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

Draft

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

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List of abbreviations

ACPA	Anti-citrullinated peptide/protein antibodies
ACR	American College of Rheumatology
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
DMARD	Disease-modifying antirheumatic drug
EMA	European Medicines Agency
EU	European Union
EULAR	European League against Rheumatism
HAQ-DI	Health Assessment Questionnaire- Disability Index
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals fro Human Use
JIA	Juvenile idiopathic arthritis
LDA	Low Disease Activity
MTX	Methotrexate
NSAID	Nonsteroidal anti-inflammatory drug
PD	Pharmacodynamic
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SDAI	Simplified Disease Activity Index
SF-36	Short-Form 36-item Health Survey
SmPC	Summary of medicinal Product Characteristics
TNF-α	Tumor necrosis factor-alpha
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 of synovial joints and other organ systems. If left untreated, it causes joint destruction, deformity and functional impairment.

Pharmacological therapies other than NSAIDs for RA are intended to treat signs and symptoms, disease activity and structural progression of disease. Available agents include synthetic disease-modifying anti-rheumatic drugs (DMARDs), biological DMARDs and glucocorticoids.

This document is a revision of the Points to Consider adopted in November 2003. Pharmacological therapy has advanced for RA in the last decade. Therapeutic strategies employing more aggressive intervention in early disease, often using combinations of non-biologic and biologic DMARDs, have shown a faster onset of action and more profound clinical responses than traditional approaches. Treat-to-target strategies are now employed, meaning that the treatment goal is remission or at least low disease activity in advanced patients. Until the desired treatment target is reached, drug therapy should be adjusted at least every 3 to 6 months**.** Moreover, new diagnostic criteria for early arthritis have been developed and validated, which allows for DMARDs to be made available in an earlier disease phase. These advancements require modified recommendations for the assessment of these therapies. This has led to new endpoints reflecting treatment targets of remission or low-disease activity at earlier time points, in place of the previous primary endpoint of change in ACR scores by 20% from baseline at 6 months. Furthermore, a distinction is currently made in this guideline between trials in populations with early RA or more advanced forms, and recommendations are also introduced on the way in which to assess the prevention of structural bone damage.

In addition, increasing knowledge of the risk associated with DMARDs treatment has been gained from trials and registries. The key elements for the assessment of safety issues which should be considered when developing new pharmacological treatments have been updated accordingly.

1. Introduction (Background)

Rheumatoid arthritis (RA) is an autoimmune disease, involving accumulation and activation of several cell subsets: 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. However, the exact pathogenesis of RA is still unknown.

The resulting hyperplastic synovial membrane, in conjunction with osteoclast activation, leads to adjacent cartilage and bone degradation. 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 the

incidence and disease expression have been identified. Smoking particularly in patients with HLA-DRB1 shared epitope alleles may influence the development and outcome of RA.

Features of the disease that are amenable to improvement by existing pharmaceutical means comprise inflammation and joint damage, and clinical features such as pain and physical disability. The treatment paradigm has changed significantly in the last decade since more successful treatment options have become available. There has been a shift towards more aggressive treatment in an earlier disease phase, with the aim to achieve tight control of disease activity (treatment to target), in order to prevent joint damage.

ACR/EULAR 2010 classification criteria for RA were specifically developed to diagnose and treat RA in an earlier phase than before, with the intention of altering the prognosis of the disease with early intervention. Further development of assessment instruments (e.g. disease activity status and response scores, remission criteria) have been elaborated in recent years. In addition, EULAR recommendations for management of rheumatoid arthritis were updated in 2013, with prominence given to a treat to target approach to aim for remission or low disease activity in all patients.

Adverse effects associated with 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 used, as with MTX-containing regimes (e.g. blood cell count, liver function, renal function, infections, malignancies).

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. flaring or more continuously persistent).

Currently, several biomarkers which may predict disease progression and response are under development. In the future, this may lead to a more individually targeted treatment approach.

Despite significant advances in the treatment of RA in the last decade, there are still a considerable number 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. synthetic as well as biological DMARDs) for the treatment of RA diagnosed according to international classification criteria, e.g. ACR/EULAR 2010.

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

3. Legal basis and relevant guidelines

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 Missing Data in Confirmatory Clinical Trials (EMA/CPMP/EWP/1776/99 Rev. 1)
- Guideline on Summary of Product Characteristics (Revision 2, September 2009)

4. Criteria and Standards for Patient selection

Patients with RA diagnosed according to internationally established criteria, e.g. ACR_EULAR 2010 could be eligible. In contrast to the prior diagnostic criteria, patients can be diagnosed with RA at a much earlier disease stage, before the occurrence of late-stage manifestations like erosions, and with a limited number of joints affected with synovitis.The ACR-EULAR 2010 criteria were developed to allow an earlier intervention with disease-modifying therapy and prevention of long-term damage. The institution of these revised diagnostic criteria will have consequences for the study populations of future trials, and the target population. Therefore, separate trials are required for newly diagnosed early arthritis patients, and more advanced treatment-experienced patients.

5. Possible indications/treatment goals

In current practice, the guiding principle for the treatment of RA is disease modification, by obtaining and maintaining low disease activity and preferably remission of signs and symptoms such as inflammation, pain and joint swelling.

The ultimate treatment goal is sustained remission of symptoms and synovitis, and the prevention of structural damage. Other treatment goals are improvement of physical function, fatigue and quality of life.

This should be reflected by the choice of the primary endpoint which should ideally be remission, but other less stringent primary outcome objectives like low disease activity can be acceptable if appropriately justified (e.g. in advanced patients).

The prevention of complications and/or RA-related co-morbidities like cardiovascular disorders can be additional goals provided these have been established before commencing the study.

6. Assessment of efficacy

In general, combined measures reflecting the different signs and symptoms are to be used to document efficacy. For this purpose diverse validated composite endpoints (e.g.DAS28, including EULAR categories, ACR response criteria, Simplified Disease Activity Index (SDAI) or Clinical Disease Activity Index (CDAI)) are available.

6.1. Assessment of symptoms and disease activity: Primary endpoints

EULAR-ACR remission or EULAR remission/low disease activity (LDA) scores should be the primary endpoint, as these are established treatment targets in the field, and routinely used for monitoring for patients in European clinical practice. As ACR scores represent a relative change from baseline, these

do not necessarily reflect treatment targets of remission or an established level of LDA, and are therefore not considered as primary endpoints.

Depending on the target population, either remission or LDA could be considered as the primary endpoint. For example, in early arthritis and during first line treatment, remission and maintenance of remission should be the primary endpoint, whereas in more advanced patients failing on standard care of multiple DMARDs, achieving LDA is a more realistic and important goal (see for details on the choice of the primary endpoint section 7.4.3). LDA is to be defined according to EULAR criteria (DAS28<3.2). If remission is the primary endpoint, this may be either defined in accordance to the EULAR criteria (DAS28< 2.6), or in accordance with the more strict EULAR –ACR criteria (Boolean or Index-based).

Reporting assessment of disease activity

Assessments of disease activity should be made at baseline and at least at 1, 3, 6, and, in maintenance trials, 12 months after start of treatment.

Time to onset of the primary outcome and sustainability of the primary outcome should be assessed. Time to onset of effect may be presented descriptively.

6.2. Secondary endpoints

The following secondary endpoints should be reported:

- ACR20, 50, 70 responder rates
- period of sustained remission/LDA
- mean DAS28 scores (every visit)
- Tender Joint Count, Swollen Joint Count
- physical function (e.g. HAQ-DI)
- bone involvement: structural bone damage by X–rays (e.g. Sharp-van der Heijde scores)
- biomarkers: CRP
- pain: VAS or Numeric Pain Scale
- Clinical Global Impression by patients and physician (reported by responder rates per category)
- Quality of Life (e.g. validated generic scales (SF-36), or disease specific scales (AIMS)

The following secondary endpoints could also be considered:

- MRI of the joints (synovitis, bone oedema and erosions, using RAMRIS or other validated scales)
- fatigue (FACIT-F or other validated scale)
- target specific biomarkers, e.g. cytokines

Currently, ultrasound imaging is used in clinical practice to monitor synovitis. Some scales are available and may be used. However, their purpose in clinical trials has yet not been sufficiently established to make a recommendation in this guideline.

6.3. Assessment of structural damage

Demonstrating prevention of structural damage is challenging. Though validated X-ray scores are available to measure erosions, structural damage is a slowly developing process, requiring highly powered long-term studies. At the same time, the placebo control is necessarily kept short for ethical reasons, leading to limited contrast. As patients are diagnosed earlier and treated more intensively, subjects with a lower disease activity are nowadays eligible for trials, who might be less likely to develop erosions. Several long-term cohort studies have confirmed that there is a strong correlation between the level and duration of the reduction in disease activity scores - ,and the prevention of radiographic progression. Therefore, maintenance of remission and low disease activity could serve indirectly as an indicator for the prevention of structural damage.

On the other hand, there is a concern that new treatment options may cause a significant reduction in signs and symptoms, whereas 'silent' subclinical inflammation persists and structural joint damage continues. Endpoints like the DAS28 remission and LDA scores, may not capture the whole inflammatory process. Therefore, structural damage of hands and feet should be routinely monitored by X-rays in the pivotal long-term trials, as a safety measure in order to provide reassurance that structural bone damage does not deteriorate during treatment, e.g. compared to an active comparator. However, considering the challenges of demonstrating structural damage, non-inferiority does not need to be demonstrated formally –unless a specific claim regarding the prevention of structural damage is intended (see section 6.1.1.1). Additionally, MRI may be used to assess residual inflammation in the synovium and bone. Validated scales for MRI are available (e.g. RAMRIS by OMERACT), however, it is a challenge to harmonise diagnostic centres, and intra- and inter-rater agreement is reported to be modest. Computer-assisted volume measurement may improve inter-rater scores, but are not fully validated yet. Therefore, these endpoints are considered as supportive but not as confirmatory.

6.3.1. Studies in support of a specific claim of the prevention of structural damage

If a specific supportive claim on the prevention of structural damage is intended, the prevention of structural damage should be established in a randomised study, specifically powered for radiographic progression outcomes. An active control, which has been established to prevent structural damage in RA needs to be included. In addition, a placebo could be added to further establish assay sensitivity. For ethical reasons, the placebo control is necessarily limited to 3-6 months, with an escape to active treatment if the patient deteriorates, e.g. when ACR 20 is not met at 3 months. The study on radiographic progression may be integrated in a trial regarding the treatment of symptoms and disease activity.

Radiographs of the hands and possibly feet should be taken at fixed and predefined time points. Readers of the radiographs should be blinded to the treatment allocation. Sharp-van der Heijde (SvdH) scores or another validated scale like Genant-modified Sharp (GmS), could be used as a scoring instrument of erosions and joint space narrowing. Mean change from baseline of the total SvdH/GmS scores can be the primary endpoint. Additionally, to provide insight into the clinical relevance of this primary outcome, responder analyses of subjects without radiographic progression needs to be provided as co-primary or key secondary endpoint. The primary endpoint may be assessed as early as 6 months, depending on (a) the mode of action of the drug, (b) the time point at which structural damage prevention had been established for the active comparator and (c) the sensitivity of study population. As the progression of joint damage is often more prominent in the early phase of active RA

disease, a study in early arthritis would be recommended to demonstrate prevention of structural damage progression.

7. Strategy and design of clinical trials

7.1. Pharmacokinetics

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

For some medicinal products which are for intra-articular administration, 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.

7.2. 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, sensitive endpoints like ACR20 or mean DAS28 might be appropriate as primary outcome in exploratory dose finding trials. The need of a dose per kg bodyweight should be taken into consideration. In addition, different doses may be required for early stage patients or more advanced patients, and this should be taken into consideration as well.

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 may be appropriate. Additionally, endpoints may be evaluated at earlier time points before the therapeutic plateau is fully developed (e.g., weeks 2 - 8) to increase the ability to detect possible differences between doses. Dose ranging assessment could reasonably be continued in exploratory and confirmatory trials, however, this should be justified.

7.3. 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, like methotrexate, should be evaluated. Particular attention should be focused on safety and efficacy interactions with other drugs planned to be administered during pivotal trials.

The need for conducting interaction studies should be based on the known pharmacokinetic and pharmacodynamic 9PD) properties of the agent studied, concomitant anti-rheumatic agents if combined therapy is planned, 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.

7.4. Therapeutic confirmatory studies

7.4.1. Study population

Patients diagnosed according to ACR-EULAR criteria for RA are eligible for trials. Observable effects of treatment are dependent on diagnostic criteria applied to patients when entering a study and disease related factors such as disease activity, and stage and duration of disease have to be documented appropriately using predefined criteria. With respect to generally accepted predictors for progression of disease (e.g. mean DAS28 at baseline, sero-positivity of biomarkers, gender, obesity, smoking), patients have to be fully and carefully documented in all relevant respects. Stratification based on important prognostic factors is recommended.

At baseline, disease activity, radiographs, presence of non-articular symptoms and signs, and concomitant diseases all have to be recorded. While taking into consideration current therapeutic strategies and early treatment paradigms, the level of disease activity/symptoms at baseline should permit detection of relevant changes.

Dose and duration of previous and present anti-rheumatic medication have to be documented appropriately. Concomitant medication for diseases other than rheumatic disease must also be completely documented.

The patient population should be well characterised as efficacy and safety may differ in first, second and third line settings (DMARD-naïve patients, MTX failure, biologic- failures, respectively). The reasons for failure/discontinuation of previous therapy should be provided. The study population should match the proposed target population regarding 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 therapy to be tailored to the individual patient. Selection may have consequences for the labelling. At present, diagnostic criteria for the undifferentiated arthritis population need to be defined further and validated for use as reliable instruments for the definition of an appropriate study population.

7.4.1.1. Elderly

Considering the characteristics of the target population, sufficient data should be generated in elderly patients. Patients with late-onset RA differ from young-onset RA regarding gender distribution, with an increasing proportion of males at higher age, and lower rates of autoantibodies including RF and ACPA in the elderly. Disease activity may be severe in elderly and this may require intensive treatment, which may be less well tolerated than in younger subjects. In general, renal and hepatic capacity declines with age, and cardiovascular co-morbidity is more common in elderly. Because of these differences in disease characteristics, subgroup analyses regarding safety and efficacy should be provided for different age strata in elderly.

7.4.2. 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. The design should allow an assessment of the time to onset and maximal effect on the primary outcome.

For drugs with a prolonged action of several weeks or months, the study period, and preferably the blinding, should cover at least two dosing cycles.

Clinical trials in RA should be randomized, with parallel active comparator and/or placebo treatment arms, and double-blinded.

To fulfil a claim for the treatment of rheumatoid arthritis, it is expected that at least two confirmatory trials are provided, which could be performed in different disease models (e.g. treatment-naïve early arthritis patients, MTX-irresponsive patients or patients who have failed on multiple treatments including biologicals). The choice of the disease population determines the indication (see section 10).

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

For all studies, the criteria for use of rescue drugs should be pre-defined. Preferably, rescue drugs are standardised (e.g. steroids).

Assessment of relevant subpopulation or subgroup analyses should be prospectively planned, e.g. patients refractory to other treatments. If different chemical DMARDs are used as background therapy these should be stratified and analysed separately.

7.4.2.1. Maintenance of efficacy

Maintenance of efficacy should be demonstrated in a long-term randomized study, e.g. in an extension phase of a parallel study, where the blinding and an active control is maintained for in total 12 months study duration. Descriptive statistics may suffice and no formal non-inferiority exercise may be needed, if adequately justified.

The treatment to target principle should be maintained in the long-term study phase, for both the active control as well as the study drug. This implies that subjects who fail to reach and maintain remission or LDA after 3-6 months, should be considered as non-responders, and should be changed to alternative treatment options. How the treatment to target principle will be addressed needs to be established in the protocol before the start of the trial.

In addition, maintenance therapy on a lower dose level may be evaluated in stable patients in long-term remission.

7.4.3. Settings

Three separate settings are distinguished: DMARD-naïve early arthritis patients, MTX-irresponsive patients and biological DMARD irresponsive (see sections 7.4.3.1 – 7.4.3.3).

If a second and third line indication are claimed in both MTX- and biological DMARD-irresponsive patients, and this requires the same dose, these populations may be assessed within one clinical trial, stratified and analysed as pre-specified subgroups (see section 7.4.2 regarding the total number of trials that are required to support the RA indication).

As a general comment, three arm trials are foreseen. Trials including randomization to a placebo for more than (approx.) 6-12 weeks are unlikely to be feasible. For that reason, in situations where the expected onset of demonstrable effect dictates a later time-point for the primary analysis, evidence of efficacy will often need to be established via comparison to active comparator. A non-inferiority trial

may be targeted, though inclusion of a placebo-control arm should be useful for purposes of demonstrating assay sensitivity and helping to quantify effect sizes. For trials in which evidence of efficacy may be established more rapidly such that a comparison versus placebo at an earlier time-point is feasible, it remains important to contextualise efficacy and safety data against an established treatment option, in particular at later time periods, and the precision with which these comparisons can be made should be part of planning the sample size for the trial.

7.4.3.1. DMARD-naïve patients (early arthritis)

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 synthetic DMARD.

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

- As monotherapy, a two-arm superiority study to MTX is acceptable. Otherwise, for the demonstration of non-inferiority, a three-arm study comparing the test drug with MTX with inclusion of a placebo arm for assay sensitivity, is acceptable. Placebo may be limited to 6-12 weeks. The dosage of MTX should be pre-defined in the protocol and be optimised in line with clinical guidelines. The non-inferiority margin needs to be established before the trial, and should be justified.

- As combination therapy, a three-arm double-dummy study comparing the test drug alone, MTX (or another synthetic DMARD) alone, and the combination in the same trial is acceptable. Superiority of the combination to MTX alone has to be shown and needs to be clinically meaningful. The rationale for add-on or combination treatment with a DMARD needs to be clarified (e.g. reduction of drug antibody development, enhanced clinical or PD effect).

In early RA patients, remission is considered an achievable and optimal goal, and this needs to be reflected by the primary endpoint (see section 6.1). For the primary endpoint, effects on disease activity a minimum duration of 3-6 months is considered appropriate; follow-up (blinding maintained) for at least a total of 1 year is recommended for showing maintenance of effect and safety compared to the active control MTX.

7.4.3.2. MTX-irresponsive disease

Given that “MTX-irresponsive” patients may comprise insufficiently responsive as well as non-responsive patients, MTX should be continued at a stable level as background treatment in all study arms, unless its omission can be justified. The primary endpoint should be LDA, at a minimum, or remission. Depending on the mode of action and the expected onset of effect, the primary endpoint could be assessed at 3-6 months. Placebo could be as short as three months. If a placebo period of more than 3 months is considered, criteria for early conversion to active treatment should be pre-defined (e.g. if ACR20 response is not met at 12 weeks). These early converters are then considered as non-responders. In order to contextualise efficacy and safety data an established treatment option for the MTX-irresponsive disease should be included as an active comparator, in at least one of the confirmatory trials in this setting. At least one of the active-controlled trials should address maintenance efficacy of LDA or remission, where the active-control and blinding is maintained in the extension period till at least one year. For recommendations of studies on maintenance of efficacy, see above recommendations under section 7.4.2.

7.4.3.3. Biological DMARD irresponsive disease

RA patients who respond insufficiently to at least one established biologic DMARD belong to a subgroup with active progressive disease despite intensive treatment.

RA patients who have failed to achieve LDA following treatment with one or more biologic DMARDs for at least 3-6 months could be eligible. If patients with both inadequate efficacy and intolerance to biologic DMARDs are included, these subgroups should be stratified. Currently, several classes of biologicals are available targeting different elements of the immune-system, including inhibitors of TNF-alpha, IL-6 and B-cells. The mode of action of the previous failed therapy needs to be taken into account at the selection and/or randomisation since the response to the new drug, or an active comparator, will depend on the previous response to DMARDs with a common pathway. The selection of patients based on the type of prior DMARD failure might have consequences for the labelling (see Section 10).

The magnitude of response on the test drug might be less in biological DMARD irresponsive patients compared with biological DMARD naïve patients, and it may take more time to achieve a significant reduction of disease activity. For patients who have failed on one or at most two biologicals, e.g. TNF-inhibitors, LDA or remission at 6 months are still considered as realistic primary endpoints in this group.

For the specific group of patients with active RA, who have failed on multiple biological treatments from different classes, ACR20 at 3-6 months might in this circumstance be an acceptable primary endpoint. A separate trial is recommended for this specific setting.

For new agents recommended options are:

- a 2-arm study comparing the test drug with former therapy + placebo (superiority), on top of former therapy.
- a 3-arm study for establishing non-inferiority of new agent versus an established comparator, with inclusion of a placebo arm for assay sensitivity.

Given that patients will be eligible with insufficient response to one or more biologicals, the potential for some residual response at the time of inclusion risks disease deterioration if treatment is suddenly discontinued; continuation of the former treatment modalities may therefore be warranted. As a general principle, MTX or another synthetic DMARD is recommended to be given in combination with biological therapy in which case, background treatment with MTX in placebo and test drug treatment arms could be maintained, provided that there is no safety objection to the combination. However, combining multiple biologicals is in general not acceptable from a safety point of view, as the consequences of inhibiting multiple immune-modulatory pathways may be serious. Therefore, in the placebo-arm, the former treatment regimen with biologicals, with or without MTX, should be continued, whereas in the Test drug arm, only MTX may be continued.

A maximal duration of 3 months for the placebo-controlled phase is considered appropriate, for ethical reasons. After 3 months, the placebo arm could be switched (with blinding maintained) to active treatment, in order to continue evaluation of the test drug's comparative safety and maintenance of efficacy.

8. Clinical safety evaluation

8.1. Specific effects

The full-potential immune-modulatory effect of the new drug and the duration of these effects needs to be evaluated. The impact of the new medicine on both adaptive and innate immune systems needs to be evaluated with a focus on specific cell subsets, depending on the mode of action of the drug. Reversibility of the drug-effect on the immune-system after treatment withdrawal needs to be evaluated. Functioning of the immune system might be assessed by measuring the response of T cells harvested and challenged *ex vivo* to antigen, following immunisation with non-live vaccines.

Adverse events of special interest are infections, including serious ones like community acquired pneumonia and cellulitis, and opportunistic ones like e.g. candidiasis and herpes zoster. Relationships between immune system parameters (e.g. total lymphocyte, neutrophil counts) and infections should be investigated for the development of possible preventive monitoring measures. Appropriate screening for patients at high risk for opportunistic and serious infections should be undertaken (e.g. screening for latent tuberculosis and hepatitis, monitoring of vaccination status).

For biological drugs, an assay for drug-antibody forming needs to be developed. The relationship between drug-antibodies and loss of efficacy, infusion reactions and other adverse events needs to be evaluated.

Moreover, depending on the mechanism of action of the new drug, specific side effects in addition to those on the immune system should be comprehensively assessed also. RA patients are at risk for cardiovascular events. The influence of the new drug on lipids and atherogenic potential need to be monitored. Furthermore, routine monitoring of liver toxicity (e.g. ALT, AST, GGT, bilirubin, alkaline phosphatase), renal function, and vital symptoms like blood pressure is required in exploratory and confirmatory trials.

Depending on mode of action of the drug, the influence on bone resorption and osteoporosis may need consideration.

Local tolerability should be established for intra-articularly applied medicinal products by means of data from clinical efficacy trials. Systemic risks should be assessed based on systemic exposure and length of exposure but also on the residence time of the specific product (galenic formulation) in the treated joint.Imaging should be performed to control for potential deleterious effect on the joints.

8.2. Long-term effects

Considering that chronic treatment is generally aimed for DMARDs, long-term safety data of 12 months should be available before marketing authorisation, unless otherwise justified. For biologicals, a 12 months period is minimally required to evaluate possible induction of anti-drug-antibodies.

Several rare events have been associated with established DMARDs, such as demyelinating disorders, non-melanoma skin cancer and gastro-intestinal perforations. It may be difficult to assess rare events in the clinical trial setting with limited number of subjects and short-placebo control. Causality of rare events may be difficult to define, especially when these might be disease related as well, such as lymphoma, interstitial lung disease, major depression, congestive heart disease or venous thrombotic events. To get more insight in rare events and long-term safety, long-term follow-up of study participants and participation to RA registries in a post-marketing setting are strongly recommended. It

is recommended to participate in registries which include standard care as well, which may allow comparisons.

8.3. 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.

9. Risk management plan

For drugs sharing a particular mechanism of action associated with specific rare but serious drug-related risks like lymphoma or cardiovascular risks, 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.

10. Other

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

The claimed indication of treatment of moderate to severe rheumatoid arthritis should be clearly and concisely stated in SmPC section 4.1.

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, by indicating 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 certain classes of biological DMARDs). In addition, it should be indicated whether the product should be given alone or in combination (for definitions, selection criteria, study design and primary endpoints of the target populations see section 7.4.3-5).The wording of the indication should not reflect separate endpoints, but only the target disease rheumatoid arthritis. Given the various elements of disease modifying activity, information on the demonstrated effects on e.g. physical function and structural damage could be specified in the SmPC section 5.1

References

Aletaha D. et al., 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative, Ann Rheum Dis 2010;69:1580-1588

Radner H, Neogi T, Smolen JS, et al. Performance of the 2010 ACR/EULAR classification criteria for rheumatoid arthritis: a systematic literature review, Ann Rheum Dis doi:10.1136/annrheumdis-2013-203284

Smolen JS, Landewé R, Breedveld FC, et al.., EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update, Ann Rheum Dis doi:10.1136/annrheumdis-2013-204573