Guideline on clinical investigation of medicinal products for the treatment of rheumatoid arthritis

Draft Agreed by Rheumatology-Immunology Working Party (RIWP)	December 2011
Adoption by CHMP for release for consultation	5 December 2011
End of consultation (deadline for comments)	05 June 2012
Agreed by Rheumatology-Immunology Working Party (RIWP)	March 2015
Adoption by CHMP	20 March 2015
Start of public consultation	4 June 2015
End of consultation (deadline for comments)	29 November 2015
Agreed by Rheumatology-Immunology Working Party (RIWP)	24 November 2017
Adoption by CHMP	14 December 2017
Date of coming into effect	01 July 2018

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)"

Keywords	*Rheumatoid arthritis, Disease Modifying Anti-Rheumatic Drugs, clinical development, CHMP, EMA, guideline*

Guideline on clinical investigation of medicinal products for the treatment of rheumatoid arthritis

Table of contents

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 anti-rheumatic drug
EMA	European Medicines Agency
ESR	Erythrocyte Sedimentation Rate
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 for Human Use
JIA	Juvenile idiopathic arthritis
LDA	Low Disease Activity
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
PD	Pharmacodynamic
RA	Rheumatoid arthritis
RAMRIS	Rheumatoid Arthritis Magnetic Resonance Imaging Score
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
US	Ultrasound
VAS	Visual analogue scale

Executive summary

This document is intended to provide guidance on the clinical evaluation of medicinal products 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. Treatment options include synthetic and biological disease-modifying anti-rheumatic drugs (DMARDs), and glucocorticosteroids.

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 intensive 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 optimum treatment goal is remission, or at least low disease activity in patients irresponsive to earlier treatments. Until the desired treatment target is reached, drug therapy should be adjusted at least every 3 to 6 months. In addition, new classification criteria for rheumatoid arthritis have been developed and validated by the ACR-EULAR, which allows for earlier DMARD use. These advancements require modified recommendations for the development 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 meeting ACR20 improvement criteria at 6 months. Furthermore, a distinction is currently made in this Guideline between trials in DMARD-naïve RA patients or in patients who have had an inadequate response (IR) to prior therapy with DMARDs. Recommendations are also introduced on how to measure 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 anti-citrullinated peptide/protein antibodies (ACPA) 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-sixth decades. 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 treatments comprise inflammation and joint damage, and clinical features such as pain and physical disability. The treatment paradigm has changed significantly I n 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 classify RA and allow treatment with DMARDs in an earlier disease phase than before, with the intention of altering the prognosis of RA 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 and 2016, 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. 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, 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 (synthetic as well as biological DMARDs) for the treatment of RA classified according to international criteria, e.g. ACR-EULAR 2010.

Intra-articular products are beyond the scope of this guideline.

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, 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);

- Guideline on the investigation of drug interactions- CPMP/EWP/560/95/Rev. 1 Corr. 2

4. Criteria and Standards for Patient selection

Patients with RA classified according to internationally established criteria, e.g. ACR-EULAR 2010 should be enrolled. The ACR-EULAR 2010 criteria were developed to allow an earlier intervention with disease-modifying therapy, in order to prevent long-term damage. In contrast to the prior criteria, patients may be recruited into trials at an earlier disease stage, e.g. before the occurrence of manifestations like erosions, and with a limited number of joints affected with synovitis (1-5). The application of these revised classification criteria will have consequences for the study populations of future trials, and the target population. Therefore, separate trials are required for newly diagnosed DMARD-naïve rheumatoid arthritis patients, and DMARD treatment-experienced patients. Another reason for separate trials are differences in active controls that are available for each setting.

5. Possible indications/treatment goals

Possible indications are the treatment of moderate-severe rheumatoid-arthritis in naïve patients or patients irresponsive/intolerant to one DMARD, or multiple DMARDs. The indication could encompass monotherapy or combination therapy.

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.

Remission is considered as the optimal treatment goal, since sustained remission is correlated with the prevention of structural damage and maintenance of function over the long-term. Low disease activity defined by composite measures is an acceptable alternative goal for many patients who cannot attain remission, especially those with long-standing disease who actually constitutes the majority of patients in clinical care.

Therefore this should be reflected by the choice of the primary endpoint which should ideally be remission, but however, other less stringent primary outcome objectives like low disease activity could be acceptable.

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 disease activity scores could be used, such as DAS28-ESR and DAS28-CRP, Simplified Disease Activity Index (SDAI) or Clinical Disease

Activity Index (CDAI)), with established cut-off criteria for remission (DAS28-ESR or -CRP < 2.6, SDAI ≤ 3.3, CDAI ≤ 2.8) and Low Disease Activity (DAS28-ESR or -CRP < 3.2, SDAI ≤ 11, CDAI ≤10).

DAS-28-ESR or DAS-28-CRP is commonly used to monitor disease activity of patients in practice. However, it is acknowledged that there are some limitations in these disease activity scores and patients may still have ongoing inflammation at remission e.g. defined by DAS28-CRP. Therefore, more stringent remission criteria were developed by the ACR-EULAR . These criteria consist either of a Boolean definition, including tender and swollen joint counts ≤1, and CRP ≤1 mg/dl, or an index-based definition, with SDAI ≤3.3.

In addition to the afore mentioned targeted endpoints, ACR response criteria (e.g. ACR20, ACR50, ACR70 reflecting improvement of signs and symptoms from baseline of 20, 50 or 70%) should be documented.

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.

Elements of the composite disease activity scores selected for the primary endpoint (e.g. Tender Joint Count, Swollen Joint Count, Patient's or Physician's Global Assessment) should be reported separately as well.

6.1. Primary endpoints

An endpoint reflecting a target disease state (ideally remission, or Low Disease Activity (LDA) at the minimum) should be selected as the primary one, since these are established treatment targets in the field. Moreover, sustained remission, and to lesser extent LDA, are correlated with the prevention of structural damage and functional loss.

For studies on the treatment of naïve patients, remission at 3 to 6 months as established by a combined measure as listed above in Section 6 , Assessment of efficacy, is the preferred endpoint. For studies in patients who have inadequately responded to previous synthetic or biologic DMARD treatment, LDA at 3 or 6 months could be considered as the primary endpoint.

The primary endpoint of choice (either remission or LDA as defined by either DAS28-CRP, DAS28-ESR, SDAI or CDAI), should be corroborated by the other outcomes as secondary endpoints, such as the more stringent outcome SDAI remission, or by CDAI, which is the only outcome independent of biomarkers CRP or ESR.

Given that endpoints based on change of response criteria, such as ACR20, represent a relative change from baseline, these do not necessarily reflect treatment targets of remission or LDA. As their clinical relevance may not be immediately clear, improvement of response outcomes are in general not considered as primary endpoints. An exception may be a specific group of difficult to treat patients with an inadequate response to multiple DMARDs (synthetic and biologic) from different classes. A relative small improvement in disease activity without achieving LDA or remission may still be considered as a benefit for this specific group, and ACR20 at Month 6 is considered an acceptable primary endpoint.

6.2. Secondary endpoints

– The following secondary endpoints should be considered: ACR20, ACR50, ACR70 responder rates

– Structural joint damage by X–rays (e.g. Sharp-van der Heijde scores)

– Physical function (e.g. HAQ-DI)

– Remission/LDA rates defined by SDAI, CDAI, DAS28-ESR or-CRP –if not already not chosen as primary endpoint

Supportive endpoints could be:

– CRP

– Pain: VAS or Numeric Rating Scale

– Quality of Life (e.g. validated generic scales (SF-36 or other validated scales), or by the use of a disease specific instrument (e.g. AIMS, or other validated scales).

– Fatigue (FACIT-F, or another validated scale)

– Ultrasonography of the joints

– MRI of the joints (e.g. RAMRIS scale)

6.3. Imaging

Prevention of structural damage is considered an important goal of treatment. Therefore collection of relevant data is expected to be generated.

Structural joint damage should be evaluated by X-rays. Sharp-van der Heijde (SvdH) scores or another validated scale like Genant-modified Sharp (GmS), could be used as a scoring instrument. Readers of the radiographs should be blinded to the treatment allocation. Ideally, the readers should also be not be aware of baseline/previous images of the same subjects when scoring later one. Mean changes from baseline of the total score, and its components of erosions and joint space narrowing, should be reported separately. Additionally, responder analyses of subjects without radiographic progression need to be provided.

Prevention of structural damage may be demonstrated by showing superiority towards placebo or an active control. However, a formal demonstration of the prevention of structural damage in a trial setting has become increasingly challenging. Structural damage is a slowly developing process that usually occurs only in a fraction of the RA study populations, requiring highly powered long-term studies. Erosions are less likely to develop in a trial setting, since RA patients are nowadays treated more intensively and in an earlier disease phase. At the same time, a placebo control is necessarily kept short for ethical reasons, leading to limited contrast.

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 by DMARDs, and the prevention of radiographic progression. In principle, the primary endpoints of remission and low disease activity could serve indirectly as an indicator for the prevention of structural damage. However, there may be a concern that primary endpoints of remission or LDA may not fully capture 'silent' subclinical inflammation and that structural joint damage continues, despite meeting these primary endpoints. Therefore, structural damage of the hands, and possibly feet, should still be routinely monitored by X-rays in one or more pivotal long-term trials.

Considering the challenges regarding power, a formal demonstration of the prevention of progression of structural damage is not a prerequisite for an application of marketing authorisation. It is however expected that the anti-inflammatory effect is demonstrated unequivocally by the above mentioned composite endpoints, accompanied by observational data of X-rays providing reassurance that structural bone damage does not deteriorate during treatment, e.g. in comparison with an active control with established efficacy regarding the prevention of structural damage.

MRI and Ultrasound

Additionally, MRI may be used to assess residual inflammation in the synovium and bone, and structural damage (erosions and joint width narrowing). Validated scales for MRI are available (e.g. RAMRIS by OMERACT). However, it is a challenge to harmonise diagnostic centres and rates, and these modalities have not been fully validated as outcome measures in confirmatory trials. Therefore, these endpoints are considered as supportive but not as confirmatory.

Currently, ultrasound imaging is used in clinical practice to monitor residual 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.

7. Strategy and design of clinical trials

7.1. Pharmacokinetics

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

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-CRP might be appropriate as primary outcome in exploratory dose finding trials. The need of a dose per kg bodyweight or weight class 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 demonstration of 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 confirmatory trials.

In the dose finding for obese patients, both plasma exposure as well as clinical response needs to be taken into account, since response may be reduced in overweighed subjects for other reasons than PK.

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.

Guideline on clinical investigation of medicinal products for the treatment of rheumatoid arthritis
CPMP/EWP/556/95 Rev. 2

Page 9/16

The need for conducting interaction studies should be based on the known pharmacokinetic and pharmacodynamic 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 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 classified according to internationally established criteria such as ACR-EULAR 2010 criteria for RA, are eligible for trials. At baseline, disease activity, 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 tolerability may differ between DMARD-naïve patients and patients with an inadequate response to one or more DMARDs (biological and synthetic). Inadequate response to prior therapy could be defined as not achieving a target level of low disease activity, such as DAS-ESR above 3.2 points, for at least 3 months, despite optimum dosing of prior DMARDs. The reasons for failure/discontinuation of previous therapy should be provided.

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.

7.4.2. Study design

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

Standardized rescue medication should be considered in the protocol. Placebo control may need to be kept short for ethical reasons. The short-term placebo arm could be switched (with blinding maintained) to the test or active control drug, in order to continue evaluation of the test drug's comparative safety and maintenance of efficacy. In situations where the expected onset of demonstrable effect dictates a later time-point for the primary analysis than the placebo-controlled period, evidence of efficacy will need to be established via comparison to a separate active comparator arm. The precision with which these comparisons can be made should be part of planning the sample size for the trial.

Guideline on clinical investigation of medicinal products for the treatment of rheumatoid arthritis
CPMP/EWP/556/95 Rev. 2

Page 10/16

A non-inferiority trial may also be performed. Inclusion of a placebo-control arm should be considered as well in an active-controlled non-inferiority study for purposes of demonstrating assay sensitivity and helping to quantify effect sizes. If no placebo will be included, assay sensitivity needs to be discussed and justified in the dossier.

The design should allow an assessment of the time to onset and the time to 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.

It is expected that at least two confirmatory trials are provided. For a general RA indication, data should be provided from naive as well as patients with an inadequate response to one or more DMARDs. These data may be obtained from two single separate studies, e.g. one study in DMARD-naïve early arthritis patients, and one study in patients with an inadequate response to treatment with one or more DMARDs (synthetic or biologic). However, performing the two confirmatory trials in similar populations and obtaining a positive result will likely not lead to a broad RA indication, and the choice of the trial population will then help to determine the indication (see Section 10).

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

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

7.4.3. Specific study designs

Three separate target populations are distinguished: DMARD-naïve rheumatoid arthritis patients, patients with an inadequate response to one DMARD, and patients with an inadequate response to multiple DMARDs including biologics.

If a treatment option is developed for patients with an inadequate response to one DMARD, or more DMARDs including biologics, and this requires the same dose, these populations may be assessed within one clinical trial, stratified and analysed as pre-specified subgroups. Treatment response is often more limited in patients who failed on multiple DMARDs including biologics, instead of a conventional synthetic DMARD only. Therefore, in support of an indication for patients irresponsive to multiple DMARDs based on a mixed study population, the response in the subgroup of patients irresponsive to multiple DMARDs should be relevant and corroborate the total population response.

7.4.3.1 DMARD-naïve patients

In DMARD-naïve RA patients a test drug could receive an indication either as monotherapy or in combination with MTX or another conventional 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 conventional synthetic DMARD than MTX should be justified.

- As monotherapy, a two-arm superiority study to MTX is acceptable. The dosage of MTX should be pre-defined in the protocol and be optimised, and in line with clinical guidelines, low dose corticosteroids may be considered as well on top of MTX. 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 preferred. Placebo should be limited to 6-12 weeks. If placebo is not considered

feasible, assay sensitivity should be justified otherwise, such as by the demonstration of a considerable treatment response that is not likely to be achieved by a placebo effect in the chosen study population. The non-inferiority margin needs to be established before the trial, and should be justified.

- When combination therapy is considered as an option, a two-arm double-dummy study comparing methotrexate (MTX) and the combination of the new drug and MTX in the same trial is acceptable. Superiority of the combination to MTX has to be shown and needs to be clinically meaningful. A Test monotherapy arm could be included as well, to provide further confirmation of the rationale of the combination, and to generate data whether monotherapy could be a relevant option, e.g. for patients with contra-indications for MTX.

7.4.3.2 Patients with an inadequate response to one or more DMARDs

RA patients who have failed to achieve LDA following treatment with one or more synthetic and/or biologic DMARDs for at least 3-6 months could be eligible.

In order to contextualise efficacy and safety data an active comparator should be included in at least one of the confirmatory trials in this setting.

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).

Preferably, placebo administration is not continued for longer than 3 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 would then be considered as non-responders.

Prior MTX, or other conventional synthetic DMARDs, should be considered to be continued at a stable level as background treatment in the placebo arm. It may also be continued in the active treatment arms (new drug or active control), unless monotherapy is aimed for.

If patients will be eligible with insufficient response to biologicals, there is a potential for residual response of prior biological DMARD at the time of inclusion, as these are long-acting. Moreover there is a risk of disease deterioration if prior biological DMARD treatment is suddenly discontinued, potentially inflating the treatment effect. Continuation of the former treatment modalities may therefore be warranted. If continuation of the prior biologic DMARDs is not feasible, e.g. because of intolerability or complex blinding when a wide variety of prior DMARDs is involved, the robustness of the treatment effect should be adequately justified. .

The magnitude of response on the test drug might be less in patients with an inadequate response to one or more DMARDs compared with DMARD naïve patients, and it may take more time to achieve a significant reduction of disease activity. The primary endpoint, remission or LDA, may be as late as at Month 6.

For the specific group of patients with active RA, who have failed on multiple *biological* DMARDs from at least two different classes (e.g. TNF-inhibitors, monoclonal antibodies targeting interleukin-6 or B-cells), ACR20 instead of LDA might in this circumstance be an acceptable primary endpoint. A separate trial is recommended in this special population. For this specific target population with limited

treatment options available to be chosen as comparator, a two-arm study comparing the test drug with placebo, on top of former therapy, could be acceptable.

7.4.3.3 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 analyses are required.

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 maintain the treatment target such as remission or LDA after 3-6 months should be considered as maintenance failures, and alternative rescue treatment options should be considered. 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

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. 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 need to be investigated, as this may serve to adopt 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 DMARDs, an assay for anti-drug-antibody detection needs to be developed. The relationship between anti-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.

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 the minimum required to evaluate possible induction of anti-drug-antibodies. Inclusion of an active control for 12 months to contextualize long-term safety of the new treatment option is recommended.

Several rare events have been associated with registered DMARDs, such as demyelinating disorders, non-melanoma skin cancer and gastro-intestinal perforations. It may be difficult to reasonably assess rare events in the clinical trial setting, such as malignancies and MACE 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 (see section 9, Risk Management Plan). 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 to address at least the common adverse events. Reference is made to ICH-E1A guideline (see section 3 of the document). If RA is an additional indication, safety data obtained in other populations can be considered in addition to safety data obtained in RA patients, provided the dosage regimen is similar, and the population is expected to behave similarly.

9. Studies in special populations

9.1. Studies in elderly patients

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 requires intensive treatment, which may be less well tolerated than in younger subjects. In general, renal capacity declines with age, and cardiovascular co-morbidity is more common in elderly. Because of these differences in disease and population characteristics, subgroup analyses regarding safety and efficacy should be provided for different age strata in elderly.

9.2. Studies in paediatric patients

Reference is made to the EMA guideline on clinical investigation of medical products for the treatment of juvenile idiopathic arthritis.

10. Other

Labelling in the SmPC

This guidance should be read in conjunction with the SmPC guideline.

It should be specified in the wording of the indication for which specific target population the product is indicated, i.e. DMARD treatment-naïve patients or patients irresponsive or intolerant to one or multiple DMARDs. In addition, it should be indicated whether the product should be given as monotherapy, or in combination with MTX exclusively, or in combination with other conventional synthetic DMARDs.

References

1. Aletaha D. et al., Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative, Ann Rheum Dis 2010; 69:1580-8.

2. Felson DT et al, American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis. 2011; 70(3):404-13.

3. 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 2014; 73(1):114-23.

4. Smolen JS, et al., EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update, 2014; 73(3):492-509.