NOW AND THEN

# Recommendations for the registration of drugs used in the treatment of osteoarthritis

Group for the Respect of Ethics and Excellence in Science (GREES)*: osteoarthritis section

Osteoarthritis is a disorder which can potentially affect all joints. It is characterised by degeneration and regeneration of articular cartilage and bone. The pathological changes can be focal or more generalised and these changes correlate poorly with clinical symptoms and signs. However, there is some evidence that asymptomatic osteoarthritis, diagnosed radiologically, is a precursor of symptomatic disease. Osteoarthritis, particularly of the large joints of the lower limbs—for example, knees and hips—is now widely recognised as a major cause of chronic disability in the elderly population.

Recent technical advances have allowed symptomatic and structural changes associated with osteoarthritis to be measured with greater precision than previously. These advances, together with increased knowledge of the biochemical mechanisms involved in the osteoarthritic disease process, have encouraged clinical evaluation of several agents which may have a beneficial effect on the disease process.

Currently, there are inconsistencies in the classification of drugs for the treatment of osteoarthritis and the indications for their use. These inconsistencies are reflected in different approaches of national licensing authorities to the registration of drugs for the treatment of osteoarthritis. Accordingly, there seems to be an urgent need to standardise the registration requirements of such drugs. This prompted the formation of a European Working Group to consider the issue. The group comprised clinical and basic scientists working in the field of osteoarthritis in academia and the pharmaceutical industry and representatives of national drug licensing authorities. This report classifies drugs for the treatment of osteoarthritis as symptom modifying, structure modifying, or both and gives recommendations for the preclinical and clinical studies considered to be necessary prerequisites at this time for the registration of such drugs. The recommendations are based on currently available knowledge and technology. They will need updating as further scientific progress is made in this field.

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*See appendix

## Objectives and nomenclature

Osteoarthritis is a chronic disease. Drugs developed for its treatment are likely to be given continuously over many months or years with the intention of controlling the evolution of the disease in terms of symptoms and structural changes.

Committees of the International League Against Rheumatism and the World Health Organisation have recently considered guidelines for testing new drugs in osteoarthritis. The nomenclature proposed recognises three classes of drugs acting on osteoarthritis: fast acting drugs that induce symptomatic relief, slow acting drugs that induce symptomatic relief, and disease modifying drugs.

Two distinctions have been made in this classification:

- The first is between symptomatic treatment and structure modifying treatment. The correlation between severity of joint pain or disability and the pathological changes in an osteoarthritic joint is often poor between patients at any point in time.
- The second is the distinction between drugs with fast and slow effects on symptoms. Arguments for classifying drugs that induce symptomatic relief into these two subgroups are not compelling. Although drugs that act slowly may have different mechanisms of action from those that act rapidly, there is a range of duration of action of drugs which act on symptoms. The design of trials should adequately take into account the timing and duration of the action of the drug on symptoms and these factors may influence the use of any concomitant treatment which is permitted in a trial.

Based on these considerations, we propose a classification of drugs for the treatment of osteoarthritis that consists of two categories:

(1) *Symptom modifying drugs*

These act on symptoms with no detectable effect on the structural changes of the disease. Registration of such drugs would require demonstration of a favourable effect on symptoms with no detectable adverse effect on the structural changes of the disease.

(2) *Structure modifying drugs*

These interfere with the progression of the pathological changes in osteoarthritis. They can be further subclassified by their effect on symptoms:

(*a*) *Structure modifying, symptom relieving drugs*—Registration of such drugs would require demonstration of beneficial effects on both symptoms and structural indices of the disease.

(*b*) *Structure modifying drugs with no independent effect of symptoms*—There is good indirect evidence that, by favourably modifying the natural history of osteoarthritis in terms of structural changes, long term clinical benefit

will occur in a large proportion of patients. Drugs may become available which will favourably influence joint structures without appreciable short term clinical benefit. Registration of such drugs should be given serious consideration.

## Preclinical studies

A standard package of preclinical toxicity tests is required in the evaluation of any drugs and therefore also for those used in the treatment of osteoarthritis.

In vitro and in vivo studies could be conducted at the discretion of the company. The decision whether to conduct such studies could depend on the properties of the drug and whether potentially useful information could be obtained.

### IN VITRO EVALUATION

In vitro studies on cultures of chondrocytes and other connective tissue cells and organs can provide important information on the mode of action of drugs with structure modifying effects, but they are not necessary for drug registration purposes. Details of the species of origin and the cell or organ culture which are optimal for such studies will depend on the pharmacological profile of the agent to be studied.

Effects of drugs on human articular chondrocyte cultures, in which the long term preservation of the chondrocyte specific phenotype and the reconstitution of articular cartilage architecture (or at least the typical extracellular matrix molecules) from dispersed cells are maintained, might clarify aspects of the mode of action and the pharmacological profile of the drug. These studies might be performed at several realistic pharmacological doses of the drug. Absence of detrimental effects of drugs developed for long term use might be evaluated on articular chondrocyte metabolism. The chondrocyte cultures should be obtained from normal and osteoarthritic human articular cartilage.

### IN VIVO EVALUATION

*Rationale*

There are no satisfactory animal models for human osteoarthritis; however, there are at least three main reasons for using them—namely, to explore the activity of the drug in models of osteoarthritis; to explore possible modes of action of a drug, in addition to any that may have been evaluated in in vitro studies; and to explore potential joint toxicity.

*Study design*

Relevant studies would assess the ability of the test drug to prevent osteoarthritis, to retard the progression of established osteoarthritis, and to induce repair of an osteoarthritic joint. Any sensitive and reproducible method of assessing morphological changes can be used, provided it has been validated with histopathological techniques. Effects of the drug on both synovial and cartilage tissues need to be assessed.

Ideally, the drug should be tested in two different mammalian species, and, preferably, in models of both spontaneous and mechanically induced osteoarthritis.

*Dosage*

Ideally, an efficacy dose-response curve should be established. A dose substantially higher than that which is minimally efficacious should be evaluated to assess possible toxicity to cartilage.

*Duration of study*

As the osteoarthritic process evolves slowly, short term experiments are likely to be inconclusive. It is necessary for the duration of in vivo experiments to take into account the natural history of the development of osteoarthritis in the model under study; the lifespan of the animal species being studied; and the therapeutic target being investigated.

## Clinical evaluation

### SELECTION OF PATIENTS

*The different types of osteoarthritis*

Osteoarthritis is a heterogeneous disorder. The natural history and clinical outcomes of the disease vary according to the main joints affected. Therefore, for clinical trial purposes, osteoarthritis of the different joints should be regarded as separate disorders. Selection of patients for trials should be based on the prevalence and clinical importance of osteoarthritis of different joints, and on the availability of validated outcome measures.

Osteoarthritis of the spine is common and important, and often coexists with disease of the limb joints. Patients with spinal osteoarthritis may be included in trials, but as there are currently no agreed objective measures of progression or outcome for spinal osteoarthritis, the spine should not be used as a target site in clinical trials. Disease of the hand is to some extent related to a generalised susceptibility to osteoarthritis. Current methodological considerations indicate that clinical trials designed to evaluate the effects of drugs in osteoarthritis of the hand are better focused on assessing progression of the disease in proximal and distal interphalangeal joints rather than in trapezometacarpal joints, in which osteoarthritis may be more related to mechanical factors. Although osteoarthritis of the hand is a potential target for assessing evolution of disease in trials, it is less important clinically than hip or knee disease. Osteoarthritis of the hip is a common, disabling disease with two main patterns of joint damage. Superior and lateral migration of the femoral head are the commonest forms and are associated with the highest risk of progression. Less frequent are medial and concentric femoral head migration, which have a more heterogeneous natural history. Osteoarthritis of the knee is also both very common and a major

cause of disability. It presents with three overlapping patterns of joint damage: medial (common) or lateral (uncommon) tibiofemoral involvement and patellofemoral disease (common). Currently, outcome measures for both symptoms and structure are better validated for medial tibiofemoral disease than for lateral or patellofemoral disease. Accordingly, it is recommended that medial tibiofemoral osteoarthritis of the knee or superolateral osteoarthritis of the hip are the most appropriate disease subsets for pivotal phase II or III trials, and that interphalangeal joint osteoarthritis of the hand is an appropriate target for studies of the effects of a drug on evolution of disease.

*Inclusion criteria and the diagnosis of osteoarthritis*

To improve the homogeneity of the patient groups studied, inclusion criteria should limit the target joint to a single site. The presentation and natural history of the condition may be different in younger and older age groups. Therefore, the age range of patients to be entered needs to be preselected and specified. A narrower age range will increase group homogeneity, possibly at the expense of the generalisability of the data obtained.

To be enrolled in a study, patients should have both symptomatic and structural changes of osteoarthritis in the target joint. Currently, this will mean pain related to use with radiological evidence of joint space narrowing or presence of osteophytes for knee osteoarthritis, use related pain with joint space narrowing for osteoarthritis of the hip, and the diagnostic criteria of the American College of Rheumatology for hand osteoarthritis.

*Aetiology of osteoarthritis*

Patients with osteoarthritis that is obviously secondary to another form of joint disease should be excluded. However, the definition of primary osteoarthritis proposed by the American College of Rheumatology seems too restrictive. It is recommended that patients should only be excluded on the basis of secondary osteoarthritis if they have a history or present evidence of any of the following diseases in the potential target joint:

- Septic arthritis
- Inflammatory joint disease
- Gout
- Recurrent episodes of pseudogout
- Paget's disease
- Aticular fracture
- Ochronosis
- Acromegaly
- Haemochromatosis
- Wilson's disease
- Primary osteochondromatosis

Other aetiologic factors, such as trauma and dysplasias, may have to be considered, but the absence of clear criteria for quantifying past joint trauma or defining the presence or absence of dysplasia, currently preclude any specific recommendations.

BASELINE DATA

To establish the symptomatic and structural severity of the condition, and the presence or absence of any factors or concomitant treatment that might affect outcome measures or the natural history of osteoarthritis, data should be collected at or as near to the point of entry to the trial as possible.

*Symptomatic severity*

Pain and disability at entry need to be recorded. However, the minimum severity of symptoms related to disease in the target joint at entry will depend on the primary outcome measure being assessed, the potential mode of action of the drug, and the joint sites involved. For example, a higher baseline level of pain may be appropriate for entry into a trial of a symptom modifying drug than a trial of a structure modifying drug.

*Structural severity*

The severity of radiological changes in the target joint at entry should be established. The entry film must be carefully characterised so that:

- A patient group responding to an investigational drug can be fully described, so that any subsequent extrapolation of data that may permit a more generalised use of the agent is facilitated
- An extensively damaged target joint is recognised, as it is unlikely that the effects of a drug on such a joint could be shown.

In studies during which radiological changes are evaluated, the baseline film should be obtained as near to the time of entry to the study as possible, and always within three months of entry.

In some trials, changes in joints other than the target joint may be used as secondary outcome measures and, if this is done, it would be necessary to record the severity of radiological changes in these joints at entry.

*Factors affecting disease progression*

Factors that might affect the rate of evolution of osteoarthritis include age, sex, obesity, major joint injury, and certain types of use for the knee joint; and age, developmental abnormalities, presence of a generalised diathesis, and occupations such as farming, for the hip joint. Any effect of a drug on rate of progression must be examined in the context of these factors, which should be recorded at entry.

*Concomitant treatment*

Many patients with osteoarthritis who are recruited to trials are likely to have exacerbations of symptoms ("flares") which require treatment during the study, irrespective of the type of study design used. Such concomitant treatment may interfere with outcome measures, and should ideally be excluded. However, in long term studies it is neither

ethical nor practical to exclude all concomitant treatments. For all trials, concomitant treatments (drugs or interventions) that are likely to affect joint structure should be excluded, and rescue treatment should be standardised, carefully recorded, and monitored.

## OUTCOME MEASURES: CLINICAL

Irrespective of the particular joint being studied, several clinical outcomes can be assessed; in particular, pain, functional disability, mobility, quality of life, flares, consumption of concomitant medication, global rating, and time to surgery. Pain and functional disability attributable to the target joint are recommended as *primary clinical end points* in trials of a drug for osteoarthritis. The methods of statistical analysis and the timetable for collection of data should be determined before starting a trial.

### *Pain*

Pain should be measured by self assessment with validated methods, such as visual analog of Likert scales. Use related and rest pain should be assessed separately. The period of assessment should be defined—for example, now, today, this week. Pain should be measured often and at least every three months during the first year of long term trials.

### *Functional disability*

A disease specific and joint specific instrument such as the Western Ontario MacMaster University osteoarthritis index (WOMAC) or the Lequesne index is recommended to assess disability arising from osteoarthritis of the hip or knee. These instruments have been validated for osteoarthritis of these joints and seem to be sensitive to relevant changes in the clinical status of patients with osteoarthritis. The validation of outcome measures specific for other joints is ongoing. Functional disability should be assessed at least every three months during long term trials.

### *Flares*

Flares may be related to episodes of joint inflammation. Such episodes may reflect periods of rapid destruction of joints. Collection of data on flares may, therefore, be important. However, no validated measures specific for flares in osteoarthritis exist.

### *Physical signs including range of motion*

The current methods for evaluating joint mobility (for example, of motion, intercondylar distance, heel to buttock distance) are not sensitive or reproducible. Their place in long term follow up remains to be established. Physical examination (for example, joint swelling, crepitus) is not sensitive or reproducible as an outcome measure. Performance testing methods, such as timed walking capacity or muscle strength, have not been fully validated in osteoarthritis.

### *Quality of life*

Quality of life scales are receiving increased attention from physicians involved in clinical trials and from drug regulation authorities. The sickness impact profile (SIP), Nottingham health profile (NHP), and the short form-36 (SF-36) have excellent properties when used to assess a general population. They have only been partially tested in osteoarthritic populations. If further validated in these populations it would be desirable to use one or more of these scales as an outcome measure in trials of the efficacy of drugs in the treatment of osteoarthritis.

### *Global rating*

The patient's and the physician's global rating are required by some drug regulation authorities.

### *Consumption of medications*

Consumption of non-trial medications may be regarded as a semiobjective outcome measure. However, the influence of such factors as their side effects and long term variations in their use may introduce uncertainty into the interpretation of data on consumption of medications.

### *Time to surgery*

The need for major surgery, such as joint replacement, can be considered as an important outcome measure. However, there is no agreement on criteria for joint replacement surgery. At the present time, replacement rates for hips and knees vary greatly in different countries and regions. Furthermore, these rates vary over time. Thus it is not possible to recommend time to surgery as a useful outcome measure.

## OUTCOME MEASURES: STRUCTURAL

The effects of a new drug on joint structure are central to the assessment of outcome. The definition of structural changes should include changes in both cartilage and bone. The radiographic measurement of joint space width or osteophyte size remains the best established method of assessing the progression of osteoarthritis and published studies support its use to provide a *primary endpoint* in trials of structure modifying drugs in osteoarthritis. However, stringent standardisation of positioning of patients, image acquisition, and measurements must be applied. Training of investigators to achieve the desired degree of standardisation should be encouraged. In addition, films should be read centrally. The clinical relevance of the proposed treatment induced effects on joint structure should be evaluated.

Other technologies for the evaluation of the severity of osteoarthritis, such as chondroscopy, magnetic resonance imaging, scintigraphy, and ultrasonography, should also

be considered as they may provide potentially relevant outcome measures. However, none of these methods has yet been fully validated in osteoarthritis.

Materials collected during trials—for example, radiographs and videorecordings of arthroscopies—should be kept available for a further reading, because the techniques for assessing structural changes that were up to date at the start of a trial may be improved or changed during the course of a trial.

## OUTCOME MEASURES: BIOCHEMICAL

If a biochemical variable is shown to reflect the disease process of osteoarthritis, it is likely to be classified as a surrogate marker of disease and would not be acceptable as a primary end point unless this could be justified by data on its clinical relevance. Samples of different body fluids (serum, urine, and possibly joint fluid) may be obtained during clinical trials and kept frozen until required for specific assays of biochemical variables of interest. As with new imaging technologies, the relevance of measurements of a biochemical variable has to be established and this may be achieved by measurements made on specimens obtained during a clinical trial.

Measurements of some biochemical variables may be shown to be useful in characterising patients that are at increased risk of developing rapidly progressive disease or in following up the evolution of the disease. However, at the present time measurements of biochemical variables are not a requirement for drug registration.

## STUDY DESIGN

### *Phase I studies*

Phase I studies should determine the pharmacokinetics, including bioavailability, and the general safety of the compound and should provide an indication of doses of potential clinical relevance.

### *Phase II studies*

Phase II studies should provide data over a range of doses. The doses selected for these studies should enable the minimum effective dose and the dose-response profile to be determined. Evaluation of at least three doses is recommended. Pivotal studies should have a placebo controlled, randomised, double blind, and parallel group design.

Some agents may have both symptom and structure modifying effects, but the optimal dose for modification of symptoms may be different from that which alters structure.

*Modification of symptoms*—The duration of phase II studies for symptom modifying effects will depend on the expected outcome and the mode of action of the drug. Normally, even in the case of a slow acting symptom modifying drug, its effects would be expected to be apparent within six months.

*Modification of structures*—The duration of phase II studies for a drug with structure modifying effects will also depend on its mode of action, but is likely to be longer than that required to assess modification of symptoms. Studies over a range of doses and of sufficient duration to show meaningful changes in structure are required. The magnitude of these changes should be predetermined.

### *Phase III studies*

The objectives of the definitive pivotal studies are to confirm both the efficacy and the safety of the drug. At least two independent pivotal studies for showing efficacy are recommended. There should be only one target joint in a single trial—either the hip or the knee. Intention to treat analysis should be the primary method of evaluation. The $\beta$ risk should be no greater than 20%. The design and the duration of these studies may differ according to the properties of the drug.

For *symptom modification,* studies should have a randomised, double blind, parallel group design. At least one of them should be placebo controlled and have a duration of at least six months (to assess the maintenance of the therapeutic effect). The nature of the comparator in the control group of the second study may vary, depending on the characteristics of the compound under investigation. Data on adverse events should be collected for at least one year. Moreover, to establish that a symptom modifying drug does not have deleterious effects on the joint, structural changes should be monitored for at least one year.

For *structure modification* studies should have a randomised, double blind, placebo controlled, parallel group design. The duration should be predetermined and should be at least one year. One of the two pivotal studies may be combined with a phase II trial. Structural changes are required as *primary end points.* The magnitude of a clinically relevant effect of a drug on a structural variable should be predetermined, based on the best evidence currently available.

## Appendix

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