European Medicines Agency

London, 23 April 2009
Doc. Ref. CPMP/EWP/784/97 Rev. 1

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS USED IN THE TREATMENT OF OSTEOARTHRITIS

DISCUSSION IN THE EFFICACY WORKING PARTY (EWP)	October 1997/ December 1997
APPROVAL BY THE CPMP	January 1998
RELEASE FOR CONSULTATION	January 1998
DEADLINE FOR COMMENTS	April1998
RE-DISCUSSION IN THE EWP	May 1998/July 1998
ADOPTION BY CPMP	July 1998
DRAFT AGREED BY EFFICACY WORKING PARTY	April 2009
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	23 April 2009
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 October 2009

This guideline replaces Points to Consider on Clinical Investigation of Medicinal Products used in the Treatment of Osteoarthritis (CPMP/EWP/784/97).

Comments should be provided using this template to EWPSecretariat@emea.europa.eu

KEYWORDS	*Osteoarthritis, symptom modifying drugs, structure modifying drugs, NSAIDs, clinical development, CHMP, EMEA, guideline*

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EXECUTIVE SUMMARY

This document is intended to provide guidance on the clinical evaluation of medicinal products in the treatment of osteoarthritis (OA). OA is a flaring degenerative arthropathy and a disorder which can potentially affect all synovial joints.

Pharmacological therapies for OA include those intended to treat acute flares of OA such as paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) or intra-articular injection with corticosteroids for fast symptom relief. For non-acute treatment, symptom modifying slow acting drugs (e.g. symptomatic slow acting drugs for OA (SYSADOA)) are available. Medicinal products with beneficial impact on structural progression of OA or disease modifying properties in erosive hand OA may be assessed in the future. Study parameters such as patient characteristics, primary and secondary endpoints as well as study duration have to be carefully considered in order to ensure that clinical trials support the intended therapeutic claim.

This document is a revision of the guideline adopted in July 1998. It takes into account recent development relating to study design and instruments to assess symptom control, functional status and structural progression of the disease as well as the assessment of safety issues which should be considered when developing new pharmacological treatments for OA.

1. INTRODUCTION

General information

Osteoarthritis (OA) is a flaring degenerative arthropathy and a disorder which can potentially affect all synovial joints. It is rare for OA to develop before the age of 40, but after this age the incidence increases, especially in women. OA of the hip may start a decade later than OA of the knee or hand. The prevalence of symptomatic knee OA in patients aged 35-54 years is around 1%, whereas about 40% of the population aged over 65 has symptomatic OA of the knee or hip. OA of the knee is more prevalent than hip OA.

OA is characterised by degeneration and regeneration of articular cartilage and bone. The pathological changes can be focal or more generalised and these changes often correlate poorly at one time point with clinical signs and symptoms but correlate longitudinally. It has been suggested that radiologically diagnosed but asymptomatic OA is a precursor of symptomatic disease. OA may start slowly with mild to moderate symptoms; typical pain may occur on motion or after inactivity.

OA, particularly of the large weight bearing joints – for example, knees and hips – is widely recognised as a major cause of chronic disability in the population.

Specific patients (e.g. after meniscectomy) have an increased risk of developing radiological progression of joint degeneration.

Hand OA may occur as a separate entity with moderate inflammatory systemic signs, acute symptomatic onset and a worse structural progression (erosion).

In general, treatment includes non pharmacological therapies such as physical therapy, exercise, patient education as well as pharmacological intervention. An acute flare of OA is usually treated with paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) or an intraarticular injection with corticosteroids for fast symptom relief. For non-acute treatment, symptom modifying slow acting drugs (e.g. symptomatic slow acting drugs for OA (SYSADOA) are available. Medicinal products with beneficial impact on structural progression of OA or disease modifying properties in erosive hand OA may be developed in the future.

Specific consideration for clinical development

Based on these therapeutic considerations, pharmacological treatment of OA should be classified into two categories:

a) Symptom modifying drugs

These act on symptoms (e.g. pain, functional disability) 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 clinically significant adverse effects on the structural changes of the disease. The absence of structural effects cannot be extrapolated from preclinical models.

It is generally accepted that pain intensity characterisation is an important issue in the strategy of pain treatment and hence in clinical investigation. The terms mild, moderate and severe pain are the most usually employed; therefore it might be appropriate to address the severity of pain to be treated in the claimed indication.

Medicinal products for acute pain conditions differ distinctly from slow acting symptom modifying drugs in terms of onset of pain relief. This should also be addressed.

b) Structure modifying drugs

Based on their mechanism of action, these drugs are expected to have an effect on the progression of the pathological changes in OA. These drugs may or may not have an independent effect on symptoms:

1) Structure modifying, symptom relieving drugs.

   Registration of such drugs would require demonstration of beneficial effects on both symptoms and structural indices of the disease.

2) Structure modifying drugs with no direct effect on symptoms.

   There is indirect evidence that, by favourably modifying the natural history of OA in terms of structural changes, long-term clinical benefit will occur in a large proportion of patients. This, however, has to be confirmed.

2. SCOPE

The scope of this guideline is to provide a European common position on pertinent issues relating to the clinical evaluation of medicinal products for the treatment of OA.

3. LEGAL BASIS

This guideline has to be read in conjunction with the introduction and general principles (4) and Part I and II of the Annex I to Directive 2001/83/EC as amended. Applicants should also refer to other relevant European and ICH guidelines (in their current version), especially those on:

- Pharmacokinetic Studies in Man;
- Dose-Response Information to Support Drug Registration (ICH E4);
- Statistical Principles for Clinical Trials (ICH E9);
- Choice of Control Group in Clinical Trials (ICH E10);

- The Extent of Population Exposure to Assess Clinical Safety for Drugs (ICH E1A);
- Studies in Support of Special Populations: Geriatrics (ICH E7);
- Note for Guidance on Investigation of Drug Interactions (CPMP/EWP/560/95);
- Points to consider on the choice of the non-inferiority margin (CPMP/EWP/2158/99 Draft 6);
- Note for Guidance on Fixed Combination Medicinal Products(CPMP/EWP/240/95);
- Reflection Paper on Methodological Issues in Confirmatory Clinical Trials with Flexible Design and Analysis plan (CHMP/EWP/2459/02).

4. PATIENTS CHARACTERISTICS AND SELECTION OF PATIENTS

Due to the pathophysiological and functional differences in OA of the knee or hip and OA of the hand, extrapolation of results obtained in the lower limbs to the hand, or alternatively, extrapolations of data obtained in the hands to lower limbs is not possible. Compounds having demonstrated efficacy either at the hip or at the knee level will be registered for 'treatment of osteoarthritis of the knee and the hip'. Compounds having shown efficacy at the level of the hands will be registered for 'treatment of osteoarthritis of the hands'. If the applicant chooses to assess the efficacy of the new product in spinal OA, without concomitant demonstration of efficacy in lower limbs and in hands, a specific indication ‘treatment of spinal OA’ can be considered. In order to obtain indication 'treatment of osteoarthritis' in general a compound should demonstrate efficacy at the level of the hands and at the level of the knee or the hip.

To improve the homogeneity of the patient groups studied, inclusion criteria should limit the target joint to a single site. However, simultaneous assessment of other joints is always possible and such results might generate supportive evidence for «general» OA efficacy. 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 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 OA in the target joint. This will mean pain related to use with radiological evidence of OA, e.g. according to the radiographic criteria of Kellgren and Lawrence and to the diagnostic criteria of the American College of Rheumatology (ACR) or the European League against Rheumatism (EULAR). The inter- and intra-observer variability in the interpretation of radiographs is a known problem which may affect the specificity of the classification criteria. This should be addressed in the planning of the study in order to accurately document the existence of changes.

Magnetic resonance imaging (MRI) may provide better visualisation of affected structures other than bones but it is not yet sufficiently standardised to be used for classification.

Patients’ characteristics should be well documented: demographics, duration of symptoms and extent of the disease, abnormal leg alignment or relevant deformities, history of trauma or surgery, overstrained joints due to occupation or sports, previous and concomitant therapies. Concomitant physical therapy, exercise or transcutaneous electrical nerve stimulation (TENS), if not excluded, should be carefully documented as they may have an impact on the results.

In addition, special characteristics of patients may be considered in order to assess the effect of structure modifying drugs. It may be advantageous to include patients at high risk for development of OA or rapidly progressive OA such as obese women with unilateral radiographical OA or patients who have undergone meniscectomy. However, inclusion of a specific risk group in studies decreases the potential for generalisation of the results.

Depending on the target joint, the chosen endpoint or the specific patient population, it is recommended to exclude patients with a history or present evidence of other diseases (e.g. inflammatory, infectious joint disease) or treatments which may have a distinct impact on the outcome.

Pain and functional disability at entry need to be recorded. However, the required 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 and kinetics of action of the drug, and the joint sites involved. For example, a higher baseline level of pain may be required for entry into a trial of a symptom-modifying drug than a trial of a structure-modifying drug. For studies of acute symptom modifying drugs, it is recommended to include patients with at least a moderate to severe extent of symptoms (e.g. pain of at least 40 mm as measured on the 100-mm visual analogue scale (VAS)). In all cases, the level of symptoms at baseline should be of such severity to permit detection of relevant changes. The severity of radiological changes in the target joint at entry should also be established.

For studies of structure-modifying drugs, it is recommended to include patients with Kellgren and Lawrence radiographic entry criteria of grades 2 or 3 (i.e., sufficient remaining interbone distance to permit detection of worsening/progression) or a certain pre-defined amount of joint space width (in mm).

Factors that might affect the rate of evolution and progression of OA, including age, sex, obesity, major joints injury, types and extent of use, pre-existing abnormalities, and familial OA, must be taken into account as potential confounders. A documentation of weight change over the course of study may be useful for long-term trials.

All symptom-oriented studies require discontinuation of prior analgesic and anti-inflammatory medications, including topical agents and steroid injections, prior to initiating treatment with the test drug in order to permit an evaluation of unmodified pain severity. The time of withdrawal should be the time required for the clinical effect to disappear (e.g., 5 half-lives of drug). ‘Flare’ study designs may be supportive for the investigation of treatment effects, e.g. for NSAIDs, since the extent of symptoms at entry allows a more homogeneous course of symptoms during the study; additionally, these studies reflect the conditions of daily clinical practice (treatment of symptomatic OA).

5. METHODS TO ASSESS EFFICACY

OA is a heterogeneous disorder. Observing an effect of a treatment for OA in one major joint does not necessarily mean that it will be effective in every joint. It is the responsibility of the applicant to show that a proven therapeutic effect in a certain joint can be extrapolated to other joints. If locally applied drugs shall be assessed, it is the responsibility of the applicant to justify the therapeutic usefulness of the application form at the joint which should be treated.

Clinical trials aimed at evaluating the effect of drugs in OA of the hand may be focused on assessing progression of the disease in the proximal and distal interphalangeal joints (PIP, DIP) or in the thumb base joint. Erosive OA may be assessed separately.

For OA of the hip the radiographic features considered most important include joint space narrowing (JSN), subchondral bony lucencies, marginal osteophytes and subchondral bony sclerosis.

In OA of the knee outcome measures for both symptoms and structures are better validated for medial tibiofemoral disease than for lateral or patellofemoral disease.

If the spine is the target joint, it is the responsibility of the applicant to demonstrate the validity of the endpoints chosen and their clinical relevance.

The primary and secondary endpoints and their prioritisation should be in accordance with the intended indications and study design. In pivotal clinical trials where pre-defined primary variable analysis has failed to demonstrate efficacy, favourable results on secondary variables will not be sufficient to grant a

marketing authorisation.

From a regulatory point of view the following potential claims should be distinguished:

1) improvement of symptoms such as pain,
2) improvement of functional disability,
3) slowing or prevention of structural damage.

5.1 Medicinal products intended to improve symptoms

Primary endpoint(s)

Pain attributable to the target joint is recommended as the primary endpoint for symptom modifying drugs for OA. Functional disability is an important additional primary endpoint for symptom modifying drugs and should preferably be included as co-primary endpoint. Studies should therefore be powered to demonstrate a clinically relevant and statistically significant effect both on pain and on functional disability. If a significant benefit is demonstrated only for pain, at minimum no deterioration in functional ability should be observed and this might influence the indication granted to the compound.

Pain

OA pain intensity should be measured by self-assessment with validated methods, such as the visual analogue or Likert scales. The VAS allows for a continuous variable and is preferred. The Likert scale is a verbal rating scale (7-point scale). Pain on motion and pain at rest should be assessed separately. Pain assessment should refer to a recent past period (e.g. the past 24 hours).

Whenever possible, the time-specific absolute pain intensity difference *versus* baseline in the target joint is to be considered as the primary endpoint.

Validated multidimensional assessment tools have been developed for OA symptom evaluation. They can give information on specific situations in daily practice and typical movements which might be painful or impaired in patients with OA. These questionnaires can be used as total score but as they are graduated in units related to certain symptom qualities it is also possible to choose the pain sub-scale only. For the main OA localisations, different specific questionnaires are available. The questionnaire to be used should be validated.

The period of assessment should be defined; for example: « now/today/this week ». Frequency of measurements of pain intensity should provide an assessment of the time needed for the onset of pain relief as well as an assessment of the duration of the analgesic effect and the maintenance of improvement.

Functional disability

Functional disability is an important co-primary variable that may be measured using validated disease-specific and joint-specific instruments.

Secondary endpoints

As OA is a flaring disease an appropriate time point to assess changes in pain intensity should be chosen by taking into consideration the impact of the self healing effect on the extent of the results. Recently, the time point of maximum effect over placebo was determined to be 2 to 4 weeks for systemically applied NSAIDs and 1 to 3 weeks for intra-articular steroid injections and topical NSAIDs, respectively.

In addition, it is recommended to present the results as percentage of responders as a complementary endpoint in order to demonstrate individual relevance and robustness. A pre-defined responder definition should be provided in the study protocol.

As secondary endpoint, the course of pain intensity (area under the curve (AUC)) might be used. However, the clinically relevant difference should be justified.

- Pain intensity (additional measurement time point);
- Functional disability (if not assessed as co-primary endpoint);
- Patient's global assessment of disease activity;
- Treatment response (percentage of patients achieving a predefined level of symptom relief) ;
- Percentage of patients having reached the PASS (patients acceptable symptom state);
- Percentage of patients achieving an improvement >MCII (minimal clinically important improvement);
- Osteoarthritis Research Society International (OARSI) set of responder criteria;
- Onset of action;
- Physician's global assessment of disease activity;
- Total score of a questionnaire;
- AUC pain intensity;
- Quality of life;
- Consumption of rescue medication.

5.2 Assessment of structural damage

Epidemiological data support a relation between structural changes and long-term clinical outcome. Plain x-ray for measurement of JSN has been shown to correlate with the subsequent need for total joint replacement. However, precision of this measurement is quite variable and dependent on the quality of radiographic techniques. Small positional changes from one measurement to the other can jeopardize the reproducibility of JSN measurements. Several methods, including fluoroscopy, foot maps and positioning devices can be used to obtain satisfactory measurements and are thus recommended.

It is essential to standardise radiographic technique based on published, validated data. The method should define the radio-anatomic position of the joint and beam alignment and should define the anatomic boundaries for measurements. Positioning of the patient should be based on validated methods but in all cases, weight bearing anterior-posterior views (standing) should be used in studies involving the hip or the knee. Correction for radiographic magnification has been shown to improve accuracy and precision of measurements. Films should be read centrally. Material collected during trials (radiographs) should be kept available for re-reading because the techniques for assessing structural changes may be improved or changed during the course of the trial.

Magnetic resonance imaging (MRI) has recently been seen as having potential for evaluation of joint OA due to its ability to evaluate morphology and integrity of the whole cartilage. It also provides a direct image of the soft tissues around the joint. Significant efforts and studies have been dedicated to use MRI as a method of quantification of cartilage volume and thickness. However, no strong correlations have been shown between loss of cartilage volume measured by MRI over time on the one hand and changes in x-ray, JSN, or clinical symptoms on the other hand. Hence, larger longitudinal studies are still needed to clarify the clinical relevance of MRI measured cartilage volume in OA disease progression.

The joint is a complex structure involving cartilage, synovial tissue and bone. Alterations and destruction of these components during progression of OA will release enzymes or biological markers

specific of these tissues in synovial fluids, blood and urine. There has been progress into the use of some of these markers for the prediction or measurement of progression of OA as well as for the evaluation of response to pharmacological intervention with compounds of potential structure-modifying activity. The potential of a reliable and responsive marker is large. However, further work is still needed on now changes measured in some of these biochemical markers of cartilage turnover correlate with OA disease progression.

Overall, the alternative technologies for the evaluation of the severity of OA, e.g. chondroscopy, MRI, scintigraphy, ultrasonography or biochemical measurements (serum, urine, joint fluids) may be considered as secondary endpoints.

6. STRATEGY AND DESIGN OF CLINICAL TRIALS

6.1 Early Studies in Man

6.1.1 Pharmacokinetics

The pharmacokinetic properties of the medicinal product should be investigated following existing guidelines. In addition, appropriate studies should be conducted according to the treatment duration, administration route and target population.

For medicinal products which are locally administered onto the skin the systemic availability of the active substance should be investigated in order to show systemic safety (see IV.1).

If the medicinal product is for intra-articular administration the residence time in the joint and the systemic availability of the active substance should be investigated.

6.1.2 Dose-Response 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. Depending on the mechanism of action and mode of application, efforts should be made to identify appropriate doses, concentrations, treatment-duration or -intervals according to the respective patient characteristics. Medicinal products to be used in (fixed) combinations need appropriate studies to find the best dose regimen for the intended combination. Phase II should be performed in accordance with the EU guidelines.

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

Studies should have a placebo-controlled, randomised, double blind, and parallel group design.

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. In the case of a slow acting symptom modifying drug, its effects would be expected to be apparent within at least 1 to 2 months.

Modification of structure: 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.

6.1.3 Interactions

Interaction studies should be performed in accordance with the existing guidelines. Efficacy and safety implications of concomitant use of drugs likely to be co-administered in clinical practice should be evaluated. Particular attention should be focused on safety and efficacy interactions with other drugs planned to be administered during pivotal trials (e.g. ibuprofen and low dose ASA).

6.2 Therapeutic confirmatory Studies

Because of the heterogeneity of OA, limiting the number of different joints investigated can limit the potential for generalisation of the results. In each trial one joint, preferably the hip or the knee, should be selected as the target joint, although simultaneous assessment of further joints is possible. The primary analysis population should be defined according to the intention to treat principle. The design and the duration of these studies may differ according to the properties of drug.

6.2.1 Study design

Modification of symptoms: Studies should have a randomised, double blind, parallel group design. Efficacy of products claiming improvement in symptoms is generally established by means of placebo controlled trials with an established active comparator as a relative control.

Primary endpoints for efficacy (change of symptom intensity) should be evaluated at a time point appropriate to show the maximum effect over placebo. Maintenance of improvement should be evaluated after at least 3 months for medicinal products claiming acute symptom relief. For symptom modifying slow acting drugs an evaluation after at least 6 to 12 months may be considered appropriate. The design of trials should adequately take into account the timing and duration of the action of the drug on symptoms. Although efficacy (change in symptom intensity) may be demonstrated in trials with shorter duration, long-term maintenance of the effect should be shown. A double-blind placebo-controlled phase may be followed by a long-term double-blind phase with the remaining active comparator only or by an open label extension phase to assess safety and/or efficacy. For symptom modifying slow acting drugs it might be possible to show that the beneficial effect is sustained long-term by means of a withdrawal period in which actively treated patients and responders to treatment are randomised to discontinue or continue treatment.

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. In addition, the adequate duration of treatment should be addressed and data obtained after stopping therapy should be provided.

Modification of structure: Studies should have a randomised, double blind, parallel group design. As stated in section II.2, clinical variables, or alternatively structural changes when their surrogacy value is proven, are required as primary endpoints. Clinical endpoints, such as the necessity of joint replacement, time to the need for surgery and long-term clinical evolution (pain and disability) are preferable in the assessment of efficacy of such drugs. If structural changes are chosen as primary endpoint, the magnitude of a clinically relevant effect of a drug on such variables over a specified time should be predetermined based on previously established findings. Due to the expected mechanism of action of these drugs, long-term studies, no shorter than two years, will be required both for efficacy and safety assessment. The benefit of a radiographic improvement in the absence of any clinical improvement at the time of assessment (i.e. at least 2 years) is difficult to predict and is insufficient for marketing authorisation.

6.2.2 Choice of control

For symptom modifying drugs placebo controlled trials with an established most favourable active comparator as relative control are recommended.

For structure modification, studies should have a randomised, double blind, placebo controlled, parallel group design.

6.2.3 Concomitant interventions

Many patients with OA who are recruited for 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 avoided. 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 or symptom changes assessment should be excluded, and rescue treatment (including physical therapy) should be standardised, monitored and carefully recorded for each individual patient. The time points of endpoint assessment should be appropriately chosen to avoid confounding effects of the rescue medication.

7. CLINICAL SAFETY EVALUATION

7.1 Specific adverse events to be monitored

Prior to licensing the safety database should be sufficient to characterise the safety profile of the medicinal product including, where relevant, a focus on specific adverse effects known for the corresponding substance class (e.g. for NSAIDs: increased gastrointestinal risk). Adverse effects that occur after drug discontinuation should be evaluated and documented for at least 2 month post study.

For topically applied medicinal products (e.g. topical NSAIDs) additional data should be provided on systemic exposure after application of therapeutic doses, in order to show the systemic safety. Local tolerability (local allergic and irritative/inflammatory skin effects) should be proven by means of validated methods (skin tests). However, substantial trials to demonstrate efficacy may provide an adequate safety data base. It should be taken into account that excipients may have local effects as well.

Intra-articularly applied medicinal products should prove local tolerability by means of data from clinical efficacy trials. Systemic risks should be assessed based on the residence time in the treated joint and on data for systemic availability.

7.2 Extent of population exposure to assess clinical safety

The safety data base to be submitted for assessing a new product should comply with ICH E1A. If OA is an additional indication for an already approved product, safety data obtained in other populations can be considered, provided the dosage regimen is the same and the population is expected to behave similarly.

For substance groups for which specific serious drug-related risks are known a larger safety population may be needed.

7.3 Long-term safety

Symptomatic OA is a prevalent chronic disease and most of systemic and intra-articular drugs will need to be approved for long-term treatment or chronic repeated use. Thus, safety assessment should be consistent with standard CPMP requirements for safety data on long-term treatments.

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