National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Autologous chondrocyte implantation with chondrosphere for treating articular cartilage defects ID851

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Co.don AG	Yes	Comment noted. No action required.
Wording	Co.don AG	Yes	Comment noted. No action required.
Timing Issues	Co.don AG	There is an unmet need as there are no available ATMP product or therapy for patients requiring autologous chondrocyte implantation for the repair of cartilage defects.	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Co.don AG	No comment	Comment noted. No action required.
The technology/ intervention	Co.don AG	In the product chondrosphere®, similar as to other MACI products, the chondrocytes are embedded in a three-dimensional scaffold resulting in an equal distribution of the cells resulting in improved proliferation, differentiation, migration and attachment of the cells compared to 1st ACI generation products. However, chondrosphere® can be considered as a new generation compared to the other MACI products, as no xenogenous scaffold is used as in the other MACI products, but it contains an extra-cellular matrix produced by the cells themselves. Due to the 3D cell culture system used to produce chondrosphere®, the cells aggregate, condense and develop cell-cell and cell-matrix contacts. This results in the enhanced differentiation of the cells and production of a hyaline-like extra-cellular matrix. The product chondrosphere® therefore contains cells that are already in a chondrogenic state and started to produce extra-cellular matrix, which they continue to produce upon implantation into the cartilage defect. Moreover, chondrosphere® is a pure autologous product and xenogenous substances are completely absent, which reduces the risk of infections, allergic reactions and rejections compared to other MACI products that do contain a xenogenous scaffold. In addition, for implantation of chondrosphere® also no xenogenous substances as fibrin glue or suturing are required as for implantation of other MACI products, as chondrosphere® adheres itself to the defect bottom after implantation. Our clinical trials Phase II and III are currently ongoing. Results of the 4 years follow up will be expected in March 2017. Due to a prolonged patient	Comment noted. No action required.

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		recruitment Phase III results with data 2 years after treatment (Final Assessment) will be available in September 2017. **Setting Phase III:** Eight orthopaedic clinics in Germany and three orthopaedic clinics in Poland **Study title:** Prospective, randomised, open label, multicentre Phase III clinical trial to compare the efficacy and safety of the treatment with the autologous chondrocyte transplantation product co.don chondrosphere® (ACT3D-CS) with microfracture in subjects with cartilage defects of the knee with a defect size between 1 and 4 cm^2 **Comparator intervention** Microfracture **Objectives** Assessment of the short-term and long-term efficacy and safety of the three-dimensional autologous chondrocyte implantation product ACT3D-CS compared with microfracture for the treatment of cartilage defects of knee joints. **Study population:** Treated and analysed: 102 patients (52 patients by ACT3D-CS and 50 by microfracture).	

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		Phase II **Study title** Prospective, randomised, open-label, multicentre Phase II clinical trial to investigate the efficacy and safety of the treatment of large defects (4–10 cm2) with 3 different doses of the autologous chondrocyte implantation product chondrosphere® (ACT3D-CS) in subjects with cartilage defects of the knee **Study centres** Ten orthopaedic clinics in Germany **Objectives** Assessment of the short-term and long-term efficacy and safety of 3 different doses of the three-dimensional autologous chondrocyte implantation product ACT3D-CS for the treatment of cartilage defects (4–10 cm²) of knee joints.	
Population	Co.don AG	Please refer to the Comment 4 section/planned indications for the technology, which also includes the hip.	Comment noted. No action required.
Comparators	Co.don AG	We suggest deleting ”Mosiacplasty” because: - it is for Osteochondral Transplantation (which includes bone) and not specifically singularly for cartilage repair - it is little used in the UK - has no long term efficacy data nor any data, that we are aware of, to support cost-effectiveness We would also suggest deleting	Attendees at the scoping workshop agreed that mosaicplasty and debridement are used in clinical practice.

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		"Knee Lavage with/without Debridement" because: - Without debridement is an investigative procedure only - With debridement is for the removal of damaged cartilage with no repair of the damaged cartilage We do not consider osteotomy as suitable realistic comparator to the whole population of patients with cartilage lesions of the knee. Malalignment of the knee must be treated prior to or in conjunction with damaged cartilage repair. We would also like to kindly request clarification on the definition of "Best supportive care (non-operative intervention)".	
Outcomes	Co.don AG	Appropriate	Comment noted. No action required.
Economic analysis	Co.don AG	No comment	Comment noted. No action required.
Equality and Diversity	Co.don AG	Chondrosphere© overcomes any objections to the procedure on religious grounds; no porcine/bovine derived collagen membrane is needed.	This issue has been included in the equality impact assessment and will be considered during the development of the appraisal.
Innovation	Co.don AG	**Chondrosphere© is a 4th generation innovative product which can be implanted with arthroscopy – conventional ACIs require arthrotomy for implantation.**	Comment noted. No action required.

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		Traditional 1st generation ACI-P was with the periosteal cap that was superseded by 2nd (ACI-C) and 3rd (MACI) generations, with techniques where the cells are seeded on to a collagen membrane. **Chondrosphere© requires a shorter, simpler and less invasive treatment compared to conventional ACIs.** Chondrosphere© overcomes any objections to the procedure on religious grounds o No porcine/bovine derived collagen membrane Please also refer to the technology/ intervention section for a more detailed description of the technology.	
Other considerations	Co.don AG	No comment	Comment noted. No action required.
Questions for consultation	Co.don AG	*Q=Question* *A=Answer* Q: Is Chondrosphere likely to be used in clinical practice to treat adolescents who have a closed epiphyseal growth plate? A: yes, PIP.	The scope refers to "people" in the population, this includes adolescents and adults.
Questions for consultation	Co.don AG	Q: Have all relevant comparators for Chondrosphere been included in the scope? A: please refer to section on draft scope/comparators.	Comment noted. No action required.

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Questions for consultation	Co.don AG	Q: Are the outcomes listed appropriate? A: please refer to section on draft scope/comparators.	Comment noted. No action required.
Questions for consultation	Co.don AG	Q: Are there any other outcomes that should be included? A: no.	Comment noted. No action required.
Questions for consultation	Co.don AG	Q: Are the subgroups suggested in 'other considerations' appropriate? A: Duration of symptoms is an appropriate subgroup, due to the fact that better outcomes were expected for shorter durations of symptoms. The phase II included patients with defect sizes of 4 – 10 cm² and the phase III smaller defects of 1- 4 cm². Therefore a defect size is not an appropriate subgroup, as chondrosphere can be used for cartilage defects up to 10 cm². Previous surgical treatments e.g. more than 50 % resection of a meniscus in the affected knee, previous treatment with ACT in the affected knee, microfracture performed less than 1 year before screening in the affected knee, meniscal transplant in the affected knee, meniscal suture in the affected knee three months prior to baseline or mosaicplasty (Osteoarticular Transplant System, OATS) in the affected knee as well as malalignments (Valgus or varus malalignment; more than 5° over the mechanical axis) are predefined exclusion criteria in both trials phase II and III.	Attendees at the scoping workshop agreed that the subgroups are appropriate.
Questions for consultation	Co.don AG	Q: Are there any other subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately? A: no.	Comment noted. No action required.
Questions for consultation	Co.don AG	Q: NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you	Comment noted. No action required.

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		think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which Chondrosphere will be licensed; • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. A: please refer to section on draft scope/Equality	
Questions for consultation	Co.don AG	Q: Do you consider Chondrosphere to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? A: please refer to section on draft scope/Innovation	Comment noted. No action required.
Questions for consultation	Co.don AG	Q: Do you consider that the use of Chondrosphere can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. A: Please refer to section on draft scope/Innovation	Comment noted. No action required.

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Questions for consultation	Co.don AG	Q: NICE intends to appraise this technology through its Technology Appraisal Process. NICE is currently consulting on an additional technology appraisal process; known as the Abbreviated Appraisal Process (ATA). More information on the consultation is available at https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/abbreviated-technology-appraisal-process-consultation. We welcome comments on the appropriateness and suitability of considering the new ATA process for appraising this topic. Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction A: **Process:** We understand that the appraisal can be changed to ATA at a later stage. Can it be switched from ATA to STA at a later stage? **PAS:** We understand that PAS has to be obtained before the ATA process begins. We also understand that PAS can be further extended if required as per STA. Can you confirm this assumption?	The ATA process is now called a cost-comparison case. For the cost-comparison case the company compares their product to another product for which there is a positive NICE recommendation (i.e. where final guidance has been published). Information on this method is available at: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf Companies are given the opportunity to make either a full STA submission or a cost-comparison submission when they are invited to

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			submit and the final scope is issued. Please refer to section 5 of the "Guide to the single technology appraisal processs" for details on "Patient access and flexible pricing schemes" for cost-comparison and multiple or single technology appraisals
Questions for consultation	Co.don AG	Additional Questions: **Comparators:** Assuming that intervention should show similar or greater health benefits, what are the comparators to Chondrosphere©? **Tools and resources:** NICE is not publishing resource impact tools/statements. How are the payers informed about the impact/benefit of a new technology?	The comparators are as listed in the final scope. NICE publishes either resource impact tools and/or statements for all single or multiple technology appraisals.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health