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Reflection paper on *in-vitro* cultured chondrocyte containing products for cartilage repair of the knee

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Reflection paper on *In-Vitro* Cultured Chondrocyte Containing Products for Cartilage Repair of the Knee

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1. Introduction (background)

This reflection paper addresses specific points related to medicinal products containing *in vitro* cultured autologous chondrocytes intended for the repair of cartilage lesions of the knee. This reflection paper is considered to supplement the 'Guideline on human cell-based medicinal products' (EMEA/CHMP/410869/2006) and therefore it should be read in conjunction with the guideline.

2. Discussion

CONSIDERATIONS ON QUALITY DATA

For novel products as well as for products with clinical experience gathered before entry into force of Reg. No. (EC) 1394/2007 the same level of quality is expected for a central marketing authorisation application.

Starting material

The active substance is based on chondrocytes obtained from a cartilage biopsy. Due to dedifferentiation tendency of the chondrocytes when cultured in monolayer, the yield in cell number is limited by the size of the biopsy and will limit the size of the defect that can be treated with the resulting product. Therefore specific consideration should be given to the amount and quality of the starting material to ensure that sufficient cell numbers can be produced for the presented defect to be treated.

The collection of the cartilage biopsy should be standardised in order to minimise possible contaminants (fibroblasts) arising from fragments of the synovial membrane. The presence / absence of fibroblasts should be controlled through appropriate in-process testing. Acceptance criteria in relation to cellular impurities should be set through process validation.

Manufacturing process

The ratio of cells to return to differentiated state after surgical implantation depends on the number of duplications in monolayer culture *in vitro*, thereby limiting the overall expansion of cells isolated from the biopsy. Therefore adequate limits to population doubling / passage number should be set during process validation considering appropriate functional markers related to the differentiation stage and the resulting cartilage forming capacity of the cells.

In cases where a 3-dimensional cell culture process in combination with a structural component is used, attention should be paid to the functionality and number of cells in the combination product, and not only of the cell suspension.

Process validation is a prerequisite to ensure consistent manufacture. Given the limitations related to the cellular material available (especially for autologous products) for process validation, alternative material with comparable characteristics could be used e.g. collected from joint replacement surgery. In such case, the validity of the material must be demonstrated.

Potency

A main aspect for the biological characterisation and control of chondrocytes containing products is the cartilage forming capacity. Potency can be expressed through (a) functional assay(s) established for characterisation of the product and for process validation. The functional assay is expected to be suitable to detect changes in the product in relation to the aspects described above which may be clinically meaningful.

Due to time constraints, for batch release, an assay based on surrogate marker(s) could be envisaged. In case mRNA based assays or other surrogate markers are used, their correlation with a functional assay is expected.

Product development

During product development, biocompatibility of all materials coming into contact with the cells in the final product should be demonstrated. This includes not only materials used during the manufacturing process, but also those selected components that come into contact with the cells as part of the clinical application (e.g. membranes for local containment, fibrin glues).

CONSIDERATIONS ON NON-CLINICAL DATA

Clinical experience gathered prior to entry into force of Reg. No. (EC) 1394/2007 can be considered on a case-by-case basis. Clinical experience might substitute for some parts of the non-clinical development. However, the acceptability of such approach will clearly depend on the quality of the data that have been collected. Such approaches have to be justified by the Applicant and are at the Applicant's risk. Of high importance are, as part of such justification, what changes have been made to the manufacturing process over time, and what impact these had, i.e. it needs to be justified that the data submitted to substitute for non-clinical data are indeed relevant to the product which is applied for. In any case, justification for the omission of any non-clinical analyses has to be provided.

Pharmacology

Initial proof of principle studies could be initiated with the use of *in vitro* cell culture methods such as 3-dimensional cell culture models (i.e. Pellet culture model, 3-dimensional alginate cell culture). Attention should be paid to use of the final product composition in the proof of principle animal studies. This includes the use of the proposed cell-device combination and other non-cellular components (e.g. membranes, fibrin glues), where appropriate.

First *in vivo* proof of principle studies can be conducted in small animal models where, usually, data can be generated easily with a larger sample size. An example could be the Ectotopic Cartilage Forming Assay (ECFA) model, in which human chondrocyte suspension are implanted ectopically in immuno-compromised animals. However, such models have limitations, e.g. the different anatomical structure of the knee joint, or difficulties of manipulation and mimicking the clinical use. Another model is the rabbit which can be employed to establish key proof of principal parameters before embarking on pivotal nonclinical investigations in large species. Small animal models will normally not be sufficient as a proof of concept.

The pivotal non-clinical study should be conducted in an (orthotopic) large animal model to mimic as much as possible the situation in humans and to allow for more invasive testing than possible in humans. This could include the validation of MRI methods as structural endpoints (see section on Clinical Pharmacology). As immuno-compromised large animal models are not available it is recommended to use autologous animal cells. Currently the best available large animal models are goat, horse or sheep. However, other suitable animal models, e.g. (mini-) pig or cow, may also be appropriate Deviation from these principles should be justified.

The pivotal non-clinical studies should be long enough to show regeneration and repair and to obtain enough evidence for a long term clinical use in humans. These studies could include testing for biomechanical properties and tissue integrity (morphological characteristics of the cartilage) and the feasibility of the administration procedure. The number of animals in these studies should allow robust analysis of the data.

The animal cells should be equivalent to the cells in the medicinal product for clinical use. The impact of deviations in the manufacturing process used for the animal cells on quality should be discussed.

Biodistribution

Biodistribution studies in a relevant animal model are considered necessary in cases where the product might not be sufficiently physically retained, e.g. by a membrane and/or when a scaffold is not applied together with a physical barrier. Absence of biodistribution studies should be justified.

Toxicology

The necessity of conventionally designed, GLP-compliant toxicity studies depends on the nature of the product and should follow a risk-based approach. Safety endpoints may be incorporated into proof of concept studies in justified cases. These studies should be GLP-compliant if feasible.

CONSIDERATIONS ON CLINICAL DATA

Potential claims

The principal aim for autologous chondrocytes containing product is to repair cartilaginous defects either from traumatic damage or degenerative disease. The indication could be further defined by relevant components, particularly, number of defects treated (multiple or single defect), size of defect, localisation of the defect (such as femoral condyle or trochlea), symptomatic or asymptomatic defect, grading of the defect (such as ICRS score), and previous failed therapies (such as after failed previous therapeutic or surgical intervention). Due to different aetiologies of the lesions, separate safety and efficacy studies may be appropriate. In vitro cultured chondrocytes may be administered as a first line or second line treatment for cartilage repair of the knee. For claims of the product as second line treatment, special attention should be paid to the characteristics of the previously treated lesion.

Subject characteristics and selection of subjects

The patient population included in the studies should be selected by relevant criteria like symptoms, functionality, localisation, size and depth of the knee defect(s), concomitant joint pathology(ies), and previous treatments of the defect. Restriction of target population may increase precision of study (such as excluding patients with previous mosaicplasty, advanced osteoarthritis etc.) but also could diminish generalisation of benefit of the results (such as limiting the defect size).

Strategy and design of clinical trials

A. Clinical Pharmacology.

Pharmacodynamics. Macroscopic, histological and MRI assessment of the repair tissue are considered adequate tools for pharmacodynamic assessment of autologous chondrocytes containing products. MRI is to date, considered clinically relevant and could be included in trial protocols, although it is acknowledged that it is not validated as such in the follow up of the repair tissue. MRI results in a large animal with histopathological investigations might yield supportive data to surmount the clinical database (see non-clinical section).

Pharmacokinetics. As there is no clear common agreement for conventional clinical kinetic data needed to be analysed in clinical setting, the majority of the issues regarding clinical pharmacology are expected to be addressed during the non-clinical phase. If non-cellular components are present, their combination with cells is expected to be assessed clinically for compatibility, degradation rate and functionality.

B. Exploratory trials.

Exploratory clinical trial endpoints should be suitable to address pharmacodynamics, dose and safety.

Preexisting data from relevant published literature or from nonclinical studies could be supportive for dose definition, provided that the cellular and structural components and formulation of both products are equivalent.

The dose definition should be carefully chosen reflecting both actual numbers of the cells engrafted and adjustments for particular defect sizes (e.g. expressed in minimal number of cells/cm^2).

The chosen dose should be justified with data using the actual product under investigation.

Dose definition could be justified also by unequivocally observed effect size.

Depending on the amount and quality of clinical data gathered before entry into force of Reg No. (EC) 1394/2007 exploratory studies might not be required. Justification for the omission of exploratory studies should be provided, including evidence that in case of changes in the manufacturing process over time these do not affect the clinical development program.

The clinical data should be sufficient to justify the administration procedure and the design of the confirmatory studies.

C. Confirmatory trials.

Methods to assess efficacy

Definition of the primary endpoints. Patient-reported outcome data is acceptable as primary endpoint in the pivotal studies (for general aspects on single pivotal studies see Points to Consider on Applicantion with 1. Metaanalysis; 2. One Pivotal study, CPMP/EWP/2330/99), given the current lack of other outcome measures that are both sensitive and objective. For patient-reported outcomes, validated methods to assess improvement of function and pain should be used (e.g. Knee injury and Osteoarthritis Outcome Score (KOOS) or other validated scoring systems). In case a subjective endpoint is used as a primary endpoint an objective endpoint such as a structural endpoint (i.e. MRI) and / or an endpoint based on treatment failure and/or functionality should be considered in combination with the primary endpoint. The Applicant is encouraged to develop objective endpoints based on functionality.

Definition of secondary endpoints. Endpoints based on structural improvement could be the main secondary endpoint or a co-primary endpoint depending on the study design. The results based on structural endpoints should confirm the results based on primary patient-reported endpoints. The suitable structural endpoints could be chosen from blinded standardised MRI with/or without histological evaluations. Until validated methods are available, it is the Applicant's responsibility to demonstrate that the method is qualified for its intended use. Structural endpoint could also serve as a relevant supportive surrogate marker for benefit risk assessment in case of need for long-term efficacy that could be performed post-marketing.
Other specific secondary endpoints could be used e.g. responder analysis, the ones representing clinical / functional assessments (such as IKDC subjective scale, Lysholm score, ICRS objective scale, physical findings for the knee) or the ones representing structural assessments (such as arthroscopic and X-ray assessments).

Trial design. The study design should follow a randomised, controlled approach with appropriate comparator.

For patients with lesions of less than 4 cm^2 clinical superiority or alternatively non-inferiority in combination with supporting structural superiority against currently employed reasonable surgical comparative therapy (such as microfracture) is a reasonable option. If non-inferiority design is chosen, the assay sensitivity as well as delta margin should be justified (see guidance document on Choice of a Non-Inferiority Margin, CPMP/EWP/2158/99).

For the confirmatory trials and due to the nature of the product, blinding of the trial design may be difficult to be maintained. For these trials prospective randomised, open label, blinded evaluation is recommended.

Various options can be considered for the design of confirmatory trials, e.g.

- A randomized controlled trial including microfracture as comparator. In this case the appropriateness of the microfracture procedure with respect to the lesion size to be treated needs to be addressed, since microfracture is only recommended in smaller lesions.
- A randomized controlled trial including an active pharmaceutical comparator. If a licensed chondrocyte-containing product that has been validated in a randomized controlled trial is used as comparator, a non-inferiority design may be considered.
- A randomized controlled trial including a standardized exercise program as control arm. The standardized exercise program should be suitable to stabilize muscle function and could be viewed as an active placebo control. The design should consider a switch of patients from active placebo to the verum arm according to predefined criteria.
- Any other clinical trial design, when appropriately justified.

For larger lesions larger than 4 cm^2, a superiority study based on patient-reported outcome confirmed with structural repair data would be the best approach. A dose response assessment is desirable, if applicable. This could be done by including the assessment of the dose-response relationship in the confirmatory study, whereby the dose (of chondrocytes) per size (cm^2) of the defect would be added as a covariate.

For patients with lesions of more than 4 cm^2, no standard therapy has shown unequivocal efficacy, therefore superiority against best standard of care is currently the reasonable option. However, the use of a non-authorised medicinal product is problematic as it has not been validated for clinical use and the quality of the product has not been assessed.

In cases where an indication is sought for both small lesions (smaller than 4 cm^2) and large lesions (larger than 4 cm^2), it may be possible to include a third arm in large lesions larger than 4 cm^2) to a randomised controlled trial in small lesions against a comparator (i.e. Microfracture).

Study duration. A 3 year follow-up for clinical efficacy evaluation is normally necessary. However, for registration purposes, structural repair by histological / MRI analysis could be acceptable at earlier evaluation timepoints, where appropriately justified. The follow-up period for clinical efficacy could be envisaged post-authorisation (Efficacy follow-up within Art. 14 of Reg. (EC) 1394/2007) provided positive benefit risk profile is obtained.

D. Methodological considerations

Numerous procedures and treatment related risk factors are emerging and include: (1) *Patient factors,* especially size of the defect. Other patient factors to be considered are BMI, gender, age, sports activity, and defect localisation; (2) *Variability due to other therapies*, such as variability of surgical procedures among different centres and surgeons (standardised surgical protocols should be done); symptomatic treatment allowed (both as pre-procedurally or peri-procedurally prior the implantation), peri-surgical procedures (such as arthroscopy or open surgery procedures prior the implantation), rehabilitation protocols and the follow-up programs are reasonable to be considered. These considerations demonstrate that a standardized approach might be valuable in order to reduce variability between study arms that could render interpretation of data difficult.

At best the most important factors should be identified beforehand and be taken into consideration by proper stratification of the randomisation and/or inclusion of these factors into the analysis model by prospectively planned subgroup analyses.

Clinical safety evaluation

General safety issues The autologous chondrocytes-containing products have been used for more than 15 years in clinical practice and the experience for this class of products is relevant and has to be considered. For the safety assessment, the clinical program could consider results of quality and non-clinical investigations as well as unresolved issues that could not have been assessed non-clinically.

For products for which clinical data has been gathered before entry into force of Reg No. (EC) 1394/2007, the acceptability of safety data will depend on the quality of the data and their collection over the years.

Specific safety issues Special attention has to be paid on long-term structural changes, such as local histological or MRI detectable changes, rates of treatment failures, as defined through relevant investigation techniques, including re-operation for revision purposes. In cases of treatment failure, a root-cause analysis should be performed in order to identify the factors, which gave rise to treatment failure (i.e. quality of the product, surgical procedure, patient characteristics).

3. References

Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006).

Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L 324 of 10.12.2007, p 121)

Points to Consider on Applicantion with 1. Metaanalysis; 2. One Pivotal study (CPMP/EWP/2330/99)

Guideline on the Choice of a Non-Inferiority Margin (CPMP/EWP/2158/99)