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Guideline on clinical investigation of medicinal products other than NSAIDs for treatment of rheumatoid arthritis

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This guideline replaces the POINTS TO CONSIDER ON THE CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS OTHER THAN NSAIDS IN RHEUMATOID ARTHRITIS (CPMP/EWP/556/95 REV. 1)

Comments should be provided using this template. The completed comments form should be sent to R-IWP@ema.europa.eu

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[1] First day of the 7th month.

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List of abbreviations

ACPA	Anti-citrullinated peptide/protein antibodies
ACR response	American College of Rheumatology response criteria
AE	Adverse event
AIMS	Arthritis Impact Measurement Scale
BMI	Body mass index
CCP	Anti-cyclic citrullinated protein/peptide
CDAI	Clinical Disease Activity Index
CHMP	Committee for Human Medicinal Products
CRP	C-reactive protein
DAS	Disease activity score
DMARDs	Disease-modifying antirheumatic drug
EMA	European Medicines Agency
EU	European Union
EULAR	European League against Rheumatism
HAQ	Health Assessment Questionnaire
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals fro Human Use
IA	Intra-articular
IM	Intramuscular
JIA	Juvenile idiopathic arthritis
MTX	Methotrexate
NSAID	Nonsteroidal anti-inflammatory drug
PIP	Paediatric Investigational Plan
PK	Pharmacokinetic
PSUR	Periodic safety update report
RA	Rheumatoid arthritis
RF	Rheumatoid factor
RMP	Risk Management Plan
SDAI	Simplified Disease Activity Index
SF-36	Short-Form 36-item Health Survey
SPC	Summary of Product Characteristics
TNF-α	Tumor necrosis factor-alpha
TNF(R)	Tumor necrosis factor (receptor)
VAS	Visual analogue scale

Executive summary

This document is intended to provide guidance on the clinical evaluation of medicinal products other than non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of rheumatoid arthritis (RA). RA is a chronic systemic inflammatory disease which mainly affects specific synovial joints but also has an impact on other organ systems. It often causes joint destruction, deformity and functional impairment.

Pharmacological therapies other than NSAIDs for RA are intended to treat symptoms, disease activity and structural progression of disease. Available are synthetic disease-modifying antirheumatic drugs (DMARDs) such as methotrexate (MTX) and sulfasalazine, biological DMARDs and corticosteroids. 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 Points to Consider adopted in November 2003. It takes into account recent developments relating to study design and also validated disease activity evaluation tools to assess important clinical and structural outcomes. Pharmacological therapy has advanced for RA. Therapeutic strategies employing more aggressive intervention in early disease, often using combinations of non-biologic DMARDs with targeted biologics, have shown a faster onset of action and more profound clinical responses than traditional approaches. Goal-directed treat-to-target strategies are now employed. This makes a modified recommendation for the assessment of these therapies necessary. Adapted study designs and validated assessment tools are needed.

In addition, the elements for the assessment of safety issues which should be considered when developing new pharmacological treatments have to be updated. The demonstrated safety profile will be essential for the benefit-risk balance in a defined patient population. Long-term safety of disease modifying agents requires careful attention in view of potential serious adverse events caused by immunomodulation.

1. Introduction (Background)

Rheumatoid arthritis (RA) is thought to be an autoimmune disease, manifested by accumulation and activation of several cell systems: T cells with release of T-cell derived cytokines; B cells with subsequent autoantibody responses, and macrophage- and fibroblast-like cells which produce large amounts of pro-inflammatory cytokines. The resulting hyperplastic synovial membrane, in conjunction with osteoclast activation, leads to the degradation of adjacent cartilage and bone. Blood levels of C-reactive protein (CRP), rheumatoid factor (RF) and ACPA (anti-citrullinated peptide/protein antibodies, such as anti-cyclic citrullinated protein/peptide (CCP) antibodies) are increased in many patients. The main clinical symptoms arise from a chronic fluctuating inflammation of the joints which, if uncontrolled, leads to progressive joint destruction resulting in deformities and disability. The disease can be accompanied by systemic manifestations (e.g. vasculitis, nodules).

The prevalence of RA is in the order of 0.5-1% of the population. It occurs about two to three times more commonly in women than in men, although this gender difference disappears in later life as the overall prevalence increases. Onset is maximal in the fifth decade. Genetic and ethnic influences on prevalence have been identified. Smoking particularly in patients with HLA-DRB1 shared epitope alleles may influence the development and outcome of RA. The exact pathogenesis of this disease is still unknown.

Because of the severity of clinical symptoms and the progressive nature of the disease, the early institution of medication and tight control of therapy is now recommended in order to control symptoms and suppress the disease process.

Features of the disease that are amenable to improvement by existing pharmaceutical means comprise pain, inflammation, physical disability and destruction of joints. In addition non-pharmacological intervention such as, joint protective or joint replacing orthopaedic surgery may need to be performed. Physical and occupational therapy, as well as psychotherapeutic support, are applied concomitantly in many patients.

Adverse effects from current anti-rheumatic medication occur frequently, affect various organ systems, and are sometimes serious. Special measures of surveillance and follow-up are often required depending on the specific characteristic of the drug or the combination (e.g. blood cells, liver function, renal function or infections, development of antibodies, malignancies) or of the older population being treated.

Current and future developments will influence the understanding of underlying pathogenetic mechanisms. RA is a disease with multiple phenotypes. Joint involvement and damage is variable from patient to patient as can be the course of the disease (e.g. cyclic or persistent). The population may be seronegative or may have many different autoantibodies. Variable combinations of these characteristics create a broad heterogeneity that is manifested by differences in disease outcomes from remission to severe disability and even premature mortality.

Further development of diagnostic instruments (e.g. disease activity status and response scores, remission criteria) have been elaborated in recent years and efforts are still ongoing. Any claim based on these instruments must show convincing evidence, including validation and demonstration of clinical relevance.

New ACR/EULAR classification criteria for RA have been validated as being more sensitive in early disease. Strategies for the development and validation of predictive tools for individual clinical situations in RA based on biosignature data are ongoing. A combination of tools such as clinical assessments, with a novel approach to biomarker validation may help an improved understanding and prediction of the course of the disease and response to treatment for individual patients.

Despite significant advances in the treatment of RA in the last decade, there is still approximately one third of patients who do not tolerate or who are resistant to available pharmacological treatment options. New treatment options are therefore in demand.

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 (e.g. DMARDs, biologicals) for the treatment of RA diagnosed according to ACR/EULAR classification criteria 2010.

NSAIDs and other symptomatic treatments that will be used in RA patients, but are not specifically disease modifying, are outside the scope of this document.

This guideline gives guidance on the performance of studies involving the drug treatment for RA only. Separate guidance is available for other rheumatic diseases such as osteoarthritis, juvenile idiopathic arthritis, ankylosing spondylarthritis and psoriatic arthritis in view of their different pathogeneses and natural histories.

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:

- Choice of Control Group in Clinical Trials - CPMP/ICH/364/96 (ICH E10);
- The Extent of Population Exposure to Assess Clinical Safety for Drugs - CPMP/ICH/375/95 (ICH E1A);
- Studies in Support of Special Populations: Geriatrics - CPMP/ICH/379/99 (ICH E7);
- Reflection Paper on Methodological Issues in Confirmatory Clinical Trials with Flexible Design and Analysis plan - CHMP/EWP/2459/02;.
- Guideline on Summary of Product Characteristics (Revision 2, September 2009).

4. Goals of treatment, potential labelling claims and methods to assess efficacy

4.1. Goals of RA treatment and potential labelling claims

Section 4.1 of the SmPC should contain the indication and a brief description of the indicated patient population. All relevant endpoints that have been assessed as supportive for the claims for efficacy should be detailed in section 5.1 of the SmPC.

In current practice, the leading principle of the treatment of moderate-severe RA is disease modification, by obtaining and maintaining low disease activity state or even remission. This should be reflected by the choice of the primary endpoint (see section 4.2 & 5.2 of this document).

Though controlling disease activity is the general principle of treatment of RA in all stages, response may differ between treatment-naïve patients in early disease stage and (very) advanced, treatment-experienced patients. Some products may be effective both in early and advanced stage, but safety issues may limit its use in first-line treatment. Therefore, it should be specified in the wording of the indication for which specific target population the product is indicated, once the benefit-risk balance has been considered positive. For definitions, selection criteria, study design and primary endpoints of the target populations see section 5.4 of this guidance document.

The following goals should be addressed in the treatment of RA:

a. relief of symptoms, e.g. pain
b. achievement of remission/low disease activity state
c. decrease of inflammatory synovitis
d. improvement or sustainment of physical function
e. prevention or slowing of structural joint damage

The goals should be assessed by objective measures or scales/scores all of which have to be validated. Which of these goals individually or combined are incorporated into study protocols depends on the nature of the agent being studied. The prevention of concomitant treatment-related complications and/or RA-related co-morbidities can be additional goals provided this has been established before commencing the study and by the application of appropriate methods.

Claims in the SmPC (Sections 4.1 and 5.1, respectively)

The claimed indication should be clearly and concisely stated in SmPC section 4.1. The target indication should be the **treatment of rheumatoid arthritis** provided that disease-modification has been demonstrated in a clinically meaningful way.

The target population in which a positive benefit-risk profile has been demonstrated should be identified concisely by indicating main characteristics as the disease activity (e.g. "moderate to severe, active rheumatoid arthritis") as well as previous treatment (e.g. DMARD-naive patients) and – if appropriate – the response (e.g. patients who have not responded adequately to one or more DMARD treatments including MTX, or TNF-inhibitors). In addition, it should be indicated whether the product should be given alone or in combination.

Given the various elements of disease modifying activity, information on the demonstrated effects should be indicated in the SmPC section 5.1 The presentation should be in conjunction with the description of the clinical studies where such effect was demonstrated in a clinically meaningful manner (i.e. in SmPC section 5.1, sub-section "Clinical efficacy and safety"). The therapeutic indication (SmPC section 4.1) should make cross-reference to this section.

The specific claims to be reported with the clinical studies in SmPC section 5.1 usually concern the following:

- treatment of signs and symptoms
- prevention/slowing of structural joint damage
- improvement of physical function.

All these claims should be supported with appropriate clinical data.

The initial claim of treatment in RA can be for treatment of signs and symptoms and improvement of physical function. However, planning studies to demonstrate the prevention/slowing of structural joint damage is also expected and when demonstrated will be added to section 5.1 of the SmPC.

Criteria for disease remission in RA have been redefined by ACR/EULAR and will need to be addressed before designing clinical trials that could support a labelling claim for remission of disease.

For the indication claim "***treatment of rheumatoid arthritis***" all listed treatment goals are important. Therefore it is expected that development programmes are designed to address all these elements including the demonstration of long-term disease modification. Additional data might be requested to demonstrate such beneficial effect (see section 5).

Only clinical efficacy and safety data related to the approved therapeutic indication should be presented when describing clinical studies in SmPC section 5.1. The only exception is data in the paediatric population, where all clinically relevant data should be presented.

4.2. Tools to measure efficacy (primary or secondary endpoints)

The following efficacy parameters should be reported at least at baseline, during and at the end of the blinded study phase:

a) swollen joint count (28 joints or more)
b) tender joint count (28 joints or more)
c) physician's global assessment of disease activity (e.g. VAS)
d) patient's global assessment of disease activity (e.g. VAS)
e) pain score (patient's assessment of pain, VAS, Likert scale)
f) physical function (e.g. HAQ, AIMS)
g) acute phase reactants (e.g. erythrocyte sedimentation rate, C-reactive protein)

h) radiographic outcomes (e.g. erosions, joint space narrowing; e.g. Sharp van der Heijde scores)

The efficacy measures a) to f) refer to symptoms and signs characterising the state of the disease. Depending on the pharmacological characteristics of the treatment studied the primary efficacy measure(s) has/have to be chosen appropriately. Results from the studies will have to be compatible with claimed indications (see section 5, confirmatory studies). Other measures may be acceptable, if validated.

4.2.1. Assessment of symptoms and disease activity

In general combined measures are to be used to document efficacy. For this purpose only validated composite endpoints (e.g. DAS28, including EULAR categories, ACR response criteria, Simplified Disease Activity Index (SDAI) or Clinical Disease Activity Index (CDAI)) are acceptable as primary or secondary endpoints and results need to be consistent with the single efficacy parameter(s) described. In general, it is expected that both EULAR and ACR outcomes should be reported. Other composite endpoints will be accepted after validation only.

The chosen outcome measures should not only be used to show improvement of signs and symptoms as a change in disease activity (response) but also status of disease activity and worsening of disease.

Appropriate descriptive statistics of the baseline, the endpoints and change of the single variables included in the core set are recommended.

In confirmatory trials the full potential of a test drug should be assessed. Depending on the properties of the product and patient characteristics this may also be reflected by using the ACR70 response and/or validated remission criteria. ACR/EULAR has currently elaborated a new definition of remission. Further remission criteria are those based on the SDAI and CDAI. Remission may be assessed as remission on drug or where appropriate on a drug-free period. The percentage of patients achieving a low disease activity state by composite scores (DAS, DAS28, SDAI, CDAI) could additionally be assessed subject to validation of the endpoints chosen.

It is important that response criteria are adequately justified, chosen before the study is initiated and the thresholds predefined. Time to onset of the primary outcome and sustainability of the primary outcome should be assessed.

For improvement in signs and symptoms the ACR20/50 and/or low disease activity should be assessed after 3 to 6 months depending on the properties of the product and the trial design. For trials with an active comparator the ACR70 and remission can be assessed at 6 months as these endpoints demonstrating higher efficacy can take a longer time to become evident.

Concomitant symptomatic treatment may be used, but should be documented carefully and the possible influence on the results and the way to analyse this should be indicated in the protocol. Additionally, careful documentation of concomitant non-pharmacological treatment has to be performed. Medication for diseases other than rheumatic should be clearly documented and it is recommended that wherever possible that treatments be standardised and pre-defined.

4.2.2. Assessment of structural damage

Radiographic progression of RA and long term response to therapy are generally assessed by quantifying changes in joint space narrowing and erosions visible on serial plain radiographs. Sharp-van der Heijde scoring system is recommended. The use of other assessment methods should be justified.

It is recommended to demonstrate radiological differences of hands and forefeet on the basis of before/after comparisons using full randomisation and pre-agreed criteria. The conduct of the radiological analysis should be described in detail. Deviations from published and validated methodology should be justified. Radiographs should be taken on fixed and predefined time points and be assessed by at least two assessors blinded to the treatment allocation of the patient, sequence of the radiographs and initial assessment(s) of the other assessor(s). The method for obtaining the final score should be described in detail (e.g. consensus) and be predefined. Intra- and inter- observed variation should be discussed with regard to the observed differences between treatment arms. Handling of missing information should be described and justified. Slowing of radiographic progression does not in itself define a patient benefit and demonstration of such an effect is considered to be a surrogate for long-term clinical benefit (signs and symptoms and/or physical function benefits). However, there is good indirect evidence that, by favourably modifying the natural history of rheumatoid arthritis in terms of structural changes, long-term clinical benefit will occur in a large proportion of patients. It would be expected that an applicant will provide additional evidence to support this surrogacy.

The extent of radiographic changes in RA varies greatly across populations and is related to the extent of baseline damage and the disease activity. The minimal clinically important difference in progression of structural damage in a given target population should be defined consistently across trials. Any chosen cut-off value will need to be defined in the study protocol and be justified carefully considering the demographic and baseline disease characteristics of the target population.

Using the existing validated technique to assess radiographic progression, i.e. radiographs, measurement after 1 year may be sufficient to confirm efficacy in terms of endpoints relevant to slowing/prevention of structural damage claim. In exceptional cases a measurement after at least 6 months may be sufficient depending on the properties of the test drug; this has to be justified by robustness of the method and convincing clinical data. It is important to demonstrate long-term maintenance of this effect for an additional 12 months.

Development of imaging techniques, e.g. radiograph, MRI, ultrasound, may lead to increased sensitivity. Where MRI is used to supportively document efficacy, clinically relevant changes should be defined and justified. At present this technique is not established as a sufficiently recognised measure of anti-rheumatic drug efficacy.

4.3. Secondary or supportive evidence for efficacy

This can include the following if not assessed as primary endpoints:

a) ACR 50 response at Week 12
b) DAS28 (using CRP) response at Week 12
c) Remission at weeks 12 and/or 24
d) HAQ score and FACIT scores

Extra-articular manifestations of RA (e.g. nodules, vasculitis) are important to assess in this systemic disease.

Other methods such as arthroscopy, scintigraphy, ultrasonography, or other biochemical measurements (e.g. serum, urine, joint fluid) may also be used to show supportive evidence for efficacy but only when the methods have been subjected to prior validation and their clinical relevance predefined.

Biomarkers are optional, but might provide more insight into which specific target population the test drug may be most useful.

5. Strategy and design of clinical trials

5.1. Pharmacokinetics

The pharmacokinetic properties of the medicinal product should be investigated following existing guidelines.

For some medicinal products which are for intra-articular administration (e.g. corticosteroids) the residence time in the joint and the systemic availability of the active substance may be investigated in order to obtain data about maintenance of effect and systemic safety.

5.2. Dose-Response studies

Dose-response studies should be conducted in accordance with existing guidelines.

Specifically for the RA patient population, Phase II clinical trials may show efficacy but not reveal the full potency of a new compound over time. Therefore, for most products using ACR20 as primary outcome might be appropriate.

In some cases ACR20 may be not sensitive enough to detect differences between doses, especially in early arthritis or when non-biological agents are assessed. Instead, an outcome like swollen joint count may be more appropriate.

In general, duration of dose finding studies depends on the mode of action of the specific drug. For drugs claiming modification of signs and symptoms 3 months is considered appropriate.

5.3. Interactions

Interaction studies should be performed in accordance with the existing guidelines. Efficacy and safety implications of concomitant 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.

Due to the high proportion of patients using anti-rheumatic therapy other than the one studied or treatments other than anti-rheumatic because of co-morbidity, interaction studies regularly have to be performed. Selection of substances for conducting interaction studies should be based on the known pharmacokinetic and pharmacodynamic properties of the agent studied, the existing anti-rheumatic agents, and other possibly interacting medications. Recommendations from the guideline on interactions have to be taken into account.

If discontinuation of prior DMARD/biologic medication is required, the time of withdrawal prior to initiating treatment with the test drug should be the time required for any important pharmacological interaction to disappear.

5.4. Therapeutic confirmatory studies

5.4.1. Target population

Observable effects of treatment are dependent on diagnostic criteria applied to patients when entering a study and disease related factors such as stage and duration of disease or disease activity have to be documented appropriately using predefined criteria. With respect to generally accepted predictors for progression of the disease, patients have to be fully and carefully documented in all relevant respects; the mechanism of action and the indication sought have to be taken into consideration too. Thus initial symptoms and signs of active disease (as a minimum measure a) to f) of "tools", (see 4.2. above)), radiographs, presence of non-articular symptoms and signs, and concomitant diseases all have to be recorded. The level of disease activity/symptoms at baseline should be of sufficient severity to permit detection of relevant changes.

Dose and duration of previous and present anti-rheumatic medication have to be documented appropriately.

Other treatment modalities potentially interfering with the effect of study treatment are of particular importance. Careful documentation of concomitant medication for diseases other than rheumatic must be completely documented.

The patient population should be well characterised as they may show distinct differences in responsiveness to treatment and observed safety profile (e.g. early RA, DMARD failure, TNF-inhibitor-failures, multiple-mode of action failures, co-morbidities). The reasons for failure/discontinuation of previous therapy should be provided. The target population should match the proposed therapeutic indication and its demographics.

Specifically selected populations may be defined in the future: biomarkers and genetic markers for example might serve to predict patients with early RA who are more likely to progress to persistent or erosive arthritis and might benefit from specific treatments. These markers might also serve to differentiate responders from non-responders thereby enabling tailoring therapy to the individual patient.

At present diagnostic criteria for the undifferentiated arthritis population are controversial and need to be defined further and validated for use as reliable instruments for the definition of an appropriate study population.

5.4.2. Study design

Study design, outcome measures and duration should be appropriately chosen and justified with regard to the mode of action, magnitude and time course of effect related to the test drug.

Clinical trials in RA should be randomized and blinded, and the parallel group design is the preferred means of assessing efficacy and safety. There are several recognised design variants of a parallel group trial (e.g. add-on design) (see 5.4.3 to 5.4.5 below).

Each of these designs allows the continuation of randomised therapy for sufficient time to establish effects on chosen endpoints. In all of these designs current therapeutic strategies favouring early treatment should be taken into account.

Additionally, the time to onset of primary outcome (a particular response or a certain disease activity) should be assessed.

If studies (e.g. add-on design) require stable disease severity on DMARD medications (e.g. MTX), this medication should be given for at least the time required for the clinical effect to be fully established (e.g. MTX: 6 month) and a stable dose should be given 6 weeks to 3 months prior to initiating treatment with the test drug.

Assessment of relevant subpopulation or subgroup analyses should be prospectively planned, e.g. early disease, degree of structural damage at baseline, concomitant medication, patients refractory to other treatments.

In order to support a chronic treatment claim, maintenance of efficacy on treatment and/or after discontinuation (drug free period) should be demonstrated by a randomised withdrawal trial. In particular, the length of treatment needed for early disease has to be explored.

Three separate indications are distinguished: first (DMARD-naïve patients), second (MTX-failure or -intolerant patients) and third line (anti-TNF-failure or -intolerant patients). See sections 5.4.3 – 5.4.5 below for endpoints and design.

5.4.3. First line indication

DMARD-naïve (or MTX-naïve) patients

In DMARD-naïve (or MTX-naïve) RA patients a test drug could receive a first-line therapy indication either as monotherapy or in combination with MTX or another DMARD. For inclusion criteria, the ACR/EULAR classification criteria (2010) can be applied.

As MTX is the standard DMARD treatment in RA a direct comparison to MTX in Phase III trials should be performed. The use of another DMARD should be justified.

- As monotherapy a two-arm study comparing the test drug with an established active comparator (MTX) is recommended. Superiority to MTX should be demonstrated. In exceptional circumstances non-inferiority to MTX with an appropriately justified non-inferiority margin and an overall favourable benefit-risk profile could be accepted if the test drug demonstrates a clear advantage (such as faster onset of action, better tolerability) and also has a large safety database in RA (e.g. a drug already licensed for second and third line indications in RA)

- As combination therapy, a three-arm study comparing the test drug alone, MTX alone, and the combination in the same trial is normally recommended. Superiority of the combination to MTX alone has to be shown and needs to be clinically meaningful. The need for add-on treatment needs to be justified (e.g. reduction of drug antibody development, PD effect).

Different time of onset of effect between test and active comparator may have an impact on the results and this should be sufficiently considered.

Low disease activity may serve as the primary endpoint.

In early RA remission responder rate is an achievable and optimal goal. Since regulatory experience is limited and scientific discussion is ongoing, selection of patients and trial design should be discussed in a scientific advice procedure.

To assess disease activity a minimum duration of 6 months is considered appropriate; follow-up (preferably blinding maintained) for at least up to 1 year may be required for showing maintenance of effect and safety.

Structural damage should be assessed at 12 months but in some cases 6 months may be sufficient. An additional 12 months to demonstrate maintenance of efficacy is required (i.e. a total of 24 months data is required where structural data demonstrating efficacy has been shown at 12 months initially and a total of 18 months data is required where the structural assessment has demonstrated efficacy at 6 months).

5.4.4. Second line indication

MTX-failure or MTX–intolerant patients

In this context, failure is defined as inadequate clinical response to previous MTX therapy after treatment with MTX. A MTX-failure is usually defined as a patient with persistent disease activity despite MTX therapy on a stable dose of at least 15 mg/week (and < 25 mg/week) of MTX for at least 4 weeks prior to screening and have at least 4 swollen and 4 tender joints and C-reactive protein (CRP) ≥ 1.5 mg/dL at screening.

In clinical studies with MTX-failure patients it is recommended to exclude MTX–intolerant subjects. Similar principles would apply to other DMARDs.

One of the confirmatory studies should be a 3-arm trial which compares the test product with an appropriate and established comparator and placebo. In case add-on to MTX is planned, MTX has to be added in each arm. Non-inferiority to the active control could be an acceptable goal for products that have additional advantages over the standard anti-TNF comparator such as improved tolerability and better safety prolife in phase III trials. If further safety data is available from other populations, particularly RA patients, demonstrating less safety concerns than anti-TNFs, then this will also support acceptance of a non-inferiority trial. Low disease activity may be the primary endpoint.

There are several effective treatment options available for MTX-failure patients, such as TNF-inhibitors, with a more rapid onset of action. Therefore, the placebo-period should be limited to 3 months. After 3 months (imaging at this time point should be considered), the placebo comparator arm should be switched to, or receive as add-on, another DMARD or a targeted biologic (e.g. a TNF inhibitor) in order to continue evaluation of the test drug's comparative safety and maintenance of efficacy long-term. For assessment of disease activity, a minimum duration of 3 months is considered appropriate; follow-up for at least up to 1 year will be required for showing maintenance of effect and safety.

In addition to the confirmatory 3-arm trial as proposed above a two-arm study comparing the test drug with an established active comparator is recommended. Low disease activity may serve as the primary endpoint. Non-inferiority to the active control could be an acceptable goal with the caveats noted above. For assessment of disease activity, a minimum duration of at least 6 months is considered appropriate; follow-up for at least up to 1 year (preferably blinding maintained) will be required for showing maintenance of effect and safety.

Structural damage should be assessed at 12 months but in some cases 6 months may be sufficient. An additional 12 months to demonstrate maintenance of efficacy is required.

5.4.5. Third-line indication

Anti-TNF-failure or anti-TNF–intolerant patients

RA patients who respond insufficiently to anti-TNF treatment belong to a group with active progressive course of disease despite intensive treatment and have limited treatment options. The response on the test drug might therefore be of less magnitude than expected for first and second line indication.

RA patients should have demonstrated an inadequate efficacy response to one and/or more anti-TNF inhibitors after being treated for at least 3 months.

For new agents a randomized, blinded study is required.

For new agents recommended options are:

- a 2-arm study comparing the test drug + MTX with the prior anti-TNF + MTX unchanged (superiority) upon enrolment into the study.
- a 2-arm study comparing the test drug + MTX with MTX + placebo (superiority) for anti-TNF-intolerant patients only.
- Non-inferiority of new agent + MTX versus established comparator in 3rd line + MTX

For superiority trials (see above) the test drug would need to demonstrate superior efficacy (disease activity) to the placebo/prior therapy comparator. A minimum duration of 3 months for the placebo-controlled phase is considered appropriate. After 3 months, the placebo + MTX or prior anti-TNF + MTX comparator arm should be switched (with blinding maintained) to a comparator established in 3rd line + MTX in order to continue evaluation of the test drug's comparative safety and maintenance of efficacy. Structural damage should be assessed at 6 months.

Non-inferiority trials (see above): Non-inferiority to the active control (comparator established in 3rd line + MTX) is an acceptable goal. For assessment of disease activity, a minimum duration of at least 6 months for the blinded phase is considered appropriate. Structural damage should also be assessed at 6 months.

Low disease activity or at least clinically relevant improvement may be the primary endpoint.

For both study designs 6-months blinded controlled phases seem acceptable in this advanced disease state.

5.4.6. Comparators/concomitant interventions

Active comparator studies are preferred, taking the number of established and approved therapies in this disease into account. The need for and the appropriate choice of an active comparator is determined by the intended therapeutic position of the product or the population to be treated. Since there are several different classes of new agents with different specific modes of action, the appropriateness of the chosen active comparator should be justified. A demonstration of the superiority of the test drug to an appropriate comparator in at least one study is more persuasive of its efficacy than a demonstration of equivalence or non-inferiority.

Treatment with combinations is increasingly used in patients who have failed monotherapy. A pharmacological rationale should be presented and the choice of doses justified. Claims of additive or synergistic efficacy would need to be supported by specific efficacy data using the proposed combination.

A placebo arm of short duration reinforces the robustness of the study. However, the use of placebo-only trials should be restricted to products for which this comparison is strictly necessary for a meaningful outcome. The placebo control group should be rescued. It is recommended to provide predefined escape rules to provide rescue therapy for non-responding patients; those patients demonstrating response could continue therapy unchanged.

Rescue treatment should be standardised, monitored and carefully recorded for each individual patient. The time points of endpoint assessment should be appropriately chosen to avoid confounding the effects of the rescue medication.

5.4.7. Duration of clinical trials

The required duration of clinical trials depends largely on the chosen endpoint, the sensitivity of applied and accepted assessment methods, and the characteristics of the agent and the magnitude of its effects as well as the disease characteristics of the patients (see also 5.4.3 – 5.4.5).

Generally, the chosen duration depends on the mode of action of the product and should be justified; it should be of sufficient time to allow a meaningful comparison of the effect and to obtain a clear outcome.

6. Clinical safety evaluation

6.1. Specific adverse events to be monitored

Prior to licensing the safety database should be sufficient to characterise the safety profile of the medicinal product. A sufficiently robust and extensive safety database is required particularly for early disease stages.

The analyses of safety data should particularly focus on specific adverse effects related to the mode of action or risks known for the specific substance class (e.g. for TNF-alpha blocker: increased infectious risk, malignancies, infusion reactions). Some of these specific adverse effects might occur after drug discontinuation and should be evaluated and documented for an appropriate period post study.

As cardiovascular safety problems are common in RA patients, this should be specifically monitored.

In order to show that the medicinal product has no deleterious effects on the joints, evidence should be provided that structural damage is not accelerated.

It is important to realise that because of the nature of the disease, normally characterised by life-long progression and because of long-lasting medical treatment with highly active options to treat RA, adverse drug reactions must be detected as early as possible and signals be identified with high sensitivity. With drug substances severely affecting important physiologic organ functions, the early detection of the comprehensive adverse reaction profile for any newly introduced drug substance and especially any newly introduced therapeutic class presents a considerable challenge. Therefore it is clearly required that the general principles to achieve this are applied and efficiently introduced to the development of any new drug product to treat RA. In addition, clinical trials should evaluate immune system function, e.g. serum immunoglobulins and lymphocyte subsets, as well as assessing immunogenicity for biologicals in order to better characterize the long-term safety consequences of any adverse findings.

To assess clinical safety and identify relevant adverse reactions an observation period of not less than 12 months is required. Taking into consideration the chronicity of the disease, and the need for long-term treatment, longer periods may be more appropriate.

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. For clinical safety reasons (e.g. anticipation of deleterious effect on the joints) it may be advisable to perform radiograph examinations.

6.2. Extent of population exposure to assess clinical safety

The safety database to be submitted for assessing a new product should be sufficiently large taking into consideration the mechanism of action, safety profile and co-morbidities of the patients. If RA 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.

Considering the characteristics of the patient population sufficient data should be generated in geriatric patients. Available data should be reported separately for patients aged 65-74, 75-85 and 85 and older.

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

For further identification of rare adverse events associated with new therapies, intensive safety evaluation during randomised trials may be considered supportive, and emphasis should be placed on post-marketing surveillance and use of registries.

6.3. Extent of population exposure to assess clinical safety

RA is a chronic disease and most of the 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 CHMP requirements for safety data on long-term treatments. Detailed RMP's will need to be drawn up tailored to the likely risks and knowledge of the product.

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