudden onset	49 (46.7)
Activity at injury	Activities of daily living	33 (31.4)
	Sport	56 (53.3)
	Traffic accident	1 (1.0)
	Work	1 (1.0)
	Unknown	13 (12.4)
	Other	1 (1.0)

N = total number of patients in treatment group; n = number of patients in subgroup for a specific parameter
* Percentages are related to the total number of patients in the FAS
Source: Table 14.2.1

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 activity during which the injury occurred was 'sports' in most patients (56 [53.3%]).

Table: Knee Examination (IKDC Surgical Documentation Form; FAS)

Characteristic	Category	Sub-Category/ Statistics	Total (N=105) n (%)
Diagnosis*	Cartilage lesion caused by trauma		54 (51.4)
	Osteochondritis dissecans (OD)		42 (40.0)
	OD Grade°	Grade I	0 (0.0)
		Grade II	2 (4.8)
		Grade III	14 (33.3)
		Grade IV	26 (61.9)
	Osteoarthritis		0 (0.0)
	Avascular necrosis		1 (1.0)
	Other		8 (7.6)
Number of defects per patient*	Patients with 1 defect		101 (96.2)
	Patients with >1 defect		4 (3.8)
Location$	Femur		57 (52.3)
	Tibia		2 (1.8)
	Patella		50 (45.9)
Femur°	Condylus	Medial	35 (61.4)
		Lateral	22 (38.6)
	Sagittal plane	Anterior	4 (7.0)
		Central	46 (80.7)
		Posterior	5 (8.8)
		Trochlea	2 (3.5)
	Frontal plane	Lateral	9 (15.8)
		Central	31 (54.4)
		Medial	17 (29.8)
Tibia°	Plateau	Medial	0 (0.0)
		Lateral	2 (100.0)
	Sagittal plane	Anterior	0 (0.0)
		Central	1 (50.0)
		Posterior	1 (50.0)
	Frontal plane	Lateral	0 (0.0)
		Central	2 (100.0)
		Medial	0 (0.0)
Patella°	Sagittal plane	Distal	14 (28.0)
		Central	36 (72.0)
		Proximal	0 (0.0)
	Frontal plane	Lateral	12 (24.0)
		Central	20 (40.0)
		Medial	18 (36.0)
Grade of cartilage lesion (ICRS)$	Grade 1		0 (0.0)
	Grade 2		2 (1.8)
	Grade 3		20 (18.3)
	Grade 3 Group°	A	2 (10.0)
		B	5 (25.0)
		C	13 (65.0)
		D	0 (0.0)
	Grade 4		87 (79.8)
Defected area size (cm^2)		N	105
		Mean	4.07
		SD	1.95
		Median	4.00
		Range (Q1, Q3)	(3.00, 4.95)
		Range (Min, Max)	(0.75, 12.00)

N = total number of patients in treatment group; n = number of patients in subgroup for a specific parameter
* Percentages are related to the total number of patients in the FAS
° Percentages are related to the total number of patients in the subgroup
$ Percentages are related to the total number of defects in the FAS. This includes also multiple defects in 4 patients ([redacted], [redacted], [redacted], and [redacted]) treated concomitantly.
Source: Table 14.2.3

The Committee noted the following:

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 cm^2 to a maximum of 12.00 cm^2.

Most patients had 1 defect (101 [96.2%]). The most common location for the cartilage defect was the femur (57 [52.3%]), followed by the patella (50 [45.9%]) and the tibia (2 [1.8%] patients). Most of the cartilage lesions were classified as ICRS grade 4 (87 [79.8%] patients).

Most patients had lesion ICRS Grade 3 or 4:

Grade 3: severely abnormal (cartilage defects extending down to more than 50% of cartilage depth)

Grade 4: severely abnormal (lesion extending past subchondral plate, bone exposed).

Biopsy and implantation data are summarized in the table below. Open implantation was performed in 80 (76.2%) patients and arthroscopic implantation in 25 (23.8%) patients. The mean number of spheroids used was 117.4± 50.9; the mean co.don chondrosphere dose was 33.5 ± 18.9 spheroids/cm^2.

Table: Biopsy and implantation with co.don chondrosphere

		FAS (N=105)
Biopsy		
Number of osteochondral cylinder samples[a]	n	103
	Mean (SD)	2.4 (0.7)
	Median (Min, Max)	2.0 (1, 4)
Cylinder diameter [mm]	n	103
	Mean (SD)	4.5 (3.3)
	Median (Min, Max)	4.0 (2, 30)
Epiphysis at implantation[b]	Open	28 (26.7)
	Closed	61 (58.1)
	Not documented	16 (15.2)
Concomitant diseases[b]	No	90 (85.7)
	Yes	15 (14.3)
Implantation type [n (%)][b]	Open	80 (76.2%)
	Arthroscopic	25 (23.8%)
Number of spheroids	n	105
	Mean (SD)	117.4 (50.9)
	Median (Min, Max)	111 (15, 300)
Product dose [spheroids/cm^2]	n	105
	Mean (SD)	33.5 (18.9)
	Median (Min, Max)	30.0 (6.7, 93.3)
Duration of hospitalisation [days]	n	105
	Mean (SD)	4.5 (1.8)
	Median (Min, Max)	4 (2, 10)
Physicians' recommendation for the treatment [n (%)][a]	Yes	102 (97.1%)
	No	3 (2.9%)

[a] Patients [redacted] and [redacted] have empty values for number of cylinder samples. For this reason, n=103, instead of n=105.
[b] Percentages are based on the total number of patients in the FAS.
Source: Table 14.2.3.1.

The Committee noted that in 15% of the patients, the status of epiphysis (open or closed) was not documented.

Concurrent surgeries

Concurrent surgeries during biopsy were documented in 40 (38.1%) patients. The most common type of surgery that took place during biopsy was 'other' (27 [67.5%] patients) followed by cartilage surgery (7 [17.5%] patients), meniscus surgery (5 [12.5%] patients), patellofemoral surgery (4 [10.0%] patients), ligament surgery (3 [7.5%] patients) and osteotomy (2 [5.0%] patients).

Concurrent surgeries during implantation were documented in 41 (39.0%) patients. The most common type of surgery that took place during implantation was patellofemoral surgery (28 [50.9%]) followed by other (20 [36.4%] patients), cartilage surgery (4 [7.3%] patients), meniscus surgery (2 [3.6%] patients) and osteotomy (1 [1.8%] patient).

The MAH explained that the main reason for the concurrent surgeries is related to the need to address the underlying reason for the defect and/or to address e.g. teared ligaments or meniscus related issues.

In the study cod 16 HS 17 paed, 63 patients out of 105 underwent concurrent surgeries during biopsy and/or implantation, 42 patients did not. Major types of procedures were bone reconstruction (24), e.g. for reconstruction of osteochondritis dissecans defects and patellofemoral realignment surgeries (23), e.g. following a traumatic injury. In a few cases, non-ACI cartilage repair techniques (N=4) have been used in addition to ACI either for smaller other defects not needing necessarily ACI. In a descriptive subgroup analysis, overall KOOS ± SD (standard deviation) yielded similar values for patients that received concurrent surgeries with biopsy and/or implantation as those without these additional interventions (76.8 ± 18.0 vs. 80.6 ± 13.5). MOCART scores were also similar. Similar results were obtained in the adolescent subpopulation with closed EGP.

Overall, the company's conclusion that it is therefore unlikely that concurrent surgeries alone caused ACI treatment success can be understood.

Numbers analysed

The full analysis set (FAS) thus comprised 105 patients and the physical examination subpopulation comprised 94 patients (88.7%). The median follow-up time was 53.5 months (range: 12.5, 94.1).

Outcomes and estimation

- Treatment failure

Table: Treatment failure rate (physician decision) - FAS

		Status of Epiphysis			
Characteristic	**Statistics/Category**	**Overall (N=105) n (%)***	**Open (N=28) n (%)***	**Closed (N=61) n (%)***	**Not Documented (N=16) n (%)***
Patients with at least one additional surgery	No	79 (75.2)	22 (21.0)	46 (43.8)	12 (11.4)
	Yes	26 (24.8)†	6 (5.7)	15 (14.3)	4 (3.8)
Treatment failure	No	21 (20.0)	5 (4.8)	13 (12.4)	3 (2.9)
	Yes	5 (4.8)	1 (1.0)	2 (1.9)	2 (1.9)
Treatment failure rate		0.048	0.036	0.033	0.125
Time up to treatment failure (months)	n	5	1	2	2
	Mean	36.6	53.9	46.6	18.0
	SD	19.8	NC	17.31	8.75
	Median	34.3	53.9	46.6	18.0
	Range (Q1, Q3)	(24.1, 53.9)	(53.9, 53.9)	(34.3, 58.8)	(11.8, 24.1)
	Range (Min, Max)	(11.8, 58.8)	(53.9, 53.9)	(34.3, 58.8)	(11.8, 24.1)

N = total number of patients in treatment group; n = number of patients in subgroup for a specific parameter; NC = not calculated
* Percentages are related to the total number of patients in the FAS
Note: Patient [redacted] (see †) is a treatment failure due to a corresponding SAR (NtF), but not listed originally by the investigator as treatment failure. This patient was hardcoded into this table subsequently after database lock (refer to Narratives in Section 12.3.2).
Source: Table 14.2.4

The Committee noted that twenty-one of the 26 patients who underwent additional surgeries were not performed with the intent to restore the originally treated chondral lesion. Instead, most of them targeted other joint structures. The MAH provided a descriptive table that outlines these cases.

A descriptive subgroup analysis of patients who received additional surgeries after ACI yielded KOOS ± SD of 70.7 ± 20.5. For patients without these additional interventions KOOS ± SD was numerically higher, reaching 81.1 ± 13.7, perhaps reflecting the more complex conditions in the patients requiring the additional surgeries. MOCART score ± SD was 72.5 ± 16.3 for patients with additional surgeries after ACI and 75.1 ± 16.9 for patients without these.

The subpopulation of patients with closed EGP data showed the same pattern.

Thus, the company's conclusion that it is less likely that the additional surgeries affected the ACI treatment success can be agreed.

- PE examination and IKDC knee examination evaluation

Physical examination (PE) 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.

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.

Table: Follow-up IKDC – Knee examination (knee and ligament) – Subpopulation FAS

IKDC Group	Group Grade±	Overall (N=94) n (%)*	Status of Epiphysis		
			Open (N=27) n (%)*	Close (N=54) n (%)*	Not Documented (N=13) n (%)*
Final Evaluation Group Grade	A	47 (50.0)	10 (10.6)	28 (29.8)	9 (9.6)
	B	32 (34.0)	15 (16.0)	14 (14.9)	3 (3.2)
	C	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	D	7 (7.4)	0 (0.0)	7 (7.4)	0 (0.0)
	Missing	8 (8.5)	2 (2.1)	5 (5.3)	1 (1.1)

Table shortened by assessor – for full table see Table 16 of the cod 16 HS 17 CSR.

No baseline data were reported.

- MRI Examination Results

An MRI examination was performed in 79 (84.0%) patients in the PE subpopulation. Defect repair and filling were complete in 47 (59.5%) patients, incomplete (>50% of adjacent cartilage) in 12 (15.2%) patients and incomplete (<50% of adjacent cartilage) in 3 (3.8%) patients. Subchondral bone was exposed in 1 (1.3%) patient and 16 (20.3%) patients experienced hypertrophy.

An MRI within a time window of ± 3 month 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.

Table: Follow-up MRI examination and MOCART scores – Subpopulation FAS

Characteristic	Category	Total (N=94) n (%)*°
MRI examination (performance during the last 2 months)*	No	14 (14.9)
	Yes	79 (84.0)
	Missing data	1 (1.1)
Degree of Defect Repair and Defect Filling	Complete	47 (59.5)
	Hypertrophy	16 (20.3)
	Incomplete: >50% of adjacent cartilage	12 (15.2)
	<50% of adjacent cartilage	3 (3.8)
	Subchondral bone exposed	1 (1.3)
Integration to Border Zone	Complete	59 (74.7)
	Incomplete: Demarcating border visible	7 (8.9)
	Defect visible <50% of length of repair tissue	11 (13.9)
	Defect visible >50% of the length of repair tissue	2 (2.5)
Surface of the Repair Tissue	Surface intact	44 (55.7)
	Surface damaged: <50% of repair tissue depth	31 (39.2)
	>50% of repair tissue depth or total degeneration	4 (5.1)
Structure of the Repair Tissue	Homogenous	42 (53.2)
	Inhomogeneous or cleft formation	37 (46.8)
Signal Intensity of the Repair Tissue: (Dual T2-FS)	Isointense	35 (44.3)
	Moderately hyperintense	39 (49.4)
	Markedly hyperintense	5 (6.3)
Signal Intensity of the Repair Tissue: (3D GE-FS)	Isointense	40 (50.6)
	Moderately hyperintense	37 (46.8)
	Markedly hyperintense	2 (2.5)
Subchondral Lamina	Intact	59 (74.7)
	Not intact	20 (25.3)
Subchondral Bone	Intact	50 (63.3)
	Edema/granulation tissue/cysts/sclerosis	29 (36.7)
Adhesions	No	75 (94.9)
	Yes	4 (5.1)
Effusion	No	65 (82.3)
	Yes	14 (17.7)
MOCART Score	**Statistics**	**Overall (N=94) n (%)$**
	n	79
	Mean	74.4
	SD	16.7
	Median	75.0
	Range (Q1, Q3)	(65.0, 90.0)
	Range (Min, Max)	(30.0, 100.0)

N = total number of patients in treatment group; n = number of patients in subgroup for a specific parameter
* Percentages are related to the total number of patients in the subpopulation
† As per the observational plan, an MRI within a time window of ± 3 month of physical examination could be used for MOCART-Analysis. The eCRF however asked for a shorter window. The latter has been followed by the investigators.
° Percentages are related to the total number of patients in the subgroup
$ MRI optional (SAP 2.2)
Source : Tables 14.2.7.1 and 14.2.7.2

The Committee noted that MOCART is a standardized and frequently used MRI-based assessment system that includes 9 variables used to describe the morphology and signal intensity of the repair tissue compared with the adjacent native cartilage, the degree of filling of the defect, the integration to the border zone, the description of the surface and structure, the signal intensity, the status of the subchondral lamina and subchondral bone, the appearance of adhesions and the presence of effusion/synovitis. The total score ranges from 0 to 100 (higher score indicates better health state). A median value of 75 seems consistent with the values observed with the pivotal study values in adults

(post-baseline). However, as there are no baseline assessments available and no repeated measures over time for individual patients, these results are difficult to interpret.

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 was 78.13 (16.52). The highest mean (SD) KOOS subscale score for the overall FAS population was observed for 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]).

Table: KOOS total and subscale scores (FAS)

KOOS	Statistics	Overall (N=105)	Status of Epiphysis		
			Open (N=28)	Close (N=61)	Not Documented (N=16)
Total	n	92	24	53	15
	Mean	78.13	83.20	75.47	79.42
	SD	16.52	14.11	18.19	12.07
	Median	82.14	85.80	78.98	77.04
	Range (Q1, Q3)	(70.56, 89.80)	(79.27, 91.21)	(65.34, 88.77)	(68.92, 91.73)
	Range (Min, Max)	(18.00, 100.00)	(31.65, 97.50)	(18.33, 99.71)	(58.53, 100.00)
Pain	n	92	24	53	15
	Mean	86.23	92.25	82.97	88.15
	SD	16.52	11.29	19.04	10.52
	Median	91.67	95.83	91.67	91.67
	Range (Q1, Q3)	(81.94, 97.22)	(90.28, 98.61)	(75.00, 97.22)	(77.78, 97.22)
	Range (Min, Max)	(16.67, 100.00)	(47.22, 100.00)	(16.67, 100.00)	(63.89, 100.00)
Symptoms	n	92	24	53	15
	Mean	81.68	82.89	80.59	83.57
	SD	16.22	15.30	17.13	14.96
	Median	85.71	85.71	85.71	89.29
	Range (Q1, Q3)	(75.00, 92.86)	(75.00, 92.86)	(71.43, 92.86)	(78.586, 92.9)
	Range (Min, Max)	(32.14, 100.00)	(39.29, 100.00)	(32.14, 100.00)	(53.57, 100.00)
ADL	n	92	24	53	15
	Mean	91.54	95.04	89.21	94.22
	SD	12.60	9.11	14.77	6.00
	Median	95.59	99.26	94.12	95.59
	Range (Q1, Q3)	(90.44, 100.00)	(94.12, 100.00)	(86.76, 100.00)	(89.71, 100.00)
	Range (Min, Max)	(25.00, 100.00)	(61.76, 100.00)	(25.00, 100.00)	(80.00, 100.00)
Sports	n	92	24	53	15
	Mean	70.00	80.21	65.75	68.67
	SD	23.97	19.48	25.69	20.31
	Median	80.00	85.00	75.00	60.00
	Range (Q1, Q3)	(55.00, 90.00)	(75.00, 92.50)	(55.00, 85.00)	(50.00, 90.00)
	Range (Min, Max)	(0.00, 100.00)	(10.00, 100.00)	(0.00, 100.00)	(40.00, 100.00)
QoL	n	92	24	53	15
	Mean	61.21	65.63	58.84	62.50
	SD	24.03	22.80	25.20	22.03
	Median	62.50	68.75	62.50	62.50
	Range (Q1, Q3)	(50.00, 75.00)	(59.38, 78.13)	(37.50, 75.00)	(43.75, 81.25)
	Range (Min, Max)	(0.00, 100.00)	(0.00, 100.00)	(0.00, 100.00)	(31.25, 100.00)

N = total number of patients in treatment group; n = number of patients in subgroup for a specific parameter
ADL = Activities of daily living; QoL = Quality of life
"Sports" in end-of text tables named "sport/rec "refers to sport and recreation.
Interpretation of total: 0 - 100 (Higher score indicates better health state)
Source: Table 14.2.9

The committee noted the following:

KOOS is a 42-item, self-administered, self-explanatory questionnaire that covers five patient-relevant dimensions: Pain, Other symptoms, Function in daily living (ADL), Function in sport and recreation (Sport/Rec), and Knee-related quality of life (QoL).

The 5 dimensions are first scored separately: pain (9 items), symptoms (7 items), ADL function (17 items), sport and recreation function (5 items), and QoL (4 items).

The last week is taken into consideration in answering the questions. Standardised answer options are given (5 Likert boxes) and each question receives a score from 0 to 4. Scores are assigned as follows: None, 0; mild, 1; moderate, 2; severe, 3; extreme, 4. Scores are then transferred to a 0-100 scale (100 indicating no symptoms and 0 indicating extreme symptoms) which is then calculated for each subscale.

The overall KOOS score is determined by averaging transformed subscores.

As a patient-reported outcome measure, KOOS is considered an appropriate and validated scoring system to assess improvement of function and pain in patients with cartilaginous defects (e.g. EMA/CAT/CPWP/568181/2009). A level of 10 points or more of improvement or decline has been suggested as a cut-off representing a clinically significant difference (Roos et al, Health Qual Life Outcomes. 2003). KOOS scores were used as primary endpoint variables in the pivotal studies in adults.

As stated above, as there are no baseline assessments available and no repeated measures over time, these results are difficult to interpret. There is also risk for bias e.g. due to inaccurate recall of information by the patients on pain medications. There was no systematic reporting on analgesic use in the report.

- IKDC Current Health Assessment Form and IKDC Subjective Knee Evaluation

A summary of the IKDC general health assessment form scores is provided below.

Table: IKDC evaluation form – Summary Scores (Current health assessment form; FAS)

Characteristic	Statistics	Overall (N=105)	Status of Epiphysis		
			Open (N=28)	Close (N=61)	Not Documented (N=16)
Physical Component Summary (PCS)	n	92	24	53	15
	Mean	51.4	54.8	49.8	51.7
	SD	8.2	6.1	8.8	7.8
	Median	54.2	55.2	53.1	53.4
	Range (Q1, Q3)	(47.5, 57.3)	(52.0, 59.0)	(44.4, 55.7)	(46.6, 58.0)
	Range (Min, Max)	(24.0, 64.6)	(38.6, 64.6)	(24.0, 61.0)	(31.7, 59.6)
Mental Component Summary (MCS)	n	92	24	53	15
	Mean	51.6	49.9	51.2	56.0
	SD	10.8	11.7	11.5	4.4
	Median	54.9	53.0	55.4	56.4
	Range (Q1, Q3)	(49.1, 58.2)	(44.7, 58.5)	(47.9, 57.6)	(52.6, 58.7)
	Range (Min, Max)	(6.2, 70.4)	(18.3, 63.8)	(6.2, 70.4)	(47.5, 62.9)

N = total number of patients in treatment group; n = number of patients in subgroup for a specific parameter
Source: Table 14.2.10.2

The overall subjective mean (SD) total IKDC score was 77.4 (17.1).

Possible score range for the subjective knee evaluation is 0–100, where 100 = no limitation with daily or sporting activities and the absence of symptoms.

- Modified Lysholm Knee Scoring

Characteristic	Statistics	Overall (N=105)	Status of Epiphysis		
			Open (N=28)	Close (N=61)	Not Documented (N=16)
Modified Lysholm Knee Scale	n	92	24	53	15
	Mean	20.5	21.0	20.1	20.9
	SD	3.5	3.6	3.8	1.6
	Median	21.5	22.0	21.0	21.0
	Range (Q1, Q3)	(19.0, 23.0)	(20.5, 23.0)	(18.0, 23.0)	(20.0, 22.0)
	Range (Min, Max)	(10.0, 24.0)	(10.0, 24.0)	(10.0, 24.0)	(18.0, 24.0)

N = total number of patients in treatment group; n = number of patients in subgroup for a specific parameter
Modified Lysholm Knee scoring according to Smith et al. 2008
Total score range: 0 (worst possible score) to 24 (best possible score)
Source: Table 14.2.12

The Committee noted the following:

The Lysholm Knee Scale is an 8-item questionnaire scored on a 0-100 weighted scale measuring pain (25 points), instability (25 points), locking (15 points), swelling (10 points), limp (5 points), stair-climbing (10 points), squatting (5 points) and use of support (5 points). The scale was originally designed to assess ligament injuries of the knee, but it is commonly used as a self-complete measure in surgical studies involving patients with chondral damage. The modified version of this scale (with a score range of 0 to 24) has the Swelling item removed and utilizes unweighted scores (Smith et al, Osteoarthritis and Cartilage. 2009). An MCID has not been defined for the modified Lysholm scale.

An average score of about 20.5 seems to indicate that the patients are doing relatively well. However, again, as there are no baseline assessments available and no repeated measures over time, these results are difficult to interpret.

Analysis performed across trials (pooled analyses and meta-analysis)

Table 2.5- 4 Overview of study populations, full analysis sets and efficacy endpoints in the different analyses of study cod 16 HS 17 paed)

Study	(cod 16 HS 17 paed)	cod 16 HS 14	cod 16 HS 13	pooled
Age category	15-17 years (adolescents)	18-34 years (young adults)		
I. Overall Effectiveness analysis paediatric population				
Patients (N) in the FAS	105	n.a.	n.a.	n.a.
Follow-up time (mean ± SD; Min, Max)	52.2 ± 20.3 (12.5, 94.1)	n.a.	n.a.	n.a.
Primary efficacy endpoint	Rate of treatment failures	n.a.	n.a.	n.a.
Additional efficacy measures (in sub-population)*	• PROs: KOOS (overall, subscores), IKDC Subjective Knee Evaluation Score, PCS and MCS of the IKDC Current Health Assessment Form (SF-36), modified Lysholm score • Physical examination / IKDC Knee Examination Form • MRI/MOCART	n.a.	n.a.	n.a.
II. Comparative analysis overall				
Patients (N) in the FAS for the comparative analysis ("Compare-FAS")§	103§	42	19	61
Follow-up time (mean ± SD; Min, Max)	52.4 ± 20.4§ (12.5, 94.1)	39.6 ± 15.2 (0.0, 50.5)	39.8 ± 16.6 (0.0, 50.5)	39.7 ± 15.5 (0.0, 50.5)
Primary efficacy endpoint (in sub-population)*	overall KOOS non-inferiority analysis: paediatric population versus adult population(s)			
Additional efficacy measures (in sub-population)*	• PROs: ○ KOOS subscores (main secondary endpoint – non-inferiority analysis) ○ IKDC Subjective Knee Evaluation Score, PCS/ MCS of IKDC Current Health Assessment Form, modified Lysholm score (descriptive statistics) • IKDC Knee Examination Form (descriptive statistics) • Treatment failure (descriptive statistics) • MRI/MOCART (descriptive statistics)			
III. Comparative analysis by EGP status				
Patients (N) in the FAS for the comparative analysis ("Compare-FAS")§ by EGP status	EGP status: • Open: 27 • Closed: 60 • n.d.: 16	EGP status: Closed: 42	EGP status: Closed: 19	EGP-status; closed: 61
Primary efficacy endpoint (in sub-population)*	overall KOOS non-inferiority analysis: paediatric population (divided into subgroups as by their EGP status) versus adult population(s)			
Additional efficacy measures (in sub-population)*	Same as in II.) paediatric population (divided into subgroups as by their EGP status) versus adult population(s)			

FAS: full analysis set (paediatric patients cod 16 HS 17 paed), n.d: not documented; n.a.: not applicable, EGP: epiphyseal growth plate, PRO: patient reported outcome, KOOS: Knee injury and Osteoarthritis Outcome Score, IKDC: International Knee Documentation Committee, MRI: Magnetic resonance imaging, MOCART: Magnetic Resonance Observation of Cartilage Repair Tissue

§ 2 male patients from the overall FAS were excluded from the "Compare-FAS", since their ICRS grade was < 3. This also led to minor changes in follow-up time, numbers of patients in subpopulation data sets of the FAS.

The following analysis were performed in the cod16HS17 data in pediatric patients and cod16HS13, cod16HS14 and pooled cod16HS13+cod16HS14 data in adults. Since the cod16HS13 and cod16HS14 studies were already assessed in the marketing authorisation in adults in 2017, these studies will not be assessed again in the current marketing authorisation application, but only discussed as relevant for the analysis across trials (cf statistical methods for objective 1 were discussed above).

Statistical methods for objective 2 (comparative analysis with the adult Phase 2/3 data)

The analysis of the data aimed to evaluate the non-inferiority of treatment effect in the paediatric population compared to an adult population. The statistical analysis was conducted by comparing patients from 15 to <18 years of age (cod16HS17paed) separately with three other groups of adult patients from 18 to <35 years of age (cod16HS13, cod16HS14 and pooled cod16HS13+cod16HS14) using Compare-FAS.

Study Design. A comparative, historically controlled observational study between paediatric patients from 15 to <18 years of age (cod16HS17paed study) and three other groups of adult patients from 18 to <35 years of age (cod16HS13, cod16HS14 and pooled cod16HS13+cod16HS14).

cod16HS17paed study: This study was described above (see above).

cod16HS14 study: This study is a prospective, randomised, open-label, multi-centre Phase II clinical trial to evaluate the efficacy and safety of the treatment of large defects (4–10 cm2) with 3 different doses of ACT3D-CS treatment in subjects between 18 and 50 years with cartilage defects of the knee. The final analysis visit was at 12 months (visit 4) after implementation with a last follow-up visit at 60 months. Data was collected at ten orthopaedic clinics in Germany. For the current analysis, 19 patients from 18 years to less than 35 years of age with treatment of autologous chondrocyte transplantation product Spherox having a follow-up period of 48 months (ITT population of cod16HS13) were selected.

cod16HS13 study: The cod16HS13 study is a prospective, active-controlled, randomised, open-label, multi-centre Phase III clinical trial to compare the efficacy and safety of the treatment with the product co.don chondrosphere® (ACT3D-CS) with microfracture in subjects between 18 years and 50 years with cartilage defects of the knee with a defect size between 1 and 4 cm2. The final analysis visit was at 24 months after implementation with a last follow-up visit at 60 months. The submitted clinical study report was based on month 60 visit. Data was collected in eight orthopaedic clinics in Germany and three orthopaedic clinics in Poland. For the current analysis, 42 patients from 18 years to less than 35 years of age with treatment of autologous chondrocyte transplantation product Spherox having a follow-up period of 48 months (ITT population of cod16HS14). In addition, 18 patients from 18 years to less than 35 years of age with microfracture surgery having a follow-up period of 48 months (ITT population of cod16HS13) were selected as an additional comparator group.

Statistics. For ordered categorical data and nominal data, absolute and relative frequencies (in %) were calculated. Percentages relate to the total number of patients, if not stated otherwise. A "missing" category was added to any parameter for which information was not available for any subjects. The following descriptive statistics were calculated for continuous data: N (number of observations), Mean, Standard deviation (SD), Median, Minimum (also denoted as Min), 1st quartile (also denoted as Q1), 3rd quartile (also denoted as Q3), Maximum (also denoted as Max).

Within groups. Absolute and relative frequency (percentage) of patients, including corresponding 95% Pearson-Clopper confidence intervals were provided for the treatment failure rate for each of the four groups.

Between groups. The treatment effect of ACT3D on the overall KOOS score was compared between paediatric patients in study cod16HS17paed and three other groups of adult patients (cod16HS13, cod16HS14, and pooled cod16HS13 + cod16HS14). For each of the comparisons, non-inferiority of the treatment in paediatric patients versus adult patients was tested by calculating the mean difference (descriptively given with corresponding 95% confidence interval, but tested for non-inferiority using the lower confidence limit of one-sided 97.5% confidence interval) between patients from 15 to <18 years of age (cod16HS17paed) minus adult patients from 18 to <35 years of age (cod16HS13, cod16HS14, pooled cod16HS13+cod16HS14). These differences were evaluated with a non-inferiority margin of θ =-8.5 percent points.

All other continuous effectiveness variables were analysed descriptively including 95% confidence interval for the mean difference since no non-inferiority margins were available. Results, especially the lower confidence limit of the mean difference are discussed in the context of available literature.

All other analyses of this report primarily use descriptive statistical methods.

Multiple testing procedure. Multiple tests were performed to evaluate the non-inferiority of treatment in pediatric patients (cod16HS17paed) versus adults using comparisons with three studies (cod16HS13, cod16HS14 and pooled cod16HS13+cod16HS14).

After testing of the non-inferiority hypothesis and rejection of the null hypothesis, a superiority was tested by comparing the lower confidence bound to zero by applying a simple closed test procedure without adjustment of the local type 1 error (see also CPMP/EWP/482/99 "Points to Consider on Switching between Superiority and Noninferiority" [2000]).

Endpoints.

Primary effectiveness endpoint. Overall KOOS score.

Main secondary effectiveness endpoints: KOOS subscores

Other secondary effectiveness endpoints: 1) IKDC Knee Examination Form, 2) IKDC Score – Subjective Knee Evaluation Form, 3) IKDC Current Health Assessment Form, 4) IKDC Current Health Assessment Form – Summary Scores (PCS, MCS), 5) Modified Lysholm Knee Scoring, 6) MRI Examination and MOCART Score 7) Treatment failure rate / Time up to treatment failure (months).

Additional secondary safety endpoints are described elsewhere.

Analysis Sets.

- cod16HS17PIP vs. cod16HS13, cod16HS14, pooled cod16HS13 +cod16HS14: ACT3D-CS
    - COMPARE-FAS (Full Analysis Set for Comparison): The Compare-FAS included available patients with valid data of study cod16HS17 and all patients from 18 to <35 years of age of clinical trials cod16HS 14 and cod16HS13 having co.don chondrosphere® implantation in the knee joint, regardless of missing data at follow-up visits (ITT population of cod16HS14 and cod16HS13 at 48-month follow-up, respectively, using Last Observation Carried Forward (LOCF) for missing data imputation). All analyses (safety, efficacy, other) are based on the COMPARE-FAS. Protocol violations were not applicable for this comparative analysis. Patients not treated with co.don chondrosphere® were excluded from analyses of safety and effectiveness.
    - COMPARE-OC (Observed Case Analysis Set for Comparison): The Compare-OC included all available patients with valid data out of study cod16HS17 and all patients from 18 to <35 years of age out of studies cod16HS14 and cod16HS13 (ITT population) having an observation at 48-month follow-up (observed cases only). Hence, no missing data imputation is implemented here.
- cod16HS17PIP vs. cod16HS13MF
    - COMPARE-MF-FAS (Full Analysis Set for Comparison): The Compare-MF-FAS included all available patients with valid data out of study cod16HS17 and all patients from 18 to less than 35 years of age out of study cod16HS13 having microfracture, regardless of missing data at follow-up visits (ITT population of cod16HS13 at 48-month follow-up using LOCF for missing data imputation). Protocol violations are not applicable for this part of the study. Patients not treated with co.don chondrosphere® or microfracture will be excluded from analyses of safety and efficacy.
    - COMPARE-MF-OC (Observed Case Analysis Set for Comparison): The Compare-MF-OC will include all available patients with valid data out of study cod16HS17 and all microfracture-patients from 18 to less than 35 years of age out of study cod16HS13 (ITT population) having an observation at 48-month follow-up (observed cases only). Hence, no missing data imputation is implemented here.

Missing data. Missing data was not be replaced in the cod16HS17paed study (ie PIP data). Questionnaire data was analyzed for all patients who fully completed the respective questionnaire. In frequency tables of categorical data, a category "missing data" will be provided whenever there are patients with missing entries for the respective variable.

Missing data was imputed in the cod16HS13 and cod16HS14 studies using LOCF (last observation carried forward) because otherwise the sample size of the pooled control group would have been strongly reduced.

Sensitivity Analyses. Analyses of two age groups using *LOCF imputation* of missing values in adult patients from 18 to less than 35 years of age (pooled cod16HS13/cod16HS14) for the overall KOOS, the KOOS subscores as well as the secondary parameters.

Analyses of two age populations using *observed values* in adult patients from 18 to <35 years of age (cod16HS13, cod16HS14 and pooled cod16HS13+cod16 HS 14) for the overall KOOS, the KOOS subscores as well as the secondary parameters (cf Compare-OC analysis set).

Using only those patients of cod16HS17paed with a follow-up visit after 48 (± 3) months for the overall KOOS, the KOOS subscores as well as the secondary parameters.

Interim Analyses. In 2017, CO.DON conducted a statistical comparison of the recruited study population (15-17 years of age; n=29) with young adult patients aged 18 to 35 years, included in a currently running Phase II clinical trial (cod16HS14; subgroup n=42). A test of non-inferiority of effectiveness between both groups regarding the KOOS Total Score using the Wilcoxon rank sum test was performed. In addition, assessment of safety endpoints was performed.

Subgroup analysis. The statistical effectiveness analysis was conducted three-way: patients from 15 to <18 years of age (cod16HS17paed) were compared separately to three groups of adult patients from 18 to <35 years of age using COMPARE-FAS: 1) cod16HS13, 2) cod16HS14, and 3) pooled cod16HS13 and cod16HS14.

Stratification. Not applicable

Amendments and changes: The statistical analysis for objective 2 and 3 was described in the "Statistical Analysis Plan – Extension" (Version 1.0, May 6, 2020).

Governance. The final database lock of study cod16HS17paed was on 21-Feb-2020. The SAP-Extension (v1.0) was finalised on May 6, 2020.

The Committee noted the following:

Objective 2:

Study Design. The evaluation of the treatment effect is based on two independent open-label studies in a paediatric vs adult population based on a single visit without baseline. Therefore, comparisons of the treatment effect may be affected by confounding factors which may cause or compensate for differences in the outcome. Statistical methods are not expected to sufficiently resolve this issue.

There are additional major methodological issues:

Endpoints. The primary endpoint "Overall KOOS score" includes multiple subscores, for which sensitivity to change/responsiveness has not been demonstrated in the application. In the context of a non-inferiority study, a summary score may show no difference to the comparison group because of a lack of responsiveness of one or more subscores which dilute actual differences. In addition, to make any claims on an aggregated level the claims have to be supported by all subscores. That is, the sensitivity to change of the overall score and all subscores of the KOOS instrument by other studies (or additional analysis in the submitted studies) would need to be demonstrated.

According to the KOOS User's Guide 1.1 (Updated August 2012): *"A total score has not been validated and is not recommended. For the purpose of an RCT, KOOS subscale scores can be aggregated and averaged as the primary outcome. The five individual KOOS subscale scores are then given as secondary outcomes to enable clinical interpretation."* (see also Roos et al., 2011, PMID 26069575, for a discussion of the total KOOS score). The applicant is asked to provide the coefficients (incl 95% confidence intervals) for the psychometric test properties of the KOOS total score including objectivity, reliability, validity, and especially sensitivity to change/responsiveness describing also floor/ceiling effects. While it is acknowledged that the KOOS total score was accepted as a primary endpoint in previous studies (cod16HS13:at 24 months, cod16HS14: at 12 months), the appropriateness of the instrument to cover a follow-up period up to 8 years with average round 4 years would need to be justified, for example, regarding ceiling effects. Ceiling effects may truncate the true underlying distribution of health outcomes, thereby, causing biased estimates and reduced variance.

Although the applicant states that reliable minimal clinically important differences (MCID), which can be plausibly used as non-inferiority margins, are available for the KOOS questionnaire, such thresholds are only given for the KOOS subscores in the KOOS User's Guide 1.1 (Updated August 2012), but not for the KOOS total score. In the Clinical Study Protocol of the cod16HS13 study (v5.0, p. 81), the applicant states with regards to the NI margin for the KOOS total score: *"Definition from a clinical point of view which differences between ACT3D-CS and MF can be accepted as equivalent: Lower equivalence bound = -8.5 % caused by the presumption that equivalent clinical findings could be differ in single score items as follows: about 1/3 of the questions differ about one level between 0 to 4, in the other 2/3 of questions there is not any difference considered over the scale 0 to 100". This rationale is accepted."*

Multiple testing procedure. The applicant has performed multiple comparisons regarding PRO endpoints (total, 5 subscores) and studies (cod16HS13, cod16HS14, pooled cod16HS13 + cod16HS14) and an interim analysis without controlling the global risk for false positive conclusions. Without clear pre-specification of the tested hypothesis and relevant estimands and an appropriate multiple testing procedure, the results can only be interpreted descriptively and based on nominal statistical significance.

Missing Data. Different methods for handling missingness were used in study cod16Hs17paed (ie none) and the control groups from studies cod16HS13 and cod16HS14 (ie LOCF), potentially causing bias (see also comments on study design above).

Results for objective 2 (comparative analysis of P2/P3 data)

Table 7: Demographic characteristics (Compare FAS)

Characteristic	Statistics/Category	15 to <18 years of age	18 to <35 years of age		
		cod 16 HS 17 (N=103) n (%)*	cod 16 HS 13 (N=19) n (%)*	cod 16 HS 14 (N=42) n (%)*	Pooled (N=61) n (%)*
Sex	Female	50 (48.5)	5 (26.3)	12 (28.6)	17 (27.9)
	Male	53 (51.5)	14 (73.7)	30 (71.4)	44 (72.1)
Age (years) at implantation	N	103	19	42	61
	Mean	16.3	24.5	26.4	25.8
	SD	0.8	4.3	4.8	4.7
	Median	16.0	23.0	26.0	26.0
	Range (Q1, Q3)	(16.0, 17.0)	(21.0, 28.0)	(23.0, 31.0)	(22.0, 30.0)
	Range (Min, Max)	(15.0, 17.0)	(18.0, 33.0)	(19.0, 34.0)	(18.0, 34.0)
Height (cm) at implantation	N	103	19	42	61
	Mean	174.7	179.9	179.3	179.5
	SD	10.0	8.9	10.4	9.9
	Median	175.0	180.0	178.0	178.0
	Range (Q1, Q3)	(168.0,181.0)	(174.0,188.0)	(172.0,186.0)	(173.0,186.0)
	Range (Min, Max)	(140.0, 195.0)	(164.0, 195.0)	(159.0, 213.0)	(159.0, 213.0)
Weight (kg) at implantation	N	103	19	42	61
	Mean	70.5	80.3	79.0	79.4
	SD	13.1	15.9	15.2	15.3
	Median	70.0	83.0	74.5	76.0
	Range (Q1, Q3)	(61.0, 76.0)	(70.0, 92.0)	(70.0, 88.0)	(70.0, 89.0)
	Range (Min, Max)	(45.0, 121.0)	(54.0, 110.0)	(60.0, 130.0)	(54.0, 130.0)
	N	103	19	42	61
	Mean	23.0	24.6	24.5	24.5

Characteristic	Statistics/Category	15 to <18 years of age	18 to <35 years of age		
		cod 16 HS 17 (N=103) n (%)*	cod 16 HS 13 (N=19) n (%)*	cod 16 HS 14 (N=42) n (%)*	Pooled (N=61) n (%)*
BMI score (kg/cm^2) at implantation	SD	3.4	3.2	3.3	3.2
	Median	22.5	24.8	24.6	24.8
	Range (Q1, Q3)	(20.8, 24.7)	(21.1, 27.1)	(21.8, 26.3)	(21.8, 26.6)
	Range (Min, Max)	(15.7, 34.6)	(18.8, 29.7)	(19.0, 33.2)	(18.8, 33.2)

Patients [redacted] and [redacted] of cod 16 HS 17 study excluded because of ICRS Grade <3.
N = total number of patients in treatment group; n = number of patients in subgroup for a specific parameter
* Percentages are related to the total number of patients in the Full Analysis Set.
Source: Table 14.3.1.1

Primary Endpoint Analysis

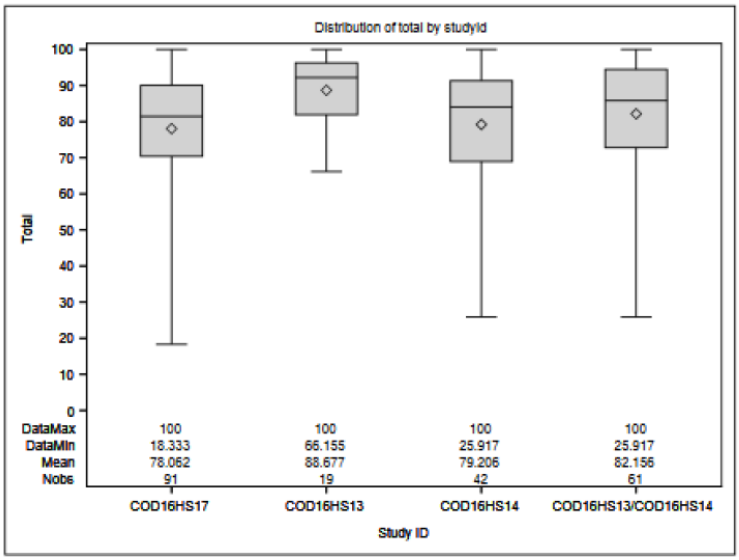
The mean (SD) KOOS total score was 78.06 (16.60) for the 15 to <18 years of age population and 82.16 (15.36) for the pooled 18 to <35 years of age population, respectively; the mean (SD) KOOS total score was 79.21 (16.61) for the 18 to <35 years of age population of the Phase II clinical trial. Non-inferiority evaluation on the lower confidence limit of one-sided 97.5% confidence interval showed that clinical outcome as measured by the mean difference of the total KOOS score of the 18 to <35 years of age population from the Phase II clinical trial (cod16HS14) was higher than the non-inferiority margin of -8.5 compared to the clinical outcome of the

pediatric 15 to <18 years of age population (cod16HS17). Hence, non-inferiority of the pediatric population was confirmed towards the adult population of cod16HS14. Non-inferiority was narrowly missed for total KOOS for the pooled dataset and was clearly not confirmed for the adult population of the Phase III clinical trial cod16HS13.

Characteristic	Statistics	15 to <18 years of age	18 to <35 years of age		
		cod 16 HS 17 (N=103)	cod 16 HS 13 (N=19)	cod 16 HS 14 (N=42)	Pooled (N=61)
Total	N	91	19	42	61
	Mean	78.06	88.68	79.21	82.16
	SD	16.60	9.68	16.61	15.36
	Median	81.43	92.19	84.03	85.81
	Range (Q1, Q3)	(70.38, 90.02)	(81.92, 96.25)	(68.93, 91.34)	(72.78, 94.44)
	Range (Min, Max)	(18.33, 100.00)	(66.16, 100.00)	(25.92, 100.0)	(25.92, 100.00)
	Mean Diff		-10.6150	-1.1442	-4.0941
	Mean Diff (97.5% CI)		(-16.2972, I)	(-7.2701, I)	(-9.3632, I)
	Mean Diff (95.0% CI)		(-16.2972, -4.9329)	(-7.2701, 4.9817)	(-9.3632, 1.1749)

N = total number of patients in treatment group
Note: this number is based on the number of patients who filled out the questionnaire in the FAS;
n = number of patients in subgroup for a specific parameter; I = Infiniy (one-sided CI)
Of the 92 people of cod 16 HS 17 study, who filled out the questionnaire, patient [redacted] had a lesion size of ICRS Grade <3.
Patient [redacted] with ICRS Grade <3 did not even fill out the questionnaire in the first place and is not included in the 92 patients.
*Results are related to the total number of MRIs.
Interpretation of Total: 0 – 100 (Higher Score indicates better health state)
Source: Table 14.3.2.1

Figure 2: KOOS total score compared across the adult and paediatric age populations



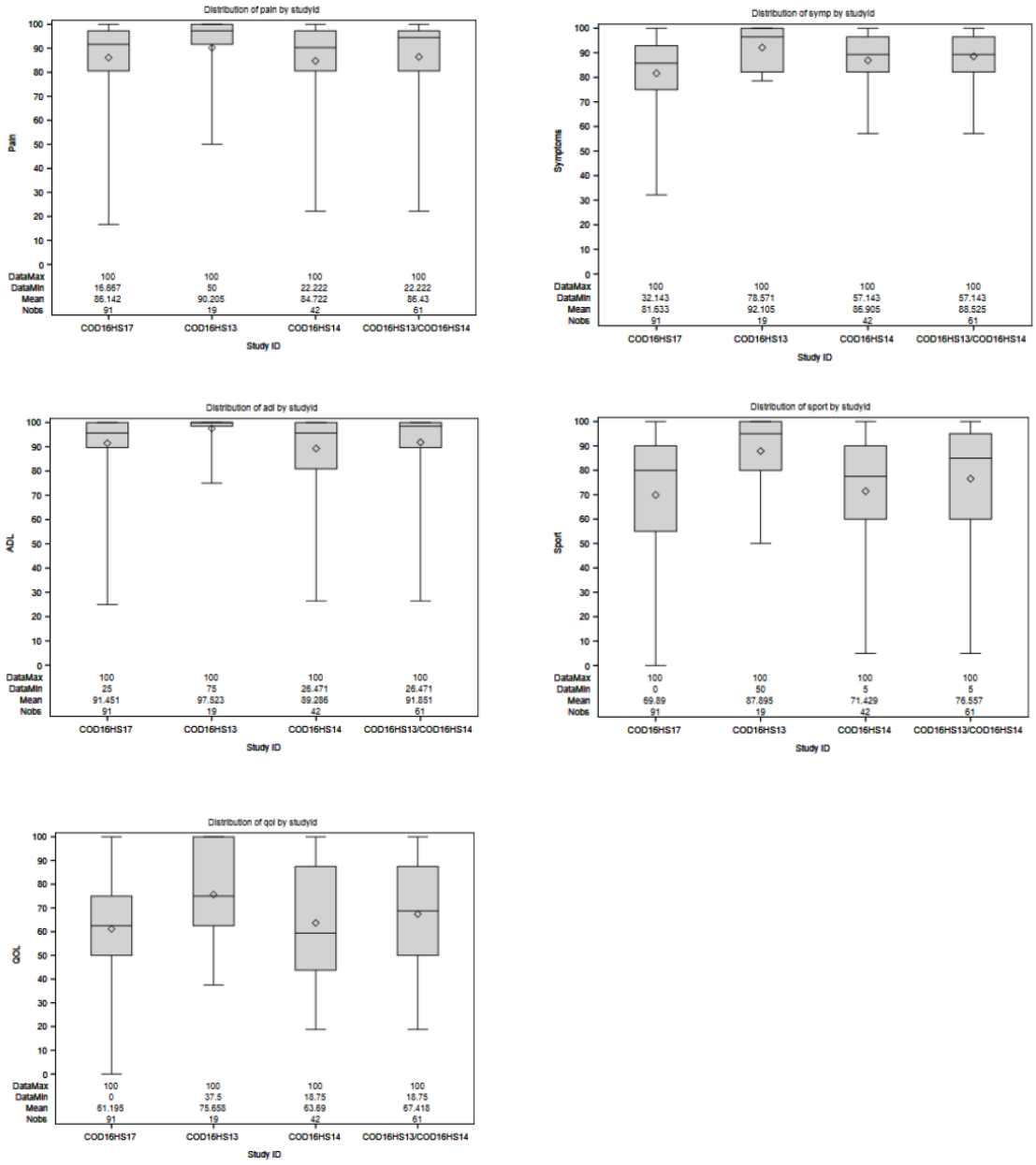
Source: Figure 15.2.1

Secondary Endpoint analysis

Figure 3 shows a graphical representation of the distribution of KOOS subscore in the populations compared across the adult and paediatric age populations, showing in the paediatric age population a wider range of scores for symptoms, sport and QoL than in the adult populations. The subscore distribution for each group of the adult age population falls, however, in the range of the paediatric age population.

All subscores of KOOS have been evaluated for non-inferiority. Non-inferiority of the subscore distribution in the paediatric age population, as evaluated on the mean difference in the 97.5% confidence interval, has been confirmed for pain and ADL in comparison to the adult age population of the Phase II clinical trial cod16HS14 and the pooled data set, but not in comparison to the adult age population of the Phase III clinical trial cod16HS13. For the subscores related to symptoms, sport and QoL non-inferiority between the paediatric population and any of the groups from the adult age population could not been confirmed. (data not shown here).

Figure 3: KOOS subscores distribution compared across the adult and paediatric age populations



Source: Figure 15.3.2.1

The Committee noted the following:

The boxplots of the KOOS total score and subscores generally show roughly similar central tendencies (mean, median) in the upper third of the scales (0-100), however, with large variability (ie wide ranges). The data suggests ceiling effects with truncated distributions at the top the scale, especially in study cod16HS13 and specific subscores (e.g. Pain, Symptoms, ADL) which may lead to bias and reduced variation (see also Assessor's comment in Methods section above).

Considering that the proposed indication targets "adolescents with closed epiphyseal growth plate", the comparison of the pediatric group with closed EGP seems most relevant for the current application. Therefore, the presented comparison of the full cod16HS17paed data (including EGP closed, open or unknown status) with adults from the cod16HS13 and cod16HS14 studies (with EGP closed status) seems less relevant. Moreover, the applicant showed nominal non-inferiority only in the comparison between the cod16HS17paed and the cod16HS14 studies.

The interpretation of the presented statistical results depends, however, on the similarity of the compared patient groups.

Statistical methods for objective 3 (comparative analysis of P2/P3 data by EGP status)

Statistical methods are the same as for objective 2 with exception of the following aspects:

Multiple testing procedure. Multiple tests were performed to evaluate the non-inferiority of treatment in pediatric patients (cod16HS17paed) versus adults using comparisons with three studies (cod16HS13, cod16HS14 and pooled cod16HS13+cod16HS14) and in three subgroups (open EGP, closed EGP, unknown EGP) and in an interim analysis. No multiple testing procedure was described to control the overall risk for false positive conclusions from these tests.

After testing of the non-inferiority hypothesis and rejection of the null hypothesis, superiority was tested by comparing the lower confidence bound to zero by applying a simple closed test procedure without adjustment of the local type 1 error (see also CPMP/EWP/482/99 "Points to Consider on Switching between Superiority and Noninferiority" [2000]).

The Committee noted the following:

Objective 3:

Multiple testing procedure. The applicant has performed multiple comparisons regarding PRO endpoints (e.g. KOOS total score, 5 subscores) and studies (cod16HS13, cod16HS14, pooled), and subgroups (EGP open, closed, unknown) and an interim analysis without controlling the global risk for false positive conclusions. Without clear pre-specification of the tested hypothesis and relevant estimands and an appropriate multiple testing procedure, the results can only be interpreted descriptively and based on nominal statistical significance, respectively.

Objective 2 and 3:

The applicant has discussed the following limitations for the comparison of paediatric patients in study cod16HS17paed and adult patients in studies cod16HS13 and cod16HS14:

- cod16HS17 (PIP) has no baseline (day of transplantation) information for the questionnaires - relevant clinical improvement cannot be shown.
- In the non-inferiority analysis, only the absolute values for the visit score can be included (not adjusted for baseline).

- The follow-up data of the cod16HS17 (PIP) are in a range of 1-8 years vs. 4 years (± 2 months) for this data at 48-month follow-up cod16HS13.
- Only for the KOOS questionnaire a reliable non-inferiority margin is available. Therefore, only confidence intervals will be specified for the other questionnaires.

The limitations described by the applicant are agreed with.

Results for objective 3 (comparative analysis of P2/P3 data by EGP status)

Table 6: Demographic characteristics (Compare FAS)

Characteristic	Statistics/ Category	15 to <18 years of age			18 to <35 years of age			
		cod 16 HS 17 (N=103)			cod 16 HS 13 (N=37)		cod 16 HS 14 (N=42) n (%)*	Pooled (N=61) n (%)*
Epiphyseal Status		Open (n=27) n(%)*	Closed (n=60) n(%)*	ND (n=16) n(%)*	Closed (N=19) n(%)*	Closed (N=18) n(%)*	Closed	Closed
Treatment		ACT3D-CS	ACT3D-CS	ACT3D-CS	ACT3D-CS	MF	ACT3D-CS	ACT3D-CS
Sex	Female	6 (22.2)	34 (56.7)	10 (62.5)	5 (26.3)	7 (38.9)	12 (28.6)	17 (27.9)
	Male	21 (77.8)	26 (43.3)	6 (37.5)	14 (73.7)	11 (61.1)	30 (71.4)	44 (72.1)
Age (years) at implantation	N	27	60	16	19	18	42	61
	Mean	15.8	16.5	15.9	24.5	27.8	26.4	25.8
	SD	0.79	0.70	0.77	4.27	5.02	4.76	4.66
	Median	16.0	17.0	16.0	23.0	30.0	26.0	26.0
	Range (Q1, Q3)	(15.0,16.0)	(16.0,17.0)	(15.0,16.5)	(21.0,28.0)	(25.0,32.0)	(23.0,31.0)	(22.0,30.0)
	Range (Min, Max)	(15.0,17.0)	(15.0,17.0)	(15.0,17.0)	(18.0,33.0)	(18.0,34.0)	(19.0,34.0)	(18.0,34.0)
Height (cm) at implantation	N	27	60	16	19	18	42	61
	Mean	177.3	173.3	175.9	179.9	174.4	179.3	179.5
	SD	11.71	9.52	7.95	8.88	8.89	10.35	9.85
	Median	179.0	174.5	175.0	180.0	175.5	178.0	178.0
	Range (Q1, Q3)	(175.0,185.0)	(166.5,180.0)	(169.0,180.5)	(174.0,188.0)	(168.0,183.0)	(172.0,186.0)	(173.0,186.0)
	Range (Min, Max)	(140.0, 195.0)	(150.0,195.0)	(165.0,192.0)	(164.0,195.0)	(160.0,189.0)	(159.0,213.0)	(159.0,213.0)
Weight (kg) at implantation	N	27	60	16	19	18	42	61
	Mean	69.9	72.1	65.4	80.3	74.2	79.0	79.4
	SD	11.57	14.14	10.49	15.90	13.93	15.15	15.27
	Median	70.0	70.0	63.0	83.0	72.0	74.5	76.0
	Range (Q1, Q3)	(65.0,75.0)	(63.0,79.5)	(57.6,71.0)	(70.0,92.0)	(63.0,80.0)	(70.0,88.0)	(70.0,89.0)
	Range (Min, Max)	(45.0,99.0)	(50.0,121.0)	(55.0,94.0)	(54.0,110.0)	(52.0,102.0)	(60.0,130.0)	(54.0,130.0)
BMI score (kg/cm^2) at implantation	N	27	60	16	19	18	42	61
	Mean	22.2	23.9	21.0	24.6	24.2	24.5	24.5
	SD	2.66	3.68	2.12	3.22	3.03	3.28	3.24
	Median	21.9	23.0	20.7	24.8	24.4	24.6	24.8
	Range (Q1, Q3)	(19.9,24.2)	(21.5,25.5)	(19.7,22.3)	(21.1,27.1)	(22.9,27.8)	(21.8,26.3)	(21.8,26.6)
	Range (Min, Max)	(15.7,26.1)	(16.9,34.6)	(18.0,25.8)	(18.8,29.7)	(18.2,28.6)	(19.0,33.2)	(18.8,33.2)

Patients [redacted] and [redacted] of paediatric NIS (cod 16 HS 17) excluded because of ICRS Grade <3.
N = total number of patients in treatment group; n = number of patients in subgroup for a specific parameter; ND = not documented
* Percentages are related to the total number of patients in the Full Analysis Set.
Source: Tables 14.4.1.1 and 14.5.1.1

Primary Endpoint Analysis

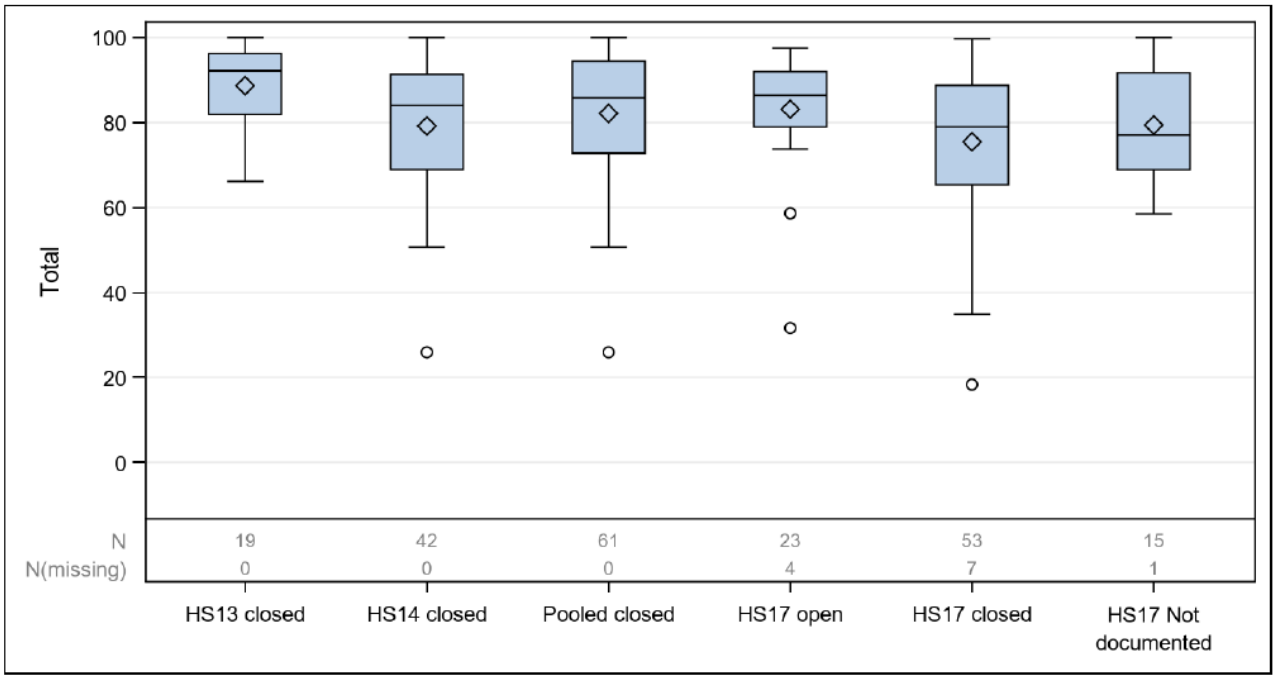
Non-inferiority evaluation on the lower confidence limit of one-sided 97.5% confidence interval showed that clinical outcome as measured by the mean difference of the total KOOS score was higher than the

non-inferiority margin of -8.5 for the following population comparisons (for details refer to Table 14.4.2.1):

- paediatric population with open EGP vs. cod16HS14 of the adult population
- paediatric population with not documented EGP vs. cod16HS14 of the adult population
- paediatric population with open EGP vs. pooled data of the adult population

Hence, (nominal) non-inferiority of the paediatric population with open or not documented EGP, respectively, was confirmed towards the adult population of the Phase II clinical trial (cod16HS14, EGP closed) for which the defect characteristics were more similar. Non-inferiority was not confirmed for the paediatric population with closed EGP vs any group of the adult population. Non-inferiority was also not confirmed for any EGP status subgroup of the paediatric population vs. adult population of the Phase III clinical trial (cod16HS13).

Figure 2: KOOS total score compared across the adult and paediatric age populations



Source: Figure 15.4.1.1.

Table 14.4.2.1: Overall and Subscores KOOS

		Status of Epiphysis			
		COD16HS13	COD16HS17		
Characteristic	Statistics	Closed (N=19)	Open (N=27)	Closed (N=60)	Not documented (N=16)
Total	N	19	23	53	15
	Mean	88.68	83.14	75.47	79.42
	SD	9.67	14.42	18.19	12.07
	Median	92.19	86.44	78.98	77.04
	Range (Q1, Q3)	(81.92, 96.25)	(78.98, 92.02)	(65.34, 88.77)	(68.92, 91.73)
	Range (Min, Max)	(66.16, 100.00)	(31.65, 97.50)	(18.33, 99.71)	(58.53, 100.00)
	Mean Diff		-5.53	-13.20	-9.26
	Mean Diff (95.0% CI)		(-13.10, 2.03)	(-19.89, -6.52)	(-17.11, -1.40)
	Mean Diff (97.5% CI)		(-13.10, I)	(-19.89, I)	(-17.11, I)

Table 14.4.2.1: Overall and Subscores KOOS

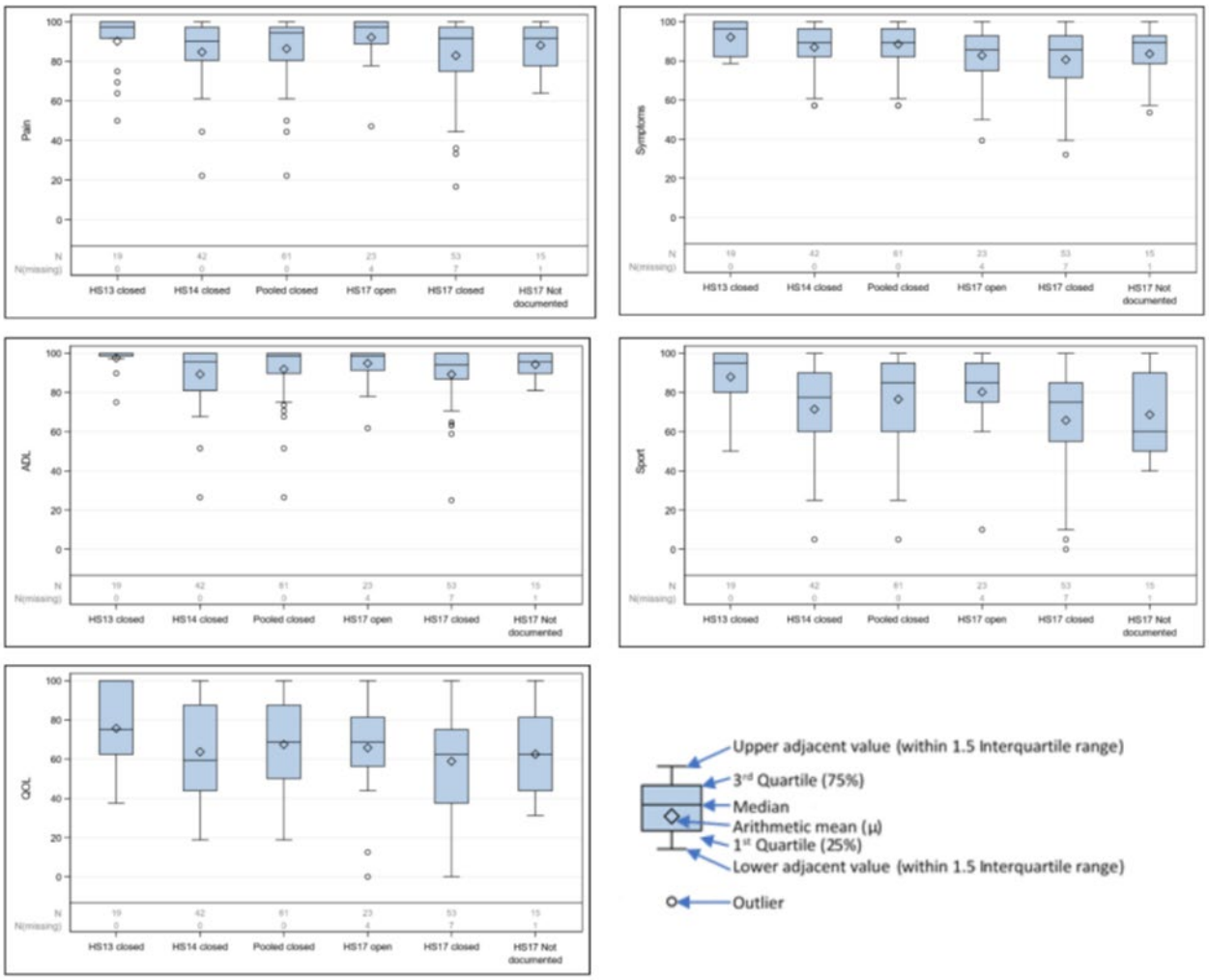
		Status of Epiphysis			
		COD16HS14	COD16HS17		
Characteristic	Statistics	Closed (N=42)	Open (N=27)	Closed (N=60)	Not documented (N=16)
Total	N	42	23	53	15
	Mean	79.21	83.14	75.47	79.42
	SD	16.61	14.42	18.19	12.07
	Median	84.03	86.44	78.98	77.04
	Range (Q1, Q3)	(68.93, 91.34)	(78.98, 92.02)	(65.34, 88.77)	(68.92, 91.73)
	Range (Min, Max)	(25.92, 100.00)	(31.65, 97.50)	(18.33, 99.71)	(58.53, 100.00)
	Mean Diff		3.94	-3.73	0.21
	Mean Diff (95.0% CI)		(-3.99, 11.87)	(-10.84, 3.38)	(-7.98, 8.41)
	Mean Diff (97.5% CI)		(-3.99, I)	(-10.84, I)	(-7.98, I)

Table 14.4.2.1: Overall and Subscores KOOS

		Status of Epiphysis			
		Pooled	COD16HS17		
Characteristic	Statistics	Closed (N=61)	Open (N=27)	Closed (N=60)	Not documented (N=16)
Total	N	61	23	53	15
	Mean	82.16	83.14	75.47	79.42
	SD	15.36	14.42	18.19	12.07
	Median	85.81	86.44	78.98	77.04
	Range (Q1, Q3)	(72.78, 94.44)	(78.98, 92.02)	(65.34, 88.77)	(68.92, 91.73)
	Range (Min, Max)	(25.92, 100.00)	(31.65, 97.50)	(18.33, 99.71)	(58.53, 100.00)
	Mean Diff		0.99	-6.68	-2.74
	Mean Diff (95.0% CI)		(-6.27, 8.24)	(-12.99, -0.38)	(-10.30, 4.83)
	Mean Diff (97.5% CI)		(-6.27, I)	(-12.99, I)	(-10.30, I)

Secondary endpoints

Figure 3: KOOS subscores distribution compared across the adult and paediatric age populations



Source: Figure 15.4.1.1.

The Committee noted the following:

The boxplots of the KOOS total score and subscores generally show roughly similar central tendencies (mean, median) in the upper third of the scales (0-100), however, with large variability (ie wide ranges). The data suggests ceiling effects with truncated distributions at the top the scale, especially in study cod16HS13 (EGP closed) and specific subscores (e.g. Pain, Symptoms, ADL) which may lead to bias and reduced variation (see also Assessor's comment in Methods section for cod16HS17ped study, see Results for objective 2).

The results show that nominally significant non-inferiority was only observed for cod16HS17paed (open EGP, unknown EGP) in comparison to the adult population of the Phase II clinical trial (cod16HS14, closed EGP) for which the defect characteristics were more similar to the pediatric population of study cod16HS17paed. However, (nominally) significant non-inferiority was not shown regarding the subgroup comparison adolescent/EGP-closed vs adult/EGP-closed, which seems most relevant for the proposed indication targeting "adolescents with closed epiphyseal growth plate".

The interpretation of the presented statistical results depends, however, on the similarity of the compared patient groups.

Clinical studies in special populations

N/A

Supportive Analysis

The non-interventional paediatric study cod 16 HS 17 paed (cod 16 HS 17 paed, 2020) has no baseline or other control. An extrapolation from adult data was therefore presented as described in the reflection paper on the use of extrapolation in the development of medicines for paediatric patients by the EMA (EMA, 2018), existing information about the pharmacology, disease manifestation and progression, and the clinical response to treatment should be collated across the source and target populations and factors that might modify the effects of treatment should be identified and investigated.

For the repair of symptomatic articular cartilage defects of the femoral condyle and the patella of the knee (International Cartilage Regeneration & Joint Preservation Society [ICRS] grade III or IV) with defect sizes up to 10 cm^2, the extension of the indication and the extrapolation from adults only applies to adolescent patients with a closed epiphyseal growth plate (EGP). Adolescent patients with a closed EGP are skeletally mature and can be considered adults from a biological point of view.

During the growth of a child, the EGPs play an essential role. In an open EGP, there is a continuous new formation of cartilage tissue that is subsequently turned over into bone tissue. By this mechanism the long bones, such as the tibia and femur, grow. Since there is new cartilage production, the healing capacity of the cartilage is still higher in paediatric patients with an open EGP. However, once the EGP is closed, the continuous new cartilage production stops. The bones and the cartilage covering the bones have reached their final size. From closure of the EGP on, there are no differences anymore in the skeleton between adolescents and adults and the cartilage has reached a mature state. In addition, there is virtually no new cartilage tissue production anymore and thereby the cartilage has lost its enhanced self-healing capacity. Early signs of normal aging, such as a decreased chondrocyte density and mechanical function, and surface wear, are generally not observed before the age of 40 (Mitrovic, Quintero et al. (1983), Temple, Bae et al. (2007)). So, from a biological point of view, adolescent patients with closed EGP are similar to young adults.

To verify whether the extrapolation of data generated with the marketed drug product in adults towards the adolescent population was justified, a comparison was performed between data generated from a subset of the adult patients from the pivotal clinical trials of Spherox (the Phase II clinical trial cod 16 HS 14 (cod 16 HS 14, 2019) and the Phase III clinical trial cod 16 HS 13 (cod 16 HS 13, 2020)) and the pooled population from both trials, and adolescent patients with closed EGP.

The overall Phase II clinical trial cod 16 HS 14 and the Phase III clinical trial cod 16 HS 13 included patients between 18 and 50 years of age. It was decided to compare against the young adult populations between 18 and < 35 years of age as: 1) articular chondral and osteochondral injuries in joints are common in people below the age of 35 and often being active in sports (Macmull, Skinner et al. (2010)), and 2) early signs of normal aging, such as a decreased chondrocyte density and mechanical function, and surface wear, are generally not observed before the age of 40 (Mitrovic et al. (1983), Temple et al. (2007)). This makes 35 a safe cut-off value to ensure there are no effects due to normal aging and that the considered age group is from the musculoskeletal point of view highly similar to adolescent patients with a closed EGP being biologically adult. As the rapporteur suggested to consider a narrower age range (e.g. <25 years of age) for the comparison, the applicant determined whether this would have an effect on the primary efficacy outcome score and the main structural repair parameter. This is described in the subsection "Comparison to adult population 18 to <25 years of age".

Pharmacodynamic parameters for comparing cartilage repair between adolescents and adults

Dosing

The dose of the drug product is 10-70 spheroids/cm² defect and this dose has been used since 2004. The bones, cartilage, and knees of adolescent patients with closed EGP are fully grown. Consequently, as a similar dose is used for adolescent patients as for adult patients, also the doses in relation to defect sizes and overall knee size are similar. Therefore, it seems likely that these dose findings from Phase II clinical trial cod 16 HS 14 can be extrapolated to the adolescent population with closed EGP.

The actual mean (SD) product dose used in cod 16 HS 17 paed (105 patients) was 33.5 (18.9), ranging from 6.7 to 93.3 spheroids/cm² defect (please refer to Table MO1- 1). Five patients received an overdose (71.5 spheroids/cm² defect, 83.9 spheroids/cm² defect, 83.3 spheroids/cm² defect, 93.3 spheroids/cm² defect and 75 spheroids/cm² defect). Despite of these overdoses, no adverse reaction (AR) was reported to be associated with the overdose. In addition, four patients received a dose below 10 spheroids/cm² (9.3 spheroids/cm² defect, 9.8 spheroids/cm² defect, 9.3 spheroids/cm² defect and 6.7 spheroids/cm² defect). In the dose confirmation Phase II clinical trial cod 16 HS 14 no differences were found in safety and efficacy between low (3 – 7 spheroids/cm²), medium (10 – 30 spheroids/cm²) and high (40 – 70 spheroids/cm²) dose groups [refer to sections 2.5.4.2.1.2 and 2.5.5.2.2.1 submitted with sequence 0052].

Furthermore, the subgroup of young adults (18 to < 35 years) from the dose confirmation Phase II clinical trial cod 16 HS 14 received a mean (SD) product dose of 22.3 (14.5) spheroids/cm², ranging from 4.7 to 59.8 spheroids/cm² (Table MO1- 1). The subgroup of young adults (18 to <35 years) from the Phase III clinical trial cod 16 HS 13 received a mean (SD) product dose of 28.1 (19.8) spheroids/cm², ranging from 10.0 to 70.0 spheroids/cm² (Table MO1- 1). Pooling the young adult populations from these two trials resulted in a mean (SD) dose of 24.1 (16.4) spheroids/cm², ranging from 4.7 to 70.0 spheroids/cm² (Table MO1- 1). Thus, there are no differences in the dose that adolescent patients and the subgroups of young adults from the pivotal studies had received. Only, some young adults from the Phase II clinical trial cod 16 HS 14 also received a dose below 10.0 spheroids/cm², which is also reflected in the pooled population. So, looking just at the administered doses, the subgroups of young adults from the pivotal trials would be suitable for extrapolation.

Table MO1- 1 Spheroid dose from different studies by age*

	15 to <18 years of age	18 to <35 years of age		
	cod 16 HS 17 paed	cod 16 HS 14	cod 16 HS 13	Pooled
Number of patients	105	42	19	61
Mean (±SD) Spheroids / cm²	33.5 ± 18.9	22.3 ± 14.5	28.1 ± 19.8	24.1 ± 16.4
Range Spheroids / cm²	6.7 – 93.3	4.7 - 59.8	10.0 - 70.0	4.7 - 70.0

*Please note that the Spherox dose is 10 – 70 spheroids/cm² cartilage defect.

Structural cartilage repair

Considering structural assessment of cartilage repair, Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) scoring on the basis of MRI assessment has been used. This is considered an adequate tool for pharmacodynamic assessment of autologous chondrocytes containing products as described in the Reflection paper on in vitro cultured chondrocyte containing products for cartilage repair of the knee by the EMA (CAT, 2010).

The mean (SD) MOCART score was 74.9 (18.5) in the adolescent population with closed EGP, 78.2 (15.1) for the young adult population from the Phase III clinical trial cod 16 HS 13, 76.0 (10.5) for the young adult population from the Phase II clinical trial cod 16 HS 14, and 76.7 (11.9) for the pooled young adult population (Table MO1- 2). The mean difference (95% CI) between the adolescent population with closed EGP and the young adult population from the Phase III clinical trial cod 16 HS 13 was -3.35 (-12.73 – 6.03), between the adolescent population with closed EGP and the young adult population from the Phase II clinical trial cod 16 HS 14 -1.12 (-7.65, 5.42), and between the adolescent population with closed EGP and the pooled young adult population -1.78 (-8.24, 4.68) (Table MO1- 2). This indicates that there was no difference in the MOCART score between the adolescent population with closed EGP and the young adult populations. An improvement in the MOCART score was observed for the young adult populations. The young adult population from the Phase III clinical trial cod 16 HS 13 had an increase of MOCART at 48 months compared to 3 months follow-up of mean (SD) 7.3 (16.0), the young adult population from the Phase II clinical trial cod 16 HS 14 of 14.1 (12.4) and the pooled young adult population of 12.4 (13.5) (Table MO1- 2). Since there were no differences in the MOCART score at follow-up between the adolescent population with closed EGP and the young adult populations, it is highly likely there was also an improvement in the MOCART score of the adolescent patients with closed EGP at follow-up compared to 3 months after treatment.

Furthermore, one of the items that is included in the MOCART score, is the degree of defect repair and defect fill. The adolescent population with closed EGP had a mean (SD, range) defect size of 3.85 (2.18, 0.75 – 12.00) cm^2 before treatment. At follow-up, 28 (65.1%) of the 43 adolescent patients with closed EGP who had an MRI, had complete filling of the chondral defect with tissue. In addition, 7 (16.3%) patients had hypertrophic (above the edge of the adjacent normal cartilage) defect fill (please note that hypertrophy on MRI can be asymptomatic). Furthermore, of the 8 (18.6%) patients with incomplete filling, filling was above 50% in height compared to the adjacent cartilage in 5 (11.6%) patients and below 50% in 3 (7.0%). None (0%) of the patients had the subchondral bone exposed (Table MO1- 2). Due to the low self-healing capacity of cartilage, as explained above, it is most likely that the neotissue filling the defect is a result of the treatment. Moreover, similar patterns were observed in the young adult populations from the other trials. The young adult population of the Phase III clinical trial cod 16 HS 13 had smaller defects, of mean (SD, range) 1.95 (0.68, 0.64 – 3.00) cm^2, but also in this population 12 (66.7%) patients had complete defect fill after 4 years, 2 (11.1%) showed hypertrophy and 4 (22.2) patients had incomplete defect fill but >50% compared to the adjacent cartilage (Table MO1- 2). The young adult population of the Phase II clinical trial cod 16 HS 14 had a mean (SD, range) defect size of 4.98 (1.27, 0.50 – 7.50) cm^2. In this population 22 (55.0%) patients had complete defect fill, 8 (20.0%) hypertrophy and 10 (5.0%) incomplete defect fill. Of the patients with incomplete defect fill, the defects of 6 (5.0%) patients were filled >50% of the adjacent cartilage and 4 (10.0%) <50% (Table MO1- 2). The pooled young adults had a defect size of 4.04 (1.80, 0.50 – 7.50) cm^2, being the most similar defect size as in the adolescent population compared to the Phase III and Phase II trials. In this population, 34 (58.6%) of the patients had complete defect fill at 4 years follow-up and in 10 (17.2%) hypertrophy was observed. Of the 14 (24.1%) patients with incomplete defect fill, in 10 (17.2%) patients the defects were filled >50% of the adjacent cartilage and in 4 (6.9%) <50% of the adjacent cartilage (Table MO1- 2).

Taking into account the limited self-repair of cartilage and the overall similar patterns between the adolescent population and the young adult populations, the MOCART score and defect fill in the adolescent population are most likely a result of the treatment. As for the young adult populations an improvement in MOCART score was shown at 48 months compared to 3 months follow-up, it is highly likely there was an improvement in the MOCART scores of the adolescent population with closed EGP as well. Furthermore, this also suggests that the outcomes on structural repair can be extrapolated from young adult populations to the adolescent population.

Table MO1- 2 MOCART score and MRI assessment of defect fill from different studies by age for patients with closed EGP

	15 to <18 years of age	18 to <35 years of age		
	cod 16 HS 17 paed	cod 16 HS 13	cod 16 HS 14	Pooled
EGP Status	**Closed**	**Closed**	**Closed**	**Closed**
Patients with MOCART score	**43**	**17**	**40**	**57**
MOCART score at follow-up	74.9 ± 18.5	78.2 ± 15.1	76.0 ± 10.5	76.7 ± 11.9
Change in MOCART score, 48 months compared to 3 months visit	-	7.3 ± 16.0	14.1 ± 12.4	12.4 ± 13.5
Mean difference MOCART (95% CI) compared to cod 16 HS 17 paed (closed EGP)	-	-3.35 (-12.73 – 6.03)	-1.12 (-7.65, 5.42)	-1.78 (-8.24, 4.68)
Defect size (cm^2)	3.85 ± 2.18 (0.75 – 12.00)	1.95 ± 0.68 (0.64 – 3.00)	4.98 ± 1.27 (0.50 – 7.50)	4.04 ± 1.80 (0.50 – 7.50)
Degree of defect repair and defect filling (% of patients with MRI examination)				
Number of patients with MRI examination	43	18	40	58
Complete	28 (65.1%)	12 (66.7%)	22 (55.0%)	34 (58.6%)
Hypertrophy	7 (16.3%)	2 (11.1%)	8 (20.0%)	10 (17.2%)
Incomplete	8 (18.6%)	4 (22.2%)	10 (25.0%)	14 (24.1%)
>50% of adjacent cartilage	*5 (11.6%)*	*4 (22.2%)*	*6 (15.0%)*	*10 (17.2%)*
<50% of adjacent cartilage	*3 (7.0%)*	*0 (0%)*	*4 (10.0%)*	*4 (6.9%)*
Subchondral bone exposed	*0 (0%)*	*0 (0%)*	*0 (0%)*	*0 (0 %)*

EGP: epiphyseal growth plate, MOCART: Magnetic Resonance Observation of Cartilage Repair Tissue.

Furthermore, the MOCART score and defect filling showed long-term effectiveness of the treatment with the drug product in adolescent patients (Table MO1- 2). Based on the comparative analysis with the adult population, it is reasonable to assume that the recommended dose for adults also applies for the adolescent population.

Follow-up times of MOCART score

As the mean (SD) follow-up time for the adolescent population with closed EGP was 48.39 (19.45) months, the structural repair was compared to the young adult populations at 4 years follow-up. The follow-up time of the adolescent patients with closed EGP ranged between 12.53 and 88.13 months. It is important to note here that it is known that the structural repair parameter, the MOCART score, increases in the first year after ACI treatment and then remains stable over a longer time up to a minimum of 10 years (Aldrian, Zak et al. (2014)). This pattern was also observed for the MOCART scores across all populations of the Phase II clinical trial cod 16 HS 14 and the Phase III clinical trial cod 16 HS 13 up to at least 5-year follow-up (Figure MO1- 1).

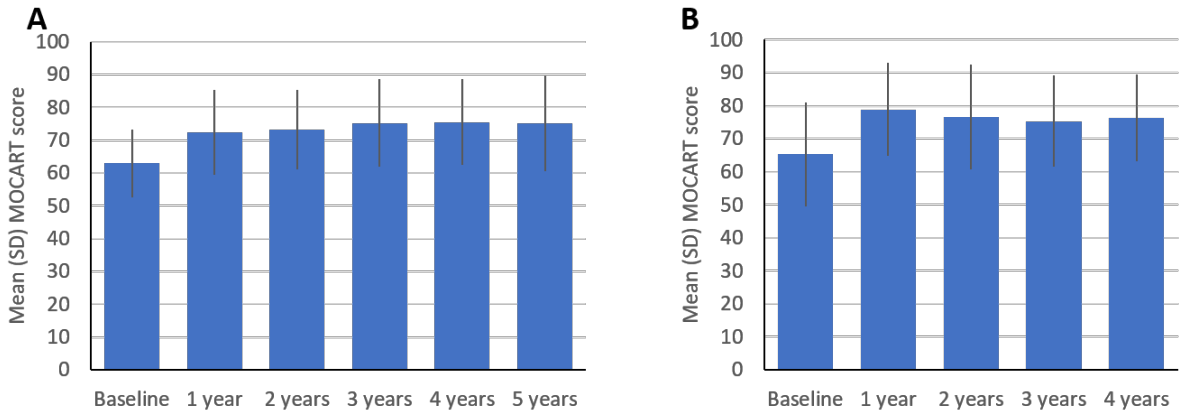


Figure MO1- 1 MOCART score from the pivotal adult trials over a 5-year follow-up time

The MOCART scores of the intention to treat population of the (A) Phase II clinical trial cod 16 HS 14 and (B) Phase III clinical trial cod 16 HS 13 at baseline (3 months) and 1, 2-, 3-, 4- and 5-years follow-up for cod 16 HS 14. For the Phase III clinical trial cod 16 HS 13 the data remained stable at 5-years follow-up as recently submitted to the EMA in the course of the PAM.

Other pharmacological aspects

Moreover, the knee tissues in adolescents with a closed EGP are not exposed to different hormones and growth factors, or other concentrations of hormones and growth factors compared to adults. Also, from a manufacturing aspect, there are no differences in the production of Spherox for adult patients and adolescent patients with a closed EGP. Furthermore, also the applied indication for the treatment of adult and adolescent patients is similar, namely the repair of symptomatic articular cartilage defects of the femoral condyle and the patella of the knee (International Cartilage Regeneration & Joint Preservation Society [ICRS] grade III or IV) with defect sizes up to 10 cm^2.

Thus, there are no differences concerning the pharmacological aspects of Spherox between adult and adolescent patients with closed EGP in the affected joint, making it justifiable to extrapolate data generated in adults to the adolescent population with closed EGP from a pharmacological point of view.

Comparison of disease manifestation and progression

Traumatic injury

In terms of disease manifestation and progression, the most frequent cause of chondral defects is a trauma (Hjelle, Solheim et al. (2002), Widuchowski, Widuchowski et al. (2007)). This is also reflected by our studies in both the adolescent (15 to 17 years of age) and young adult (18 to < 35 years of age) populations; 53 out of 103 (51.5%) adolescent patients, 32 out of 60 (53.3%) adolescent patients with closed EGP, 24 out of 42 (57.1%) young adult patients of the Phase II clinical trial cod 16 HS 14, 12 out of 19 (63.2%) young adult patients of the Phase III clinical trial cod 16 HS 13, and 36 (59.0%) of young adults in the pooled population had chondral defects caused by trauma (Table MO1- 3). The cartilage of adolescent patients with closed EGP can be considered mature and the healing rate and quality of the repair tissue is comparable to that of young adults. Furthermore, if left untreated, the progression of traumatic chondral lesions in adolescent patients with closed EGP is comparable to that of (young) adult patients (Hoburg, Loer et al. (2019), Schmal, Pestka et al. (2013)). Considering the causes of the chondral defect, the adolescent population with closed EGP and the young adult population of the Phase II clinical trial cod 16 HS 14 are mostly similar, compared to the other young adult populations.

Table MO1- 3 Chondral defects caused by trauma from different studies by age for patients with closed EGP

	15 to <18 years of age	18 to <35 years of age		
	cod 16 HS 17 paed	cod 16 HS 13	cod 16 HS 14	Pooled
EGP Status	Closed	Closed	Closed	Closed
Number of patients	60	19	42	61
Chondral defects caused by trauma	32 (53.3%)	12 (63.2%)	24 (57.1%)	36 (59.0%)

EGP: epiphyseal growth plate.

Osteochondritis Dissecans

In the adolescent population of the clinical study cod 16 HS 17 paed, the second most frequent cause of (osteo)chondral defects is osteochondritis dissecans (OCD). The chondral defects were caused by OCD in 41 out of 103 (39.8%) patients of the overall adolescent population and 24 out of 60 (40.0%) adolescent patients with closed EGP. OCD is a developmental condition consisting of a lesion of the subchondral bone progressing through the articular cartilage, causing delamination of an osteochondral fragment. These fragments can be instable or can become a loose body in the joint (Kocher, Tucker et al. (2006)). OCD is a relatively rare lesion amongst the population, with a prevalence between 0.01% and 0.06% (Fonseca & Balaco (2009)). It often presents in children and adolescents in connection with competitive sports activities (Micheli, Moseley et al. (2006)). OCD may appear at any age, but most patients are between 10 and 20 years old at the time point of diagnosis (Schmal et al. (2013)). That OCD occurs less frequent in adult patients is in agreement with our study; in our Phase II clinical trial cod 16 HS 14, 3 out of 42 (7.1%) young adult patients and 5 out of 75 (6.7%) patients with age 18 – 50 were diagnosed with OCD (OCD was an exclusion criterion in our Phase III clinical trial cod 16 HS 13).

However, OCD is not a specific condition for paediatric or adolescent patients; both acute and chronic symptomatic OCD occur in the knees of paediatric and adult patients (Detterline, Goldstein et al. (2008)).

Moreover, there are two types of OCD lesions: 1) Juvenile OCD in patient with an open distal femoral EGP, and 2) adult OCD in patients with a closed distal femoral EGP (Cahill (1995)). There are numerous examples of studies where adult patients with adult OCD have been treated with autologous chondrocyte implantation, either as a stand-alone or subgroup analysis (Cole, Deberardino et al. (2012), Pascual-Garrido, Friel et al. (2009)), or in a cohort taken together with adolescent patients with closed EGP (Aydin, Yorubutulut et al. (2020), Berruto, Ferrua et al. (2017), Bhattacharjee, McCarthy et al. (2016), Carey, Shea et al. (2020), Krishnan, Skinner et al. (2006), Minas, Ogura et al. (2018), Niethammer, Holzgruber et al. (2017), Ochs, Muller-Horvat et al. (2011), Paatela, Vasara et al. (2020), Teo, Buhary et al. (2013), Vijayan, Bartlett et al. (2012)). Aspects related to the clinical efficacy of ACI for OCD will be described in the Efficacy Section. Finally, it is important to note that although the aetiology of OCD differs from traumatic chondral defects, the disease course and progression of adult OCD is comparable to that of traumatic lesions if left untreated; adult (and also juvenile) OCD lesions that are not healed, progress to premature degenerative joint disease due to joint incongruity and abnormal load and wear patterns (Cahill (1995), Filardo et al. (2012)).

Thus, based on the facts that

- OCD is not limited to either, paediatric or adolescent patients,
- the discrimination between juvenile and adult OCD is made based on EGP status and not on age, and

- the disease progression of unhealed OCD is comparable to untreated and unhealed traumatic chondral defects,

the extrapolation of data generated in young adult patient populations can be extrapolated to the adolescent OCD patients with closed EGP.

Clinical response to treatment (efficacy and safety)

In addition to the pharmacology and the disease manifestation and progression, there are also no differences expected in relation to the clinical response to treatment (efficacy and safety) between biologically adult patients with a closed EGP above and below 18 years of age that are treated with Spherox for a chondral defect. Adolescents with a closed EGP are skeletally mature and thus biologically comparable to the young adult population up to the age of 40 (Mitrovic et al. (1983), Temple et al. (2007)).

Efficacy

No differences are expected in the clinical response to treatment between adolescent patients with a closed EGP and young adults and the indication for the treatment is the same (repair of symptomatic articular cartilage defects of the femoral condyle and the patella of the knee (International Cartilage Regeneration & Joint Preservation Society [ICRS] grade III or IV) with defect sizes up to 10 cm^2). However, for extrapolation of data generated in young adult patients to an adolescent population with closed EGP, there are other factors that influence the clinical response to treatment that need to be taken into account.

Comparison of response to treatment depending on the defect location

The first factor that can influence response to treatment is the defect location. Although the indication of Spherox comprises both the treatment of defects on the femoral condyle and the patella, patellar defects are notoriously known to be more difficult to heal and in general a higher degree of improvement is observed for defects on the femoral condyle (Chahla, Hinckel et al. (2020), Gobbi, Chaurasia et al. (2015), Kon, Filardo et al. (2016), Niemeyer, Steinwachs et al. (2008), Peterson, Vasiliadis et al. (2010)). In the adolescent population with closed EGP, 30 (50%) of the patients had the defect on the femur, 28 (46.7%) on the patella and 2 (3.3%) on both femur and patella (Table MO1- 4). In the young adult population of the Phase II clinical trial cod 16 HS 14, 14 (33.3%) patients had a defect on the femur and 28 (66.7%) on the patella (Table MO1- 4). In the young adult population of the Phase III clinical trial cod 16 HS 13 all 19 (100%) of the defects were on the femur (Table MO1- 4). This resulted in a pooled population where 33 (51.4%) of the defects were on the femur and 28 (45.9%) on the patella (Table MO1- 4). Thus, considering the defect location, the young adult population of the Phase II clinical trial cod 16 HS 14 and the pooled population are more comparable to the adolescent population with closed EGP as the young adult population of the Phase III clinical trial cod 16 HS 13. Therefore, in terms of clinical response, the young adult population of the Phase II clinical trial cod 16 HS 14 and the pooled population would be more applicable for extrapolation towards the adolescent population with closed EGP than the young adult population of the Phase III clinical trial cod 16 HS 13.

Table MO1- 4 Defect location from different studies by age for patients with closed EGP

	15 to <18 years of age	18 to <35 years of age		
	cod 16 HS 17 paed	cod 16 HS 13	cod 16 HS 14	Pooled
EGP Status Number of patients	Closed 60	Closed 19	Closed 42	Closed 61
Femur	30 (50.0%)	19 (100%)	14 (33.3%)	33 (51.4%)
Patella	28 (46.7%)	0 (0%)	28 (66.7%)	28 (45.9%)
Femur and Patella	2 (3.3%)	0 (0%)	0 (0%)	0 (0%)

Comparison of response to treatment depending on the defect size

Another factor that influences the response to treatment is the defect size; smaller defects are easier to treat and clinical improvement of treated smaller defects is usually higher compared to larger defects (Chahla et al. (2020)). This was also observed for the pivotal adult clinical trials where in the Phase II clinical trial cod 16 HS 14 defects of 4 cm^2 up to 10 cm^2 were treated and in the Phase III clinical trial cod 16 HS 13 up to 4 cm^2 (Figure MO1- 2). The mean (SD) defect size in the adolescent population with closed EGP was 3.85 (2.18) cm^2, ranging from 0.75 to 12.00 cm^2 (Table MO1- 5). The mean (SD) defect size in the young adult population of the Phase II clinical trial cod 16 HS 14 was 4.98 (1.27) cm^2, ranging from 0.50 to 7.50 cm^2 (Table MO1- 5). The mean (SD) defect size in the young adult population of the Phase III clinical trial cod 16 HS 13 was 1.95 (0.68) cm^2, ranging from 0.64 to 3.00 cm^2 (Table MO1- 5). This resulted in a mean (SD) defect size of the pooled young adult population of 4.04 (1.80) cm^2, ranging from 0.50 to 7.50 cm^2 (Table MO1- 5). Thus, also considering the defect size, the young adult population of the Phase II clinical trial cod 16 HS 14 and the pooled population are more similar to the adolescent population with closed EGP and would be more applicable to be used for extrapolation towards the adolescent population with closed EGP.

Table MO1- 5 Defect size from different studies by age for patients with closed EGP

		15 to <18 years of age	18 to <35 years of age		
		cod 16 HS 17 paed	cod 16 HS 13	cod 16 HS 14	Pooled
EGP Status Number of patients		Closed 60	Closed 19	Closed 42	Closed 61
Defect size (cm^2)	Mean ± SD	3.85 ± 2.18	1.95 ± 0.68	4.98 ± 1.27	4.04 ± 1.80
	Range	(0.75 – 12.00)	(0.64 – 3.00)	(0.50 – 7.50)	(0.50 – 7.50)

In summary, as no crucial differences in dosing, defect size or defect locations were observed for verification of the clinical response in terms of efficacy, it is justifiable to extrapolate the data generated in the young adult (18 to < 35) subgroup of the Phase II clinical trial cod 16 HS 14 and the pooled young adult population from both the pivotal trials to the adolescent population with closed EGP.

Comparison of efficacy regarding the course of patient-reported outcomes

As the mean (SD) follow-up time for the adolescent population with closed EGP was 48.39 (19.45) months, the efficacy and safety data were compared to the young adult populations at 4 years follow-up. The follow-up time of the adolescent patients with closed EGP ranged between 12.53 and 88.13 months. It is important to note here that it is known that the primary outcome parameters, the overall Knee

Injury and Osteoarthritis Outcome Score (KOOS) and the KOOS subscores increase in the first year after ACI treatment and then remain stable over 10 years follow-up (Carey et al. (2020), Peterson et al. (2010)). This pattern was also observed for the overall KOOS and KOOS subscores across all populations of the Phase II clinical trial cod 16 HS 14 and the Phase III clinical trial cod 16 HS 13 up to at least 5-year follow-up (Figure MO1- 2).

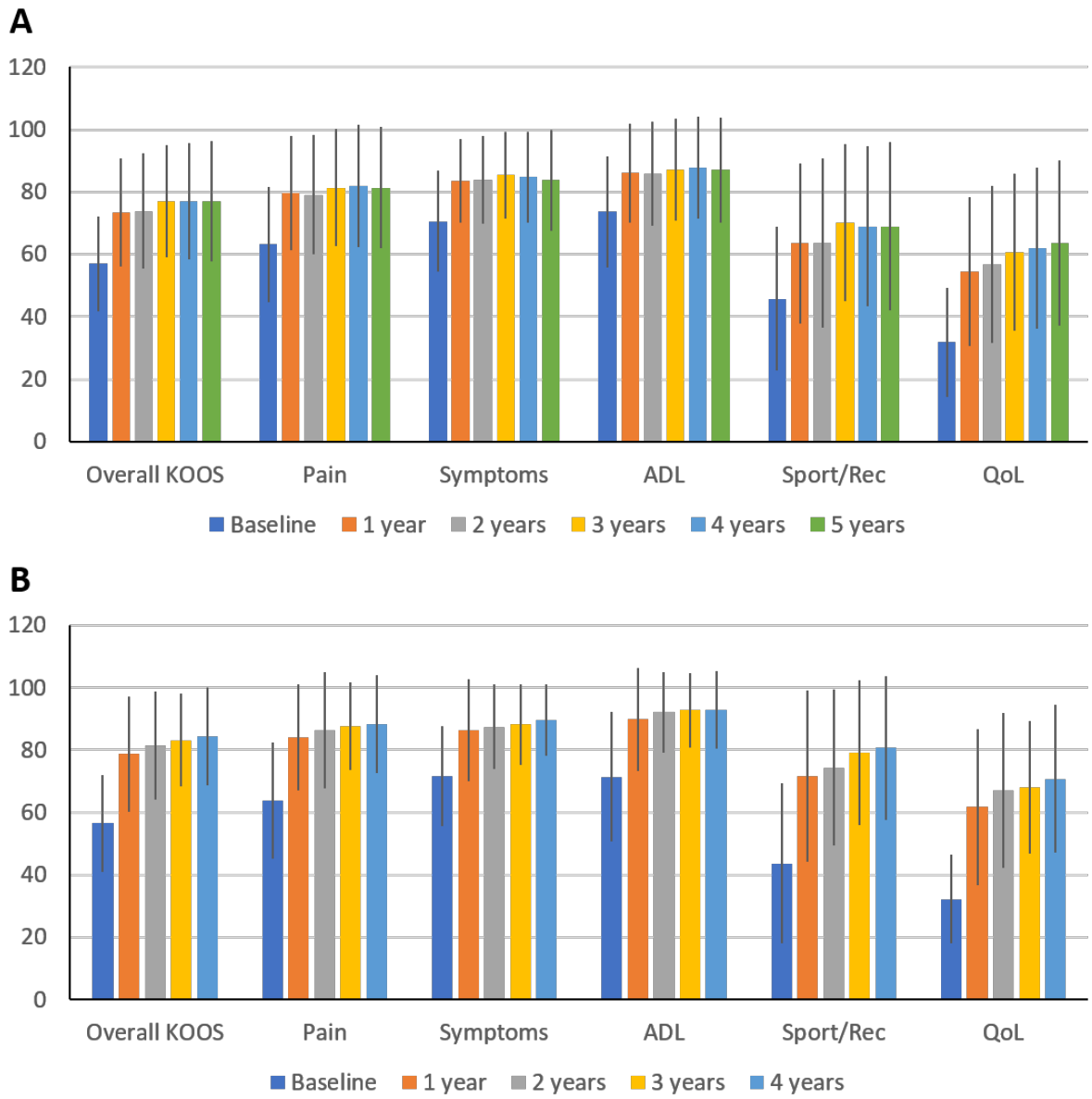


Figure MO1- 2 Overall KOOS and KOOS subscores from the pivotal adult trials over a 5-year follow-up time

The overall Knee Injury and Osteoarthritis Outcome Score (KOOS) and its subscores Pain, Symptoms, Activities of daily living (ADL), Sport and recreation (Sport/Rec) and Quality of life (QoL) of the intention to treat population of the (A) Phase II clinical trial cod 16 HS 14 and (B) Phase III clinical trial cod 16 HS 13 at baseline and 1-, 2-, 3-, 4- and 5-years follow-up (only for cod 16 HS 14). For the Phase III clinical trial cod 16 HS 13 the data remained stable at 5 years follow-up as recently submitted to the EMA in the course of the PAM.

For the overall KOOS and KOOS subscores, non-inferiority analyses could be performed with a reliable non-inferiority margin between the adolescent population with closed EGP versus the young adults from the Phase II clinical trial cod 16 HS 14 and the pooled young adult population. In the populations with

chondral defects (ICRS grade 3 or 4) the mean (SD) overall KOOS was in the adolescent population with closed EGP 75.5 (18.2), in the young adult population from the Phase II clinical trial cod 16 HS 14 79.2 (16.6) and in the pooled young adult population 82.2 (15.4) (Table MO1- 6). For adolescent patients with closed EGP status non-inferiority could not be confirmed for the overall KOOS, but the variability of the overall KOOS was relatively high in this group. Moreover, the arithmetic means and medians of the adolescent population with closed EGP did fall within the interquartile ranges of all the adult populations (refer to Figure 2.7.3- 8 submitted with sequence 0052).

For the KOOS subscores, the mean (SD) KOOS Pain was 83.0 (19.0) in the adolescent population with closed EGP, 84.7 (16.7) for the young adult population from the Phase II clinical trial cod 16 HS 14 and 86.4 (16.2) for the pooled young adult population (Table MO1- 6). For KOOS symptoms these values were 80.6 (17.1), 86.9 (11.7) and 88.5 (11.0), for KOOS activities of daily living (ADL) 89.2 (14.8), 89.3 (15.3) and 91.9 (13.6), for KOOS sport and recreation (Sport) 65.8 (25.7), 71.4 (24.7) and 76.6 (23.3), for KOOS quality of life (QoL) 58.8 (25.2), 63.7 (23.6) and 67.4 (23.3) for the adolescent population with closed EGP, the young adult population from the Phase II clinical trial cod 16 HS 14 and the pooled young adult population, respectively (Table MO1- 6). For KOOS ADL non-inferiority could be confirmed between the adolescent population with closed EGP and the young adult population from the Phase II clinical trial cod 16 HS 14 and the pooled young adult population. However, also for all KOOS subscores the arithmetic means and medians of the adolescent population with closed EGP did fall within the interquartile ranges of all the adult populations (refer to Figures 2.7.3- 9 and Figure 2.7.2- 10 submitted with sequence 0052). For the young adult populations, the baseline KOOS scores were available. For the young adult population from the Phase II clinical trial cod 16 HS 14 the overall KOOS improved with mean (SD) 21.9 (15.1) points and for the pooled young adult population the improvement was 22.6 (15.1) at 48 months follow-up compared to baseline (Table MO1- 6). For the overall KOOS a change of 8 – 10 points is considered a change needed for the effect to be clinically relevant (Roos & Lohmander (2003)). The change in overall KOOS for the adult populations is well above this minimally clinically important change.

Since there were no differences in the overall KOOS score at follow-up between the adolescent population with closed EGP and the young adult populations, it is highly likely there was also an improvement in the overall KOOS score of the adolescent patients with closed EGP at follow-up compared to baseline.

Table MO1- 6 Overall KOOS and KOOS subscores from different studies by age for patients with closed EGP

		15 to <18 years of age	18 to <35 years of age	
		cod 16 HS 17 paed	cod 16 HS 14	Pooled
EGP Status		**Closed**	**Closed**	**Closed**
Number of patients		**53**	**42**	**61**
KOOS	**overall**	75.5 ± 18.2	79.2 ± 16.6	82.2 ± 15.4
	change from baseline	-	21.9 ± 15.1	22.6 ± 15.1
KOOS subscores	Pain	83.0 ± 19.0	84.7 ± 16.7	86.4 ± 16.2
	Symptoms	80.6 ± 17.1	86.9 ± 11.7	88.5 ± 11.0
	ADL	89.2 ± 14.8	89.3 ± 15.3	91.9 ± 13.6
	Sport	65.8 ± 25.7	71.4 ± 24.7	76.6 ± 23.3
	QoL	58.8 ± 25.2	63.7 ± 23.6	67.4 ± 23.3

EGP: epiphyseal growth plate, KOOS: Knee Injury and Osteoarthritis Outcome Score, ADL: Activities of daily living, Sport: Sport and recreation, QoL: Quality of life

For the other efficacy outcomes there is no non-inferiority margin available, so these were analysed descriptively with 95% confidence intervals. The International Knee Documentation Committee (IKDC) subjective knee evaluation form score (SD) was 74.3 (17.7) in the adolescent population with closed EGP, 74.4 (18.6) for the young adult population from the Phase II clinical trial cod 16 HS 14 and 78.4 (17.8) for the pooled young adult population (Table MO1- 7). The mean difference (95% CI) between the adolescent population with closed EGP and the young adult population from the Phase II clinical trial cod 16 HS 14 was -0.18 (-7.67, 7.30), and between the adolescent population with closed EGP and the pooled young adult population -4.13 (-10.73, 2.47) (Table MO1- 7). From this it can be concluded that the IKDC subjective knee evaluation form scores are comparable between the adolescent population with closed EGP versus the young adult population from the Phase II clinical trial cod 16 HS 14 and the pooled young adult population.

Furthermore, for the Modified Lysholm score no differences could be found between the adolescent population with closed EGP and the young adult populations (from the Phase II clinical trial cod 16 HS 14 and the pooled). The Modified Lysholm score (SD) was 20.1 (3.8) in the adolescent population with closed EGP, 20.9 (3.8) for the young adult population from the Phase II clinical trial cod 16 HS 14 and 21.4 (3.4) for the pooled young adult population (Table MO1- 7). The mean difference (95% CI) between the adolescent population with closed EGP and the young adult population from the Phase II clinical trial cod 16 HS 14 was -0.83 (-2.37, 0.72), and between the adolescent population with closed EGP and the pooled young adult population -1.32 (-2.66, 0.02) (Table MO1- 7).

Table MO1- 7 Other patient-reported efficacy outcomes from different studies by age for patients with closed EGP

	15 to <18 years of age	18 to <35 years of age	
	cod 16 HS 17 paed	cod 16 HS 14	Pooled
EGP Status	**Closed**	**Closed**	**Closed**
Number of patients	**53**	**42**	**61**
IKDC subjective knee evaluative form score	74.3 ± 17.7	74.4 ± 18.6	78.4 ± 17.8
Mean difference (95% CI)	-	-0.18 (-7.67, 7.30)	-4.13 (-10.73, 2.47)
Modified Lysholm score	20.1 ± 3.8	20.9 ± 3.8	21.4 ± 3.4
Mean difference (95% CI)	-	-0.83 (-2.37, 0.72)	-1.32 (-2.66, 0.02)

EGP: epiphyseal growth plate, IKDC: international knee documentation committee.

Comparison of efficacy in patients with OCD

Considering OCD, although the aetiology of OCD (as explained above) is different to that of traumatic chondral lesions, OCD is an indication for ACI and ACI is recommended for OCD lesions in patients with a closed EGP (Pascual-Garrido et al. (2009), Teo et al. (2013)). Generally, it is believed there is no difference in the efficacy of ACI for OCD versus traumatic chondral lesions as long as the bone is reconstructed (please also refer to response to RSI - Other Concerns 5) (Cole et al. (2012), Filardo et al. (2014)). In the Phase II clinical trial cod 16 HS 14 five adult patients with OCD were treated and their primary efficacy scores were comparable to those of the overall population (Table MO1- 8).

The patient reported outcomes of both the overall adolescent population and the adolescent population with closed EGP from our study cod 16 HS 17 paed are comparable to outcomes reported in other studies

evaluating the use of ACI for OCD lesions in both adolescent patients with mostly closed EGP and adults (Berruto et al. (2017), Carey et al. (2020), Cole et al. (2012), Filardo et al. (2014), Filardo et al. (2012), Krishnan et al. (2006), Niethammer et al. (2017), Ochs et al. (2011), Pascual-Garrido et al. (2009), Teo et al. (2013)). This underlines that also efficacy outcomes for the treatment of OCD in adolescent patients can be extrapolated from adult populations.

Table MO1- 8 Overall KOOS and KOOS subscores in patients with OCD from the Phase II clinical trial cod 16 HS 14

		18 to 50 years of age	
		cod 16 HS 14 - OCD	**cod 16 HS 14 – all**
Number of patients		**5 (ITT)**	**73 (ITT)**
KOOS	**overall**	75.4 ± 17.2	77.1 ± 18.6
KOOS subscores	Pain	77.8 ± 22.5	82.0 ± 19.6
	Symptoms	83.6 ± 13.7	84.7 ± 14.4
	ADL	89.1 ± 13.1	87.8 ± 16.3
	Sport	68.0 ± 27.3	68.9 ± 25.6
	QoL	58.8 ± 21.9	62.0 ± 25.9

KOOS: knee injury and osteoarthritis outcome score, ADL: activities of daily living, Sport: sport and recreation, QoL: quality of life, ITT: intention to treat.

Summary on efficacy

In summary, taking into account the defect location and defect size, the data generated in the young adult (18 to <35 years of age) population from Phase II clinical trial cod 16 HS 14 and the pooled young adult population from both pivotal trials would be suitable for extrapolation towards the adolescent population. Comparison of the efficacy data generated in these two young adult populations to the adolescents with closed EGP showed no differences. Therefore, although no baseline data is available for the adolescent study cod 16 HS 17 paed, it is reasonable to assume that the adolescent population with closed EGP showed clinical improvement in the range of these two young adult populations based on comparable aetiology and course of the disease and comparable mode of action of Spherox in these patients.

Comparison to adult population 18 to <25 years of age

As abovementioned, the adolescent population was compared to young adult populations between 18 and < 35 years of age as: 1) articular chondral and osteochondral injuries in joints are common in people below the age of 35 and often being active in sports (Macmull et al. (2010)), and 2) early signs of normal aging, such as a decreased chondrocyte density and mechanical function, and surface wear, are generally not observed before the age of 40 (Mitrovic et al. (1983), Temple et al. (2007)).

However, as the rapporteur suggested to consider a narrower age range (e.g. <25 years of age) for the comparison, the applicant determined whether this would have an effect on the primary efficacy outcome score (overall KOOS and subscores), and the main structural repair parameter (MOCART score).

As expected, no differences were observed in the overall KOOS, the KOOS subscores and the MOCART score (Table MO1- 9). However, the number of patients in the subgroups decreased a lot (Table MO1- 9) and this would limit the reliability of statistical comparisons. Therefore, it was decided not to perform statistical analyses as the descriptive statistics was comparable between the subgroups 18 to <25 years of age and 18 to <35 years of age. For more details on the comparison, please refer to response to RSI – Major Objection – Annex 1.

For the comparison with the young adult populations from the Phase II clinical trial cod 16 HS 14 and the Phase III clinical trial cod 16 HS 13 and the pooled population from these trials, the safety evaluations for each of the studies were prepared for a follow-up time up to 4 years, because the safety data of the Phase II clinical trial cod 16 HS 14 and the Phase III clinical trial cod 16 HS 13 were available up to that time. In addition, these data were also prepared from the adolescent patients per EGP status group. In all adolescent EGP status groups, also the adolescent population with closed EGP, the most occurring ARs were 'joint effusion', 'joint swelling' and 'arthralgia'. Overall, the safety profiles of the overall adolescent population and adolescent population with closed EGP showed similar safety profiles as the young adults' populations of the Phase II clinical trial cod 16 HS 14 and the Phase III clinical trial cod 16 HS 13 and the pooled population from these trials (Table MO1- 12). For more details, please see section 2.7.4.2.1.3.1 (submitted with sequence 0052). As expected, no ARs could be identified that were specific for the adolescent population. This is in line with other studies on ACI in adolescent patients (Dai & Cai (2012), Micheli et al. (2006), (2005), Niethammer et al. (2017), Ogura et al. (2017)). As no safety issues specific for the adolescent population were expected nor occurred, the extrapolation of safety data from ACI treatment in adults towards the adolescent population is justifiable.

To summarise, as adolescent patients with a closed EGP are biologically adults, no differences were expected nor could be identified related to the pharmacology, and disease manifestation and progression in the young adult population of patients treated with ACI and the adolescent population with a closed growth plate. Considering the clinical response to treatment, the young adults (18 to < 35 years) of the Phase II clinical trial cod 16 HS 14 and the pooled young adult population from the Phase II clinical trial cod 16 HS 14 and the Phase III clinical trial cod 16 HS 13 are more similar to the adolescent population with closed EGP, based on the defect locations and defect sizes as well as dosing, and would be most applicable for extrapolation.

No differences were found in the MOCART score, defect filling based on MRI and clinical efficacy outcomes between the adolescent population with closed EGP from the study cod 16 HS 17 paed and the Phase II clinical trial cod 16 HS 14 and the pooled young adult population from the Phase II clinical trial cod 16 HS 14 and the Phase III clinical trial cod 16 HS 13. In addition, no differences considering safety were found between the adolescent population with closed EGP from the study cod 16 HS 17 paed and the Phase II clinical trial cod 16 HS 14, the Phase III clinical trial cod 16 HS 13, and the pooled young adult population from the Phase II clinical trial cod 16 HS 14 and the Phase III clinical trial cod 16 HS 13.

OCD lesions occur at a higher rate in adolescent and young adult patients between 10 and 20 years of age. However, OCD is not an adolescent-specific disease, the treatment and disease progression of OCD in adolescent patients is comparable to that of traumatic OCD lesions in adult patients. In addition, also the clinical response to treatment of OCD is expected to be comparable in adolescent patients and adult patients. Although the total number of OCD patients in the adolescent study cod 16 HS 17 paed and the Phase II clinical trial cod 16 HS 14 is too limited to allow a reliable statistical comparison, overall no differences were observed.

Thus, it is reasonable to assume that the adolescent population with closed EGP showed clinical improvement in the range of the adult patient population of the Phase II clinical trial cod 16 HS 14 and the pooled young adult population from the Phase II clinical trial cod 16 HS 14 and the Phase III clinical trial cod 16 HS 13. Consequently, clinical efficacy and safety data of the young adult population of the Phase II clinical trial cod 16 HS 14 and the Phase III clinical trial cod 16 HS 13 can be extrapolated to justify the clinical efficacy and safety of Spherox in the adolescent population with a closed EGP for the

repair of symptomatic articular cartilage defects of the femoral condyle and the patella of the knee (International Cartilage Regeneration & Joint Preservation Society [ICRS] grade III or IV) with defect sizes up to 10 cm^2. These data extrapolated from the young adult population is underlined by the clinical safety and efficacy profile generated in the adolescent population in study cod 16 HS 17 paed. The extrapolated data from the young adult population treated with the drug product and supported by the data generated in the adolescent population with closed EGP justifies the proposed indication of Spherox for the repair of symptomatic articular cartilage defects of the femoral condyle and the patella of the knee (International Cartilage Regeneration & Joint Preservation Society [ICRS] grade III or IV) with defect sizes up to 10 cm^2 in adults and adolescents with closed epiphyseal growth plate in the affected joint.

2.4.3. Discussion on clinical efficacy

The approved indication for Sperox is:

Repair of symptomatic articular cartilage defects of the femoral condyle and the patella of the knee (International Cartilage Regeneration & Joint Preservation Society [ICRS] grade III or IV) with defect sizes up to 10 cm2 in adults.

The current variation seeks to expand this indication to include paediatric patients with a closed growth plate as follows:

Repair of symptomatic articular cartilage defects of the femoral condyle and the patella of the knee (International Cartilage Regeneration & Joint Preservation Society [ICRS] grade III or IV) with defect sizes up to 10 cm2 in adults and adolescents with closed epiphyseal growth plate in the affected joint.

To support this variation, the MAH submitted the final results of the PIP study cod16HS17paed which also included additional analyses to the previously conducted Phase II and Phase III study in adults. An interim analysis of study cod16HS17paed had previously been provided in the initial MAA dossier.

Design and conduct of clinical studies

Study cod16HS17paed was a non-interventional, open-label, pro-and retrospective, multicentre surveillance study conducted in patients who had undergone ACI-M with co.don chondrosphere and who were at least 15 years of age but less than 18 years of age at the time of implantation/treatment with co.don chondrosphere. In addition, treatment had to be administered 1 to 8 years before enrolment in the non-interventional study.

There was no fixed study visit schedule. Data collected by the physicians were either derived from the medical records or documented using the specific examination form provided for this study, completed at routine visit(s) after patients had submitted their signed and dated informed consent. Patient reported outcome data were also available for a subgroup of patients.

In addition, patients were requested to complete a web-based questionnaire at home once during the course of the study. The chondroidal structure of the knee joint was assessed in a subgroup of patients undergoing physical examination including MRI, if applicable.

The primary endpoint of interest was the treatment failure rate up to the time point of the survey, defined as the 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.

All variables were analysed in an exploratory manner using descriptive statistical methods.

Efficacy data and additional analyses

cod16HS17paed

From all patients assessed for eligibility in study Cod16HS17paed, 110 were included and 122 were not included because of 'decline to participate' or 'other reason'.

The full analysis set (FAS) comprised 105 patients and the physical examination subpopulation comprised 94 patients (88.7%). The median follow-up time was 53.5 months (range: 12.5, 94.1).

Cartilage lesion caused by trauma was the most common diagnosis (54 [51.4%] patients). The mean (SD) defected area size was 4.07 (1.95) cm2 and ranged from a minimum of 0.75 cm^2 to a maximum of 12.00 cm^2.

Most patients had 1 defect (101 [96.2%]). The most common location for the cartilage defect was the femur (57 [52.3%]), followed by the patella (50 [45.9%]) and the tibia (2 [1.8%] patients). Most of the cartilage lesions were classified as ICRS grade 4 (87 [79.8%] patients). The epiphysis at implantation was closed in 61 (58.1% of patients), open in 28 (26.7%) and not documented in 16 (15.2%) patients.

During the follow-up time of the survey, 26 patients received at least one additional surgery after the ACI procedure; of which 5 cases were reportedly related to ACI with co.don chondrosphere (treatment failure rate 0.048).

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 'closed' epiphysis status.

An MRI examination was performed in 79 (84.0%) patients in the PE subpopulation. Defect repair and filling were complete in 47 (59.5%) patients, incomplete (>50% of adjacent cartilage) in 12 (15.2%) patients and incomplete (<50% of adjacent cartilage) in 3 (3.8%) patients. Subchondral bone was exposed in 1 (1.3%) patient and 16 (20.3%) patients experienced hypertrophy.

An MRI within a time window of ± 3 month 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 outcome data were available for 92 of 105 FAS patients.

The mean (SD) KOOS total score was 78.13 (16.52). The highest mean (SD) KOOS subscale score for the overall FAS population was observed for 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 overall subjective mean (SD) total IKDC score was 77.4 (17.1) and the mean (SD) Lysholm Knee Scale score was 20.9 (1.6).

A significant number of patients reported additional surgical procedures during the biopsy and/or implantation. Concurrent surgeries during biopsy were documented in 40 (38.1%) patients. Concurrent surgeries during implantation were documented in 41 (39.0%) patients. These additional surgical components, in addition to treatment with chondrosphere, may have impacted the various patient outcomes.

Also, while the reported treatment failure rate was low, affecting 5 patients only, still 26 patients in total (24.8%) underwent at least one additional surgery after the ACI procedure. The reasons for these surgeries are further discussed in the safety section.

Besides that the study is descriptive in nature, there are no baseline assessments available and only single data points for each patient, that is, no repeated measures over time. There is also significant risk for bias e.g. due to inaccurate recall of information by the patients e.g. on symptoms and/or use of pain medications.

Overall, the interpretability of the results seems to be limited because of the non-interventional, open-label, multi-centre study design with a single visit without a control group or baseline visit as a reference. Therefore, results cannot easily be interpreted or only in the context of general clinical experience, which may depend the standards of the national health system.

Analysis of cod16HS17paed vs cod16HS13 and cod16HS14 in adults

The MAH conducted additional analyses

- to compare the treatment effect in patients from 15 to <18 years of age (adolescents) in this paediatric study with the treatment effect observed in the Phase II and Phase III studies of patients aged from 18 to less than 35 years (adults) treated with of the ACT3D-CS product (objective 2), and also
- to compare the treatment effect in patients from 15 to <18 years of age by EGP (epiphyseal growth plate) status with the treatment effect in the Phase II and Phase III studies of patients aged from 18 to less than 35 years (adults) treated with of the ACT3D-CS product (objective 3).

The analyses of the data aimed to evaluate the non-inferiority of treatment effect in the paediatric population compared to an adult population. The statistical analysis was conducted by comparing patients from 15 to <18 years of age (cod16HS17paed) separately with three other groups of adult patients from 18 to <35 years of age (cod16HS13, cod16HS14 and pooled cod16HS13+cod16HS14) using Compare-FAS.

Overall, there are a number of important methodological concerns which affect the interpretability of the results.

Regarding objective 2 (overall comparison between the studies):

- **Study Design:** The evaluation of the treatment effect is based on two independent open-label studies in a paediatric based on a single visit without baseline vs repeated measurements in an adult population. Therefore, comparisons of the treatment effect may be affected by confounding factors which may cause or compensate for differences in the outcome. Statistical methods are not expected to sufficiently resolve this issue.
- **Endpoints**: The primary endpoint "Overall KOOS score" includes multiple subscores, for which sensitivity to change/responsiveness has not been demonstrated in the application. In the context of a non-inferiority study, a summary score may show no difference to the comparison group because of a lack of responsiveness of one or more subscores which dilute actual differences. In addition, to make any claims on an aggregated level, the claims should be supported by all subscores. Therefore, the sensitivity to change of the overall score and all subscores of the KOOS instrument would need to be demonstrated by other studies (or additional analyses in the submitted studies).

  Also, according to the KOOS User's Guide 1.1 (Updated August 2012): "A total score has not been validated and is not recommended. For the purpose of an RCT, KOOS subscale scores can be aggregated and averaged as the primary outcome. The five individual KOOS subscale scores are then given as secondary outcomes to enable clinical interpretation." (see also Roos et al., 2011, PMID

26069575, for a discussion of the total KOOS score). The applicant would need to provide the coefficients (incl 95% confidence intervals) for the psychometric test properties of the KOOS total score including objectivity, reliability, validity, and especially sensitivity to change/responsiveness describing also floor/ceiling effects. While it is acknowledged that the KOOS total score was accepted as a primary endpoint in previous studies (cod16HS13: at 24 months, cod16HS14: at 12 months), the appropriateness of the instrument to cover a follow-up period up to 8 years with an average around 4 years needs to be discussed, for example, regarding ceiling effects. Ceiling effects may truncate the true underlying distribution of health outcomes, thereby, causing biased estimates and reduced variance.

- **Multiple testing procedure:** The applicant has performed multiple comparisons regarding PRO endpoints (total, 5 subscores) and studies (cod16HS13, cod16HS14, pooled cod16HS13 + cod16HS14) without controlling the global risk for false positive conclusions. Without clear pre-specification of the tested hypothesis and relevant estimands and an appropriate multiple testing procedure, the results can only be interpreted descriptively and based on nominal statistical significance, respectively.
- **Results/Primary Endpoint:** The boxplots of the KOOS total score and subscores generally show roughly similar central tendencies (mean, median) in the upper third of the scales (0-100), however, with large variability (ie wide ranges). The data suggests ceiling effects with truncated distributions at the top the scale, especially in study cod16HS13 and specific subscores (e.g. Pain, Symptoms, ADL) which may lead to bias and reduced variation.
- **Results/Relevance and Significance:** Considering that for the proposed indication targeting "adolescents with closed epiphyseal growth plate" comparisons of the pediatric group with closed EGP and adult groups with closed EGP seem most relevant the current application. Therefore, the presented comparison of the full cod16HS17paed data (including EGP closed, open or unknown status) with adults from the cod16HS13 and cod16HS14 studies (with EGP closed statues) seems less relevant. Moreover, the applicant showed nominal non-inferiority only in the comparison between the cod16HS17paed and the cod16HS14 studies. The interpretation of the presented statistical results depends, however, on the similarity of the compared patient groups at baseline.

Regarding objective 3 (comparison between the studies by EGP status):

- **Multiple testing procedure:** The applicant has performed multiple comparisons regarding PRO endpoints (e.g. KOOS total score, 5 subscores) and studies (cod16HS13, cod16HS14, pooled), and subgroups (EGP open, closed, unknown) without controlling the global risk for false positive conclusions. Without clear pre-specification of the tested hypothesis and relevant estimands and an appropriate multiple testing procedure, the results can only be interpreted descriptively and based on nominal statistical significance, respectively.
- **Results/Primary Endpoint:** The boxplots of the KOOS total score and subscores generally show roughly similar central tendencies (mean, median) in the upper third of the scales (0-100), however, with large variability (ie wide ranges). The data suggests ceiling effects with truncated distributions at the top the scale, especially in study cod16HS13 (EGP closed) and specific subscores (e.g. Pain, Symptoms, ADL) which may lead to bias and reduced variation.
- **Results/Significance:** The results show that nominally significant non-inferiority was only observed for cod16HS17paed (open EGP, unknown EGP) in comparison to the adult population of the Phase II clinical trial (cod16HS14, closed EGP) for which the defect characteristics were more similar to the pediatric population of study cod16HS17paed. However, (nominally) significant non-inferiority was not shown regarding the subgroup comparison adolescent/EGP-closed vs adult/EGP-closed, which seems most relevant for the proposed indication targeting "adolescents with closed epiphyseal

growth plate". The interpretation of the presented statistical results depends, however, on the similarity of the compared patient groups at baseline.

Regarding both objectives 2 and 3:

- No baseline data is available for the primary and secondary endpoints to compare patient groups.
- No baseline data is available for the primary and secondary endpoints to calculate relative changes (adjusted for baseline).
- The follow-up data of the cod16HS17paed study range from 1 to 8 years in comparison to follow-up data at 4 years (± 2 months) from the 48-month follow-up in study cod16HS13 or cod16HS14.

Discussion on Extrapolation analysis

To support extrapolation from adults, the MAH provided a discussion addressing the pharmacology, disease manifestation and progression, and the clinical response to treatment, this with the aim to show that the evidence generated in the approved adult patient population would be sufficiently relevant to the currently sought target population of adolescent patients with closed EGP. These aspects are further discussed below.

Dosing/exposure

The proposed dosing recommendations for adolescent patients will be the same as the approved dosing recommendations in adults, 10-70 spheroids are applied per cm2 defect.

There were no remarkable differences in the mean ± SD dose between the paed study as compared to young adult patients 18 to <35 years of age (Table MO1-1). Five paediatric patients received a too high dose (71.5 spheroids/cm² defect, 83.9 spheroids/cm² defect, 83.3 spheroids/cm2 defect, 93.3 spheroids/cm2 defect and 75 spheroids/cm2 defect) but without reported adverse reactions. Four patients received a slightly too low dose, almost all close to the 10 spheroid/cm2 lower dosing limit and such cases of lower exposure were also included in study cod 16 HS 14.

The adolescent population with closed EGP had a mean (SD, range) defect size of 3.85 (2.18, 0.75 – 12.00) cm2 before treatment. This defect size is consistent with the approved indication (up to 10 cm2). Thus, it can be assumed that the relative exposure to Spherox between the young adult population and the paediatric adolescent population is comparable.

Pharmacodynamics

During the pubertal growth spurt, proliferation and differentiation of chondrocytes, secretion of extracellular matrix, calcification of the hypertrophic zone, invasion and differentiation of osteoblast, and formation of blood vessel repeat continuously in the growth plate. At the end of the pubertal stage, these processes stop, and longitudinal growth completes (e.g. Shim KS. Ann Pediatr Endocrinol Metab 2015;20:8-12). On the other hand, age-related changes in cartilage density, especially in the superficial zone of weight-bearing surfaces tends to be observed after 40 years of age (Temple MM. et al. Osteoarthritis and Cartilage. 2007;15:1042-52).

When the epiphyseal growth plates are closed, adolescents are skeletally mature and could be considered young adults biologically, regarding their skeletal system and joint cartilage. Thus, this population should be biologically comparable to the young adult population up to the age of 40.

There was no difference in the MOCART score between the adolescent population with closed EGP and the young adult patients 18 to <35 years of age (Table MO1-2). Given these similarities, the company views that the MOCART score of the adolescent patients with closed EGP must reflect an improvement, in line

with the improvement from baseline observed in the adult studies. Another indicator of this assumption would be the defect fill observed in the paed population. At follow-up, 28 (65.1%) of the 43 adolescent patients with closed EGP who had an MRI, had complete filling of the chondral defect with tissue and another 19% had incomplete filling of the defect, indicating effect from the ACI treatment. The range of the follow-up time of the adolescent patients with closed EGP was wide, ranging between 12.53 and 88.13 months. On the other hand, the company provided descriptive figures of MOCART score over time from the studies in adults which show a stable trend over time, which seems reassuring.

Disease manifestation and progression

As expected, the most common reason for chondral defects is trauma, 32 out of 60 (53.3%) adolescent patients with closed EGP in the paed study vs. 36 (59.0%) of young adults (18 to <35 years of age) in the pooled adult population. The second most frequent cause of (osteo)chondral defects is osteochondritis dissecans (OCD), 24 out of 60 (40.0%) adolescent patients with closed EGP. This occurred less frequently in adult patients, in cod 16 HS 14, 3 out of 42 (7.1%) young adult patients, and it was an exclusion criterion in study cod 16 HS 13. However, the MAH cited references that describe the successful treatment of adult OCD patients with ACI. The disease course and progression of adult OCD is also comparable to that of traumatic lesions if left untreated. Thus, in this regard, the two patient populations could be viewed as sufficiently comparable. In the Phase II clinical trial cod 16 HS 14 five adult patients with OCD were treated and their primary efficacy scores were comparable to those of the overall population (Table MO1- 8).

Further analyses of the two populations based on *defect location* and *defect size* were also provided.

In the adolescent population with closed EGP, 30 (50%) of the patients had the defect on the femur, 28 (46.7%) on the patella and 2 (3.3%) on both femur and patella. In the young adult population of the Phase II clinical trial cod 16 HS 14, 14 (33.3%) patients had a defect on the femur and 28 (66.7%) on the patella (Table MO1- 4). In the young adult population of the Phase III clinical trial cod 16 HS 13 all 19 (100%) of the defects were on the femur (inclusion criteria).

Similarly, in the Phase II clinical trial cod 16 HS 14 defects of 4 cm2 up to 10 cm2 were treated but in the Phase III clinical trial cod 16 HS 13 only up to 4 cm2. The mean (SD) defect size in the adolescent population with closed EGP was 3.85 (2.18) cm2, ranging from 0.75 to 12.00 cm2 (Table MO1- 5).

Thus, it can be agreed with the MAH that in terms of defect location and size, the adolescent population with closed EGP from the paed study more resembled the patient population enrolled in study cod HS 14 than study cod HS 13. In the populations with chondral defects (ICRS grade 3 or 4) the mean (SD) overall KOOS was in the adolescent population with closed EGP 75.5 (18.2), similar to the young adult population from the Phase II clinical trial cod 16 HS 14 79.2 (16.6). In the pooled young adult population, this was 82.2 (15.4) and in the young adult population of the Phase III study cod HS 13, it was 88.7 (9.7).

The company concludes that the adolescent population with closed EGP showed clinical improvement in the range of these two young adult populations in the respective adult studies, based on comparable aetiology and course of the disease and comparable mode of action of Spherox in these patients, in particular study cod HS 14. This can be agreed.

Comparison to adult population 18 to <25 years of age

No differences were observed in the overall KOOS, the KOOS subscores and the MOCART score (see Table MO1- 9) in this subgroup (N=25) compared to the earlier analysis comparing to 18 to <35 years of age (N=61).

Thus, it is expected that the treatment effect of Spherox as demonstrated in the young adult population will be similar in the adolescent population with closed EGP.

Safety

The safety of the whole adolescent population and the adolescent population per EGP status group were compared to the safety of young adults (18 to < 35 years) in the pivotal clinical trials of Spherox (the Phase II clinical trial cod 16 HS 14 and the Phase III clinical trial cod 16 HS 13) and the pooled population from both these pivotal trials. The most common reported ARs, both between biopsy and implantation as well as during / after implantation, were 'joint effusion', 'joint swelling' and 'arthralgia' (Table MO1- 11). The comparative safety profile generated (comparing the 2 populations) was very similar, see Table MO1-12.

Given the similarities between the populations in exposure and underlying disease conditions, the extrapolation of safety data from ACI treatment in adults towards the adolescent population seems to be justifiable.

Conclusion

The MAH has provided additional analyses and discussions, addressing the pharmacology (dose, PD effects); similarities and differences between the respective target populations (adolescents with closed EGP vs. young adults) in terms of disease and other baseline characteristics; and expectations for clinical response to treatment (efficacy and safety data).

Overall, it can be agreed that the efficacy and safety profile of Spherox, as known for the approved indication which was supported by the pivotal studies cod HS 13 and cod HS 14, could be extrapolated to the adolescent population with closed EGP.

Also, adolescents with closed epiphyseal growth plates are skeletally mature and could be considered young adults biologically, regarding their skeletal system and joint cartilage. Thus, this population should be biologically comparable to the young adult population up to the age of 40.

The data cannot be extrapolated to a population with open EGP. In this population, there is continuous production of new healthy cartilage and the B/R balance of treating such patients with Spherox would be different. In addition, the MAH has not conducted any randomized clinical trials in patients with open EGP.

2.4.4. Conclusions on the clinical efficacy

In conclusion, the sought extension of the indication:

Repair of symptomatic articular cartilage defects of the femoral condyle and the patella of the knee (International Cartilage Regeneration & Joint Preservation Society [ICRS] grade III or IV) with defect sizes up to 10 cm^2 in adults ***and adolescents with closed epiphyseal growth plate in the affected joint***

Is accepted.

2.5. Clinical safety

Introduction

A total of 120 patients aged 14 to less than 18 years have been treated with chondrosphere in the context of two non-interventional paediatric studies, cod 16 HS 17 paed (n= 105) and cod 16 HS 16 (n= 29). Of note, there is an overlap of 14 patients between both studies.

For the current procedure, the clinical safety presentation will focus on the PIP study cod 16 HS 17 with some references to prior submitted data, where appropriate. Given the issues of overlap in patients between the cod 16 HS 17 and cod 16 HS 16 studies and differences in study design, the MAH selected not to conduct a pooled safety presentation. Cod 16 HS 16 was presented in the original MAA and at the time not considered to provide useful information on safety due to the retrospective and descriptive nature of the study, as well as the issue of overlap.

Patient exposure

A total of 105 patients were treated with chondrosphere in study cod 16 HS 17 paed. Open implantation was performed in 80 (76.2%) patients and arthroscopic implantation in 25 (23.8%) patients. The mean number of spheroids used was 117.4± 50.9 (range: 15, 300); the mean co.don chondrosphere dose was 33.5± 18.9 spheroids/cm2 (range: 6.7, 93.3).

The mean follow-up time was 52.2 months (range 12.5 to 94.1 months) (1-8 years).

Adverse events

Overall summary of AEs

Table: Overview of Adverse events and adverse reactions (FAS)

Characteristic	Overall (N=105) n (%)*	Status of Epiphysis		
		Open (N=28) n (%)*	Close (N=61) n (%)*	Not documented (N=16) n (%)*
Adverse Events	26	9	13	4
By Patients:				
Patients with AEs	15 (14.3)	7 (6.7)	6 (5.7)	2 (1.9)
Serious / non-serious AEs:				
Patients with SAEs	5 (4.8)	3 (2.9)	1 (1.0)	1 (1.0)
Patients with non-serious AEs	11 (10.5)	4 (3.8)	6 (5.7)	1 (1.0)
Timepoint of adverse events:				
Patients with AEs during biopsy and until implantation	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
Patients with AEs during implantation	2 (1.9)	0 (0.0)	1 (1.0)	1 (1.0)
Patients with AEs after implantation	14 (13.0)	6 (5.7)	6 (5.7)	2 (1.9)
ARs	81	10	49	22
By Patients:				
Patients with AR	27 (25.7)	3 (2.9)	16 (15.2)	8 (7.6)
Serious / non-serious AR:				
Patients with SAR	8 (7.6)	1 (1.0)	3 (2.9)	4 (3.8)
Patients with non-serious AR	22 (21.0)	2 (1.9)	13 (12.4)	7 (6.7)
Timepoint of AR:				
Patients with AR during biopsy and until implantation	14 (13.3)	2 (1.9)	10 (9.5)	2 (1.9)
Patients with AR during implantation	9 (8.6)	0 (0.0)	9 (8.6)	0 (0.0)
Patients with AR after implantation	18 (17.1)	3 (2.9)	7 (6.7)	8 (7.6)

N = total number of patients in treatment group; n = number of patients in subgroup for a specific parameter
*Percentages are related to the total number of patients in the FAS.
AR: Adverse reaction; AE: Adverse event; SAR: Serious adverse reaction; SAE: Serious adverse event
Source: Tables 14.2.13.1 and 14.2.13.2

The Committee noted that according to the study protocol (including the latest amendment, Amendment 2, 16 March 2018), conventional definitions were to be used, i.e., an AE was defined as any unfavourable and unintended sign, symptom, or disease temporarily associated with the use of a medicinal product/surgical procedure, whether or not considered related to the medicinal product. An AE was to be classified as an adverse drug reaction if the physician classified the event as at least possibly related to the drug product (or surgical procedure).

Somewhat confusingly, the MAH filed a corrigendum to the clinical study report stating that the definitions for adverse reactions (ARs) and adverse events (AEs) were adapted such that all AEs were to be considered non-related events and ARs were to be considered related events.

Thus, for example in the table above, ARs should not be viewed as a subgroup of AEs. Rather these events are additive.

In total, 26 AEs were reported in 15 (14.3%) patients.

In total, 5 (4.8%) patients experienced SAEs. Most AEs affected the musculoskeletal system and connective tissues or were classified as injuries or procedural complications. Most AEs were experienced 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 experienced AE by preferred term was 'arthralgia' (3 [2.9%] patients).

A listing of these AEs (that were not considered related to the drug product or the surgical procedure by the treating physician) by SOC and PT is provided in the summary table below.

Table: Adverse events by time point, SOC and PT (FAS)

Time point	System Organ Class Preferred Term	Total (N=105) n (%)*
Adverse Events		
Biopsy until Implantation	Patients with at least one Adverse Event	1 (1.0)
	Musculoskeletal and connective tissue disorders	1 (1.0)
	Joint effusion	1 (1.0)
Implantation	Patients with at least one Adverse Event	2 (1.9)
	Injury, poisoning and procedural complications	1 (1.0)
	Meniscus injury	1 (1.0)
	Musculoskeletal and connective tissue disorders	2 (1.9)
	Arthralgia	1 (1.0)
	Bone cyst	1 (1.0)
	Joint effusion	1 (1.0)
Post Implantation	Patients with at least one Adverse Event	14 (13.3)
	Blood and lymphatic system disorders	1 (1.0)
	Bone marrow oedema	1 (1.0)
	Infections and infestations	1 (1.0)
	Administration site infection	1 (1.0)
	Injury, poisoning and procedural complications	6 (5.7)
	Contusion	1 (1.0)
	Graft delamination	1 (1.0)
	Joint dislocation	1 (1.0)
	Ligament sprain	1 (1.0)
	Radius fracture	1 (1.0)
	Scar	1 (1.0)
	Transplant failure†	1 (1.0)
	Musculoskeletal and connective tissue disorders	10 (9.5)
	Arthralgia	3 (2.9)
	Bone cyst	1 (1.0)
	Bone marrow oedema	1 (1.0)
	Bursitis	1 (1.0)
	Chondromalacia	1 (1.0)
	Chondropathy	1 (1.0)
	Exostosis	1 (1.0)
	Joint effusion	1 (1.0)
	Joint range of motion decreased	1 (1.0)
	Joint swelling	1 (1.0)

N = total number of patients in treatment group; n = number of patients in subgroup for a specific parameter
* Percentages are related to the total number of patients in the FAS.
Patients with more than one adverse reaction within a system organ class (SOC) were counted once in the respective SOC.
Note: Patients with more than one adverse reaction assigned the same preferred term (PT) were counted only once for the PT.
† In total, 6 transplant failures occurred, with one considered as unrelated and reported as AE
Source table: 14.2.13.4

A listing of adverse reactions by SOC and PT is provided in the summary table below.

Table: Adverse reactions by time point, SOC and PT (FAS)

Time point	System Organ Class Preferred Term	Total (N=105) n (%)*
Adverse Reactions		
Biopsy until Implantation	Patients with at least one Adverse reaction	14 (13.3)
	Musculoskeletal and connective tissue disorders	14 (13.3)
	Arthralgia	2 (1.9)
	Joint effusion	13 (12.4)
	Joint swelling	7 (6.7)
Implantation	Patients with at least one Adverse reaction	9 (8.6)
	Musculoskeletal and connective tissue disorders	9 (8.6)
	Joint effusion	5 (4.8)
	Joint swelling	7 (6.7)
Post Implantation	Patients with at least one Adverse reaction	18 (17.1)
	Blood and lymphatic system disorders	1 (1.0)
	Bone marrow oedema	1 (1.0)
	General disorders and administration site conditions	3 (2.9)
	Implant site hypertrophy	1 (1.0)
	Pain	2 (1.9)
	Infections and infestations	1 (1.0)
	Administration site infection	1 (1.0)
	Injury, poisoning and procedural complications	6 (5.7)
	Administration site hypertrophy	1 (1.0)
	Cartilage injury	1 (1.0)
	Graft loss	1 (1.0)
	Meniscus injury	1 (1.0)
	Transplant failure†	5 (4.8)
	Musculoskeletal and connective tissue disorders	15 (14.3)
	Arthralgia	4 (3.8)
	Chondromalacia	2 (1.9)
	Chondropathy	1 (1.0)
	Infrapatellar fat pad inflammation	1 (1.0)
	Joint noise	1 (1.0)
	Joint effusion	5 (4.8)
	Joint swelling	8 (7.6)
	Joint warmth	1 (1.0)
	Loose body in joint	1 (1.0)
	Osteochondrosis	1 (1.0)
	Synovitis	1 (1.0)
	Tendonitis	1 (1.0)

N = total number of patients in treatment group; n = number of patients in subgroup for a specific parameter
* Percentages are related to the total number of patients in the FAS.
Patients with more than one adverse reaction within a system organ class (SOC) were counted once in the respective SOC.
Note: Patients with more than one adverse reaction assigned the same preferred term (PT) were counted only once for the PT.
† In total, 6 transplant failures occurred, with one considered as unrelated and reported as AE
Source: Table 14.2.13.6

A total of 81 ARs were reported in 27 (25.7%) patients. In total, 22 (21.0%) patients experienced non-serious ARs and 8 (7.6%) experienced serious ARs. Most ARs occurred post implantation (18 [17.1%] patients) in the 'musculoskeletal and connective tissue disorders' SOC (15 [14.3%] patients); 8 (7.6%) patients developed 'joint swelling', 5 (4.8) patients developed 'joint effusion', 4 (3.8%) patients developed 'arthralgia', 2 (1.9%) patients developed 'chondromalacia', and one (1.0%) patient each developed 'chondropathy', 'infrapatellar fat pad inflammation', 'joint crepitation', 'joint warmth' 'loose body in joint', 'osteochondrosis', 'synovitis' and 'tendonitis'.

The Committee noted that only 26% of the patient population reported one or more adverse reactions which might signify an underreporting, e.g. due to recall bias and/or lack of documentation. The type of events reported, most frequently to the SOCs 'Musculosketelal and connective tissue disorders' and 'Injury, poisoning and procedural complications' is consistent with the pivotal clinical trials in adults.

Serious adverse event/deaths/other significant events

No deaths were reported.

Table: Serious adverse events by time point, SOC and PT (FAS)

Time point	System Organ Class Preferred Term	Total (N=105) n (%)*
SAE		
Biopsy until Implantation	Patients with at least one SAE	1 (1.0)
	Musculoskeletal and connective tissue disorders	1 (1.0)
	Joint effusion	1 (1.0)
Implantation	Patients with at least one SAE	1 (1.0)
	Injury, poisoning and procedural complications	1 (1.0)
	Meniscus injury	1 (1.0)
	Musculoskeletal and connective tissue disorders	1 (1.0)
	Arthralgia	1 (1.0)
	Joint effusion	1 (1.0)
Post Implantation	Patients with at least one SAE	4 (3.8)
	Blood and lymphatic system disorders	1 (1.0)
	Bone marrow oedema	1 (1.0)
	Infections and infestations	1 (1.0)
	Administration site infection	1 (1.0)
	Injury, poisoning and procedural complications	2 (1.9)
	Graft delamination	1 (1.0)
	Joint dislocation	1 (1.0)
	Transplant failure	1 (1.0)
	Musculoskeletal and connective tissue disorders	2 (1.9)
	Chondropathy	1 (1.0)
	Joint swelling	1 (1.0)
	Loose body in joint	1 (1.0)
	Osteochondrosis	1 (1.0)

N = total number of patients in treatment group; n = number of patients in subgroup for a specific parameter * Percentages are related to the total number of patients in the FAS.
Patients with more than one SAE within a system organ class (SOC) were counted once in the respective SOC.
Patients with more than one SAE assigned the same preferred term (PT) were counted only once for the PT.
SAE = Serious Adverse Event
Source: Tables 14.2.13.5

The SAE events in the above table were considered not (or unlikely) related to chondrosphere by the treating physician.

Table: Serious adverse reactions by time point, SOC and PT (FAS)

SAR		
Biopsy until Implantation	Patients with at least one SAR	0 (0.0)
Implantation	Patients with at least one SAR	0 (0.0)
Post Implantation	Patients with at least one SAR	8 (7.6)
	General disorders and administration site conditions	3 (2.9)
	Implant site hypertrophy	1 (1.0)
	Pain	2 (1.9)
	Infections and infestations	1 (1.0)
	Administration site infection	1 (1.0)
	Injury, poisoning and procedural complications	5 (4.8)
	Cartilage injury	1 (1.0)
	Graft loss	1 (1.0)
	Meniscus injury	1 (1.0)
	Transplant failure	5 (4.8)
	Musculoskeletal and connective tissue disorders	4 (3.8)
	Joint effusion	1 (1.0)
	Joint swelling	2 (1.9)
	Loose body in joint	1 (1.0)
	Osteochondrosis	1 (1.0)

N = total number of patients in treatment group; n = number of patients in subgroup for a specific parameter * Percentages are related to the total number of patients in the FAS.
Patients with more than one SAR within a system organ class (SOC) were counted once in the respective SOC.
Patients with more than one SAR assigned the same preferred term (PT) were counted only once for the PT.
SAR = Serious Adverse Reaction
Source: Tables 14.2.13.7

The events in the above SAR table related to serious adverse reactions considered at least possibly related to chondrosphere by the treating physician.

Treatment failure

In the study cod 16 HS 17 paed a treatment failure was 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 chondral lesion involving either extensive debridement for lesion expansion, violation of the subchondral bone, or (repeated) autologous chondrocyte implantation (ACI).

Only five out of 105 patients fell under this definition and had to be treated for failures of the transplants causing clinical symptoms. Three of them received additional ACI and one underwent microfracture procedure. Microfracture uses violation of subchondral bone and thus was considered a treatment failure. One patient was reported to have a transplant failure/cartilage ulcer that was assessed as possibly related to insufficient cartilage regeneration after ACI but could have also been linked to a former patella luxation. However, since this case was classified as transplant/treatment failure by the attending surgeon, it was counted as treatment failure although no surgical re-treatment has been performed.

Among the patients with treatment failure, two had a closed epiphyseal growth plate (EGP) and received additional ACI treatments, one had an open EGP and for two it has not been determined.

Twenty-one patients underwent additional surgeries that did not qualify for a treatment failure and were not performed with the intent to restore the originally treated chondral lesion. Instead, most of them targeted other joint structures (please refer to Table 1). For some patients, more than one type of surgery was performed within one intervention.

Table 1 Additional surgeries after ACI in cod 16 HS 17 paed

Type of surgery	Number of surgeries performed (whole adolescent population)	Number of surgeries performed (patients with open/not documented EGP status)	Number of surgeries performed (patients with closed EGP status)
Plate/screw removal	7	2	5
Shaving	8	4	4
Meniscus surgery	5	3	2
Bone reconstruction/removal	2	2	0
Arthrolysis	2	1	1
Non-ACI cartilage repair techniques for other defects	2	1	1
Infection	1	1	0
Loose body resection	1	0	1
Synovectomy/plica resection	1	0	1
Patellofemoral realignment surgery	1	0	1
ACI for other defects	1	1	0
2nd look arthroscopy for diagnostic purposes	1	0	1

The additional surgeries after the ACI were in part required as follow-up procedures to the concomitant surgeries during biopsy/implantation (please refer to response to RSI – Other Concerns 5). For example, in cases of bone reconstruction or osteotomy insertion of screws or plates was frequently needed in concurrent surgeries during ACI for stabilisation of the bone. Removal of the inserted metal parts was necessary later (N=7), as the metal implants caused problems and pain for the patients. Metal implant-related issues can have a negative impact on clinical outcome which would not be due to cartilage-related problems.

Shaving (N=8) is often used to remove non-symptomatic loose superficial cartilage layers in the transplant area or others to avoid delamination of those loose superficial layers or to ensure a smooth movement of the joint. However, shaving does not involve a violation of the subchondral bone, is not an extensive debridement and does not lead to an extension of the chondral lesion. Consequently, shaving in the transplant area is not classified as a treatment failure.

Shaving is also a method to reduce cartilage hypertrophy, a typical complication of ACI with incidence rates reported between 9% and 40% (Niethammer, Pietschmann et al., 2014). The reported rate in our study is even lower and hypertrophy must not be regarded as treatment failure, as the hypertrophic tissue may be resected and symptoms resolve.

Bone reconstruction/removal (N=2), loose body resection (N=1), synovectomy/plica resection (N=1) and patellofemoral realignment surgery (N=1) as often conducted in the course of ACI procedures can also become necessary after ACI as obvious in the study patients, independent of the originally treated cartilage lesion.

Meniscus injuries (N=5) are common in a young and active population and are not related to the treatment of cartilage performed before. The same applies for cartilage defects other than those that have been treated originally. In order to address these, non-ACI cartilage repair techniques (N=2) and ACIs (N=1) have been applied. Concerning the cases of arthrolysis (N=2) and joint infection (N=1), these are typical complications after any surgery and therefore may not be attributed specifically to the chondrosphere treatment.

Thus, additional surgeries after ACI are often needed, but are not necessarily done in order to enhance or modify the original attempt for cartilage repair but instead to treat accompanying pathologies that exist on top of a cartilage defect. In these cases, additional surgeries reflect a more complex situation and therefore outcome is not expected to be better than in patients who do not require those.

In order to assess the impact of additional surgeries after ACI on the patients` outcome, further analyses of our study data were performed. Regarding the whole study population, overall Knee Injury and Osteoarthritis Outcome Score (KOOS) ± SD (standard deviation) for patients who received additional surgeries after ACI yielded 70.7 ± 20.5, for patients without these additional interventions KOOS ± SD was higher reaching 81.1 ± 13.7 (please refer to Table 2). KOOS subscores also showed higher values throughout for patients without additional surgeries (please refer to Table 3). Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) score ± SD was 72.5 ± 16.3 for patients with additional surgeries after ACI and 75.1 ± 16.9 for patients without these (please refer to Table 5).

In the subpopulation of patients with closed EGP data showed the same pattern. For closed EGP patients who had additional surgeries after ACI overall KOOS ± SD was 68.8 ± 21.9, for closed EGP patients without additional interventions KOOS ± SD was higher yielding 78.1 ± 16.0 (please refer to Table 2). KOOS subscores also showed higher values throughout for patients with closed EGP and without additional surgeries (please refer to Table 4). MOCART score ± SD for closed EGP patients with additional surgeries was 76.0 ± 19.7 and for closed EGP patients without additional interventions reached 74.6 ± 18.2 (please refer to Table 5).

Table 2 Overall KOOS for patients with and without additional surgeries after ACI, respectively

	Whole adolescent population		Closed EGP	
	With additional surgeries	Without additional surgeries	With additional surgeries	Without additional surgeries
N	26	66	15	38
Mean	70.7	81.1	68.8	78.1
SD	20.5	13.7	21.9	16.0
Range	58.6 – 89.3	76.1 – 90.2	53.4 – 88.5	70.4 – 88.8

Table 3 KOOS subscores for patients with and without additional surgeries after ACI, respectively, in the whole adolescent population

	Pain		Symptoms		ADL*	
	With additional surgeries	Without additional surgeries	With additional surgeries	Without additional surgeries	With additional surgeries	Without additional surgeries
N	26	66	26	66	26	66
Mean	79.4	88.9	76.5	83.7	86.4	93.6
SD	20.7	13.8	19.1	14.6	17.3	9.6
Range	69.4 – 94.4	83.3 – 97.2	57.1 – 92.9	78.6 – 92.9	77.9 – 98.5	91.2 – 100.0
	Sports and Recreation		QoL†			
	With additional surgeries	Without additional surgeries	With additional surgeries	Without additional surgeries		
N	26	66	26	66		
Mean	59.8	74.0	51.2	65.2		
SD	27.9	21.1	29.6	20.4		
Range	40.0 – 85.0	60.0 – 90.0	25.0 – 75.0	50.0 – 81.3		

* ADL = activities of daily living
†QoL = knee-related quality of life

Table 4 KOOS subscores for patient with and without additional surgeries after ACI, respectively, in closed EGP subpopulation

	Pain		Symptoms		ADL*	
	With additional surgeries	Without additional surgeries	With additional surgeries	Without additional surgeries	With additional surgeries	Without additional surgeries
N	15	38	15	38	15	38
Mean	76.3	85.6	75.0	82.8	83.6	91.4
SD	23.5	16.6	18.7	16.2	20.6	11.3
Range	66.7 – 94.4	80.6 – 97.2	57.1 – 92.9	75.0 – 92.9	72.1 – 100.0	91.2 – 100.0
	Sports and Recreation		QoL†			
	With additional surgeries	Without additional surgeries	With additional surgeries	Without additional surgeries		
N	15	38	15	38		
Mean	57.7	69.0	51.3	61.8		
SD	30.4	23.3	29.6	23.0		
Range	40.0 – 80.0	55.0 – 85.0	25.0 – 75.0	50.0 – 75.0		

* ADL = activities of daily living
†QoL = knee-related quality of life

Table 5 MOCART scores for patients with and without additional surgeries after ACI, respectively

	Whole adolescent population		Closed EGP	
	With additional surgeries	Without additional surgeries	With additional surgeries	Without additional surgeries
N	20	59	10	34
Mean	72.5	75.1	76.0	74.6
SD	16.3	16.9	19.7	18.2
Range	62.5 – 85.0	65.0 – 90.0	70.0 – 90.0	65.0 – 90.0

KOOS is an outcome value reflecting a patient´s opinion on their problems associated with the whole knee. Taking into account that additional surgeries after ACI as another invasive treatment cause stress and pain for the patients, KOOS would be expected to be lower in these patients than in patients without additional surgery. This is clearly supported by our data showing clinically perceptible higher values in the group that did not receive additional surgery.

Focusing on MOCART (Magnetic Resonance Observation of Cartilage Repair Tissue) scores that particularly record morphological parameters of cartilage repair, values did not differ between patients receiving additional surgeries and patients that did not. We conclude that cartilage restoration showed success in all cases, even if other structures in the joint needed treatment along with ACI.

In the light of our results, he MAH concludes that patients with additional surgeries, as expected, seem to have suffered a more complicated disease which had an impact on clinical outcome.

Study Cod 16 HS 16

In study cod 16 HS16, 2012 AEs were collected retrospectively from 2004 to 2011 at eight clinical sites in Germany. In total, 39 patients aged below 18 years were identified as having been treated with Spherox at the participating sites. Data from 29 patients were obtained.

Two TAE (symptom progression and no therapeutic response) were reported for 1 patient at the 1st visit after 9 months. In the same patient, additional 4 non-treatment related AEs were observed, which comprised undifferentiated connective tissue disease, arthropathy and skeletal injury during the 5th time interval (78 to <156 weeks) and arthropathy during the 6th time interval (156 to <234 weeks). The remaining 5 non-treatment related AEs in 5 patients comprised infection (13 to <26 weeks), ligament sprain (156 to <234 weeks), joint surgery (52 to <78 weeks) and 2 events of muscle atrophy (1 event at 13 to <26 weeks and 1 event at 7 to <13 weeks).

Post marketing experience

By December 2019 more than thousands of patients had been treated with co.don chondrosphere. Since Marketing Authorisation of Spherox in July 2017, a wide range of patients have been treated with Spherox. Most patients treated with the product(s) were adults. However, only about 5% of patients were less than 18 years old.

So far, however, no significant safety information has been reported to CO.DON AG according to the MAH.

2.5.1. Discussion on clinical safety

A total of 105 patients were treated with chondrosphere in study cod 16 HS 17 paed. The mean follow-up time was 52.2 months (range 12.5 to 94.1 months) (1-8 years).

According to the study protocol (including the latest amendment, Amendment 2, 16 March 2018), conventional definitions were to be used, i.e., an AE was defined as any unfavourable and unintended sign, symptom, or disease temporarily associated with the use of a medicinal product/surgical procedure, whether or not considered related to the medicinal product. An AE was to be classified as an adverse drug reaction if the physician classified the event as at least possibly related to the drug product (or surgical procedure).

Somewhat confusingly, the MAH filed a corrigendum to the clinical study report stating that the definitions for adverse reactions (ARs) and adverse events (AEs) were adapted such that all AEs were to be considered non-related events and ARs were to be considered related events.

In total, 26 AEs were reported in 15 (14.3%) patients.

Most AEs affected the musculoskeletal system and connective tissues or were classified as injuries or procedural complications. Most AEs were experienced 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 experienced AE by preferred term was 'arthralgia' (3 [2.9%] patients).

A total of 81 ARs were reported in 27 (25.7%) patients. In total, 22 (21.0%) patients experienced non-serious ARs and 8 (7.6%) experienced serious ARs. Most ARs occurred post implantation (18 [17.1%] patients) in the 'musculoskeletal and connective tissue disorders' SOC (15 [14.3%] patients); 8 (7.6%) patients developed 'joint swelling', 5 (4.8) patients developed 'joint effusion', 4 (3.8%) patients developed 'arthralgia', 2 (1.9%) patients developed 'chondromalacia', and one (1.0%) patient each developed 'chondropathy', 'infrapatellar fat pad inflammation', 'joint crepitation', 'joint warmth' 'loose body in joint', 'osteochondrosis', 'synovitis' and 'tendonitis'.

In total, 5 (4.8%) patients experienced SAEs and 8 (7.6%) reported serious adverse reactions. these events did not evoke new particular concerns. In the study cod 16 HS 17 paed, 63 patients out of 105 underwent concurrent surgeries during biopsy and/or implantation, 42 patients did not. Major types of procedures were bone reconstruction (24), e.g. for reconstruction of osteochondritis dissecans defects and patellofemoral realignment surgeries (23), e.g. following a traumatic injury. In a few cases, non-ACI cartilage repair techniques (N=4) have been used in addition to ACI either for smaller other defects not needing necessarily ACI. In a descriptive subgroup analysis, overall KOOS ± SD (standard deviation) yielded similar values for patients that received concurrent surgeries with biopsy and/or implantation as those without these additional interventions (76.8 ± 18.0 vs. 80.6 ± 13.5). MOCART scores were also similar. Similar results were obtained in the adolescent subpopulation with closed EGP.

The MAH also explained that the main reason for the concurrent surgeries is related to the need to address the underlying reason for the defect and/or to address e.g. teared ligaments or meniscus related issues.

2.5.2. Conclusions on clinical safety

The clinical safety of Spherox in the proposed extended indication can is considered acceptable.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH did not submit an updated RMP with this application.

2.7. Update of the Product information

As a result of this variation, section(s) 4.1, 4.2, 4.8 and 5.1 of the SmPC are being updated to reflect the inclusion of adolescent patients with closed epiphyseal growth plate. The Package Leaflet (PL) is updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Articular cartilage is a complex structure that has an important function in load-bearing joints and joint mobility. These characteristics are determined mainly on the composition of cartilage and particularly its extracellular matrix whose production the chondrocytes are involved in. The integrity of the extracellular matrix is essential for the mechanical and structural capacity of the cartilage. Due to the lack of blood or lymphatic vessels in the cartilage, cell infiltration does not occur and the capacity of the defect to heal after trauma is reduced. Without a surgical intervention the risk for the development of arthrosis is present. A cartilage lesion can reduce the joint function, cause pain and swelling of the joint.

3.1.2. Available therapies and unmet medical need

Cartilage lesions such as in the knee commonly occur, mostly due to trauma. Articular cartilage has limited capacity for intrinsic repair and may result in fibrous tissue or fibrocartilage, which has inferior properties compared to normal healthy hyaline cartilage. Deep lesions till the subchondral bone (Outerbridge scale III-IV) may lead to osteoarthritis at young age, if left untreated. Surgical approaches to repair damaged cartilage such as microfracture (MF) are limited by the production of fibrocartilaginous tissue, which is less resistant than natural cartilage. In addition, microfracture is less suitable for treating larger lesions (exceeding ~4 cm^2). ACI (autologous chondrocyte implantation) is an alternative treatment option whereby extra-corporal cultivated autologous chondrocytes are implanted in the chondral focal

lesions with the aim to form hyaline cartilage. The first generation ACI products utilised autologous chondrocytes as a cell suspension, administered under periosteal flap or biodegradable membrane. One of the limitations of traditional ACI has been that the quality of the neocartilage has been mostly fibrocartilage type of tissue, which is considered to be less durable resulting in compromised treatment results in long-term. Furthermore, the use of a periosteal flap has turned out problematic, since it requires an additional surgical intervention and in some cases the use of a flap has induced hypertrophic growth of the treated cartilage. In an attempt to achieve repair tissue more similar to native articular cartilage, development of ACI has progressed to the third generation, in which autologous cells are cultured in a 3-dimensional (3D) matrix before implantation, such as Spherox.

Spherox is approved for repair of symptomatic articular cartilage defects of the femoral condyle and the patella of the knee (International Cartilage Repair Society [ICRS] grade III or IV) with defect sizes up to 10 cm2 in adults.

The current variation pertains to the extension of this indication with paediatric patients with a closed growth plate.

3.1.3. Main clinical studies

Study cod16HS17 paed was a non-interventional, open-label, multicentre study in adolescent patients who had undergone ACT3D with chondrosphere and who were at least 15 years of age but less than 18 years of age at the time of implantation/treatment with co.don chondrosphere. In addition, treatment had to be administered one to a maximum of 8 years before enrolment in the non-interventional study.

There was no fixed study visit schedule.

Data collected by the physicians were either derived from the medical records or documented using the specific examination form provided for this study, completed at routine visit(s) after patients had submitted their signed and dated informed consent. In addition, patients were requested to complete a web-based questionnaire at home once during the course of the study.

The knee joint was assessed in a subgroup of patients undergoing physical examination including MRI, if applicable. If a patient entered the subgroup, i.e. agreed to such a follow-up examination, a follow-up visit was arranged to perform physical examinations. A voluntary MRI examination within a time window of ±3 months from the physical examination was performed for the purpose of an MRI observation of cartilage repair tissue (MOCART) analysis.

The mean follow-up time was 52.2 months (range 12.5 to 94.1 months) (1-8 years).

3.2. Favourable effects

Less than one quarter of the 105 patients in the FAS population received at least one additional surgery after ACI; of which only 5 cases were considered related to ACI-M with co.don chondrosphere.

The majority (>80%) of patients in the PE subpopulation (92 patients) did not have serious knee complications. MRI examination showed the defect repair to be complete in almost two-thirds of paediatric patients and to be incomplete in almost a quarter of patients. The mean (SD) MOCART score was 74.4 (16.7), indicating that, in general, a favourable score in the examined patient population. There were patient questionnaires (three knee-related and one general physical and mental health questionnaire), which were answered by 92 patients. Similarly, to the MOCART score, the mean KOOS total score (78.1) was also reflective of patients, in general, experiencing mild knee-related health issues.

Concurrent surgeries during biopsy were documented in 40 (38.1%) patients and concurrent surgeries during implantation were documented in 41 (39.0%) patients, mainly related to the need to address the underlying reason for the defect and/or to address e.g. teared ligaments or meniscus related issues.

Also, overall, 25 (23.8%) patients received at least one additional surgery after the ACI procedure. Only in 5 cases was the reason for surgery considered to be a treatment failure related to ACI with co.don chondrosphere. The remaining other surgeries tended to target other joint structures.

The Applicant was requested to further substantiate the expansion of the indication by justifying the extrapolation of efficacy from the available adult data, in particular young adults.

The proposed dosing recommendations for adolescent patients will be the same as the approved dosing recommendations in adults, 10-70 spheroids are applied per cm2 defect. The actual mean (SD) product dose used in cod 16 HS 17 paed (105 patients) was 33.5 (18.9) spheroids per cm2. The average (SD) defect size, 3.85 (2.18) cm^2, ranging from 0.75 to 12.00 cm^2, was also consistent with the approved indication in adults (up to 10 cm2).

The mean (SD) MOCART score was 74.9 (18.5) in the intended target adolescent population (with closed EGP), as compared to 78.2 (15.1) for the young adult (18 to <35 years of age) population from the Phase III clinical trial cod 16 HS 13, 76.0 (10.5) for the young adult population from the Phase II clinical trial cod 16 HS 14, and 76.7 (11.9) for the pooled young adult population.

A comparison of disease and other baseline characteristics was provided. The most common reason for chondral defects in study cod 16 HS 17 paed was trauma, 32 out of 60 (53.3%) adolescent patients with closed EGP vs. 36 (59.0%) of young adults (18 to <35 years of age) in the pooled adult population. The second most frequent cause of (osteo)chondral defects was osteochondritis dissecans (OCD), 24 out of 60 (40.0%) adolescent patients with closed EGP. This occurred less frequently in adult patients, in cod 16 HS 14, 3 out of 42 (7.1%) young adult patients, and it was an exclusion criterion in study cod 16 HS 13.

A comparison of defect size and location was provided. In the Phase II clinical trial cod 16 HS 14 defects of 4 cm2 up to 10 cm2 were treated, similar to the mean (SD) defect size in the adolescent population with closed EGP of 3.85 (2.18) cm2 (range: 0.75 to 12.00 cm2). The defect size in the cod 16 HS 13 study was smaller, up to 4 cm2. In the adolescent population with closed EGP, 30 (50%) of the patients had the defect on the femur, 28 (46.7%) on the patella and 2 (3.3%) on both femur and patella. In the young adult population of the Phase II clinical trial cod 16 HS 14, 14 (33.3%) patients had a defect on the femur and 28 (66.7%) on the patella. In the young adult population of the Phase III clinical trial cod 16 HS 13 all 19 (100%) of the defects were on the femur (inclusion criteria).

A comparison of the patient reported outcome was provided. In the populations with chondral defects (ICRS grade 3 or 4) the mean (SD) overall KOOS was in the adolescent population with closed EGP 75.5 (18.2), similar to the young adult population from the Phase II clinical trial cod 16 HS 14 79.2 (16.6). In the pooled young adult population, this was 82.2 (15.4) and in the young adult population of the Phase III study cod HS 13, it was 88.7 (9.7). In an additional comparison using young adult patients 18 to <25 years of age (N=25), no differences were observed in the overall KOOS, the KOOS subscores and the MOCART score in this subgroup compared to 18 to <35 years of age (N=61).

3.3. Uncertainties and limitations about favourable effects

Effectiveness data were collected during one single visit within a time window of 1 to 8 years after ACT3D with chondrosphere. Thus, effectiveness results refer to data obtained post implantation and no baseline values for any of the efficacy parameters are available.

Overall, the interpretability of the results was limited because of the non-interventional, open-label, multi-centre study design with a single visit without a control group or baseline visit as a reference.

Accordingly, the Applicant was requested to further substantiate the expansion of the indication by justifying the extrapolation of efficacy from the available adult data, in particular young adults.

3.4. Unfavourable effects

In total, 26 AEs were reported in 15 (14.3%) patients and a total of 81 ARs were reported in 27 (25.7%) patients. Most AEs affected the musculoskeletal system and connective tissues or were classified as injuries or procedural complications. Similarly, most ARs occurred post implantation (18 [17.1%] patients) in the 'musculoskeletal and connective tissue disorders' SOC (15 [14.3%] patients). In total, 5 (4.8%) patients experienced SAEs and 8 (7.6%) reported serious adverse reactions. Most SARs related to the SOC 'Injury, poisoning and procedural complications', PTs: transplant failure (5), cartilage injury (1), graft loss (1), meniscus injury (1) and 'Musculoskeletal and connective tissue disorders', PTs: joint swelling (1), joint effusion (2), loose body in joint (1), osteochondrosis (1).

Overall, the safety profiles of the overall adolescent population and adolescent population with closed EGP showed similar safety pattern as the young adult populations of the Phase II clinical trial cod 16 HS 14 and the Phase III clinical trial cod 16 HS 13, with common adverse reactions such as 'joint effusion' and 'joint swelling'.

3.5. Uncertainties and limitations about unfavourable effects

The types of events reported are consistent with the previously conducted studies. However, the fact that only 14% of the patient population reported one or more (unrelated) AEs and only 26% of the patient population reported one or more adverse reactions over the course of many years signifies potential underreporting, e.g. due to recall bias and/or lack of documentation.

3.6. Effects Table

Table 1. Effects Table for Spherox – treatment of adolescents with closed EGP

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Failure rate	*	%	5	N/A		cod16HS17 paed
KOOS	**					
Unfavourable Effects						
Joint swelling		%	7.6	N/A		cod16HS17 paed
Joint effusion		%	4.8	N/A		
Arthralgia		%	3.8	N/A		

Abbreviations:

Notes: *physician's decision that surgical re-treatment of the lesion originally treated with chondrosphere was required. ** Knee injury and Osteoarthritis Outcome Score

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The interpretation of the results of study cod16HS17paed was considered limited because of the non-interventional, open-label, multi-centre study design using single time data points without a control group or baseline visit as a reference.

To address this, the MAH provided additional analyses and discussions, addressing the pharmacology (dose, PD effects); similarities and differences between the respective target populations (adolescents with closed EGP vs. young adults from the pivotal studies cod 16 HS 14 and cod 16 HS 13) in terms of disease and other baseline characteristics; and expectations for clinical response to treatment (efficacy and safety data).

The proposed dosing recommendations for adolescent patients will be the same as the approved dosing recommendations in adults, 10-70 spheroids are applied per cm2 defect. The adolescent population with closed EGP had a mean (SD, range) defect size of 3.85 (2.18, 0.75 – 12.00) cm2 before treatment. This defect size is consistent with the approved indication (up to 10 cm2) and similar to the defect size in the young adult population, particularly of the Phase II clinical trial cod 16 HS 14 of 4.98 (1.27) cm^2, ranging from 0.50 to 7.50 cm^2. Thus, the relative exposure to Spherox between the young adult population and the paediatric adolescent population could be considered comparable. Lesion locations (femur, patella) were also similar, in particular compared to study cod HS 14.

As expected, the most common reason for chondral defects is trauma, 32 out of 60 (53.3%) adolescent patients with closed EGP in the paed study vs. 36 (59.0%) of young adults (18 to <35 years of age) in the pooled adult population. The second most frequent cause of (osteo)chondral defects is osteochondritis dissecans (OCD), 24 out of 60 (40.0%) adolescent patients with closed EGP. This occurred less frequently in adult patients, in cod 16 HS 14, 3 out of 42 (7.1%) young adult patients, and it was an exclusion criterion in study cod 16 HS 13. However, the MAH cited references that describe the successful treatment of adult OCD patients with ACI. The disease course and progression of adult OCD is also comparable to that of traumatic lesions if left untreated. Thus, in this regard, the two patient populations could be viewed as sufficiently comparable. In the Phase II cod 16 HS 14 five adult patients with OCD were treated and their primary efficacy scores were comparable to those of the overall population.

There was no difference in the MOCART score between the adolescent population with closed EGP and the young adult patients 18 to <35 years of age.

In the populations with chondral defects (ICRS grade 3 or 4) the mean (SD) overall KOOS was in the adolescent population with closed EGP 75.5 (18.2), similar to the young adult population from the Phase II clinical trial cod 16 HS 14 79.2 (16.6). In the pooled young adult population, this was 82.2 (15.4) and in the young adult population of the Phase III study cod HS 13, it was 88.7 (9.7). Thus, the adolescent population with closed EGP showed clinical improvement in the range of these two young adult populations in the respective adult studies, based on comparable aetiology and course of the disease and comparable mode of action of Spherox in these patients, in particular study cod HS 14.

In an additional subgroup comparison of patients 18 to <25 years of age, no differences were observed in the overall KOOS, the KOOS subscores and the MOCART score (N=25) as compared to the larger group of young adults 18 to <35 years of age (N=61).

Thus, it is expected that the treatment effect of Spherox as demonstrated in the young adult population will be similar in the adolescent population with closed EGP.

The safety of the whole adolescent population and the adolescent population per EGP status group were compared to the safety of young adults (18 to < 35 years) in the pivotal clinical trials of Spherox (the Phase II clinical trial cod 16 HS 14 and the Phase III clinical trial cod 16 HS 13) and the pooled population from both these pivotal trials. The most common reported ARs, both between biopsy and implantation as well as during / after implantation, were 'joint effusion', 'joint swelling' and 'arthralgia'. Overall, the comparative safety profile generated (comparing the 2 populations) was very similar.

Given these similarities between the populations in exposure and underlying disease conditions, the extrapolation of safety data from ACI treatment in adults towards the adolescent population seems to be justified.

During the pubertal growth spurt, proliferation and differentiation of chondrocytes, secretion of extracellular matrix, calcification of the hypertrophic zone, invasion and differentiation of osteoblast, and formation of blood vessel repeat continuously in the growth plate. At the end of the pubertal stage, these processes stop, and longitudinal growth completes (e.g. Shim KS. Ann Pediatr Endocrinol Metab 2015;20:8-12). On the other hand, age-related changes in cartilage density, especially in the superficial zone of weight-bearing surfaces tends to be observed after 40 years of age (Temple MM. et al. Osteoarthritis and Cartilage. 2007;15:1042-52). When the epiphyseal growth plates are closed, adolescents are skeletally mature and could be considered young adults biologically, regarding their skeletal system and joint cartilage. Thus, this population should be biologically comparable to the young adult population up to the age of 40.

Thus, overall, in spite of the limitations of the conducted paediatric study, it is considered the efficacy and safety profile of Spherox, as known for the approved indication which was supported by the pivotal studies cod HS 13 and cod HS 14, could be extrapolated to the adolescent population with closed EGP.

3.7.2. Balance of benefits and risks

The balance of benefits and risks is considered positive for the sought extension of the indication:

Repair of symptomatic articular cartilage defects of the femoral condyle and the patella of the knee (International Cartilage Regeneration & Joint Preservation Society [ICRS] grade III or IV) with defect sizes up to 10 cm^2 in adults ***and adolescents with closed epiphyseal growth plate in the affected joint***

3.8. Conclusions

The overall B/R of Spherox is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CAT considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition	Type II	I and IIIB

	of a new therapeutic indication or modification of an approved one		

Extension of the indication to include treatment of adolescents with closed epiphyseal growth plate in the affected joint; consequently, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB are recommended.

Paediatric data

Furthermore, the CAT reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0161/2018 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-0020'