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Guideline on clinical investigation of medicinal products for the treatment of systemic lupus erythematosus and lupus nephritis

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List of Abbreviations

ACLE	Acute cutaneous LE
ANA	Antinuclear antibody
BICLA	BILAG-based Composite Lupus Assessment
BILAG2004,	British Isles Lupus Assessment Group
CKD	Chronic Kidney Disease
ECLAM	European Consensus Lupus Activity Measurement
ESRD	End Stage Renal disease
LE	Lupus erythematosus
SELENA	Safety of Estrogens in Lupus National Assessment
SLEDAI	Systemic Lupus Erythematosus disease activity index
SLAM	Systemic Lupus Activity Measure
SLAM-R	revised Systemic Lupus Activity Measures (
SLICC	Systemic Lupus Erythematosus International Collaborating Clinics
SRI	SLE Responder Index
UPCR	Urine protein/creatinine ratio

Executive summary

This document is intended to provide guidance on the clinical investigation of medicinal products for the chronic treatment of systemic lupus erythematosus (SLE), a complex autoimmune disease that can affect multiple organs.

Patients diagnosed with SLE according to the American College of Rheumatology classification criteria or Systemic Lupus International Collaborating Clinics (SLICC) criteria should be enrolled in the trials. This guideline describes patient characteristics, inclusion and exclusion criteria and concomitant use of other medicines that should be considered in the recruitment phase. Acceptable endpoints include reduction of disease activity/induction of remission parameters; prevention of flares/increased time intervals between flares (maintenance of remission) and prevention of long term damage. Criteria that should be considered for inclusion and exclusion and the required efficacy readouts for lupus nephritis and juvenile lupus are also discussed separately within this guideline.

Specific aspects of the evaluation of clinical safety which should be considered when developing new pharmacological treatments have also been highlighted.

1. Introduction (background)

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease that can present with symptoms affecting almost any organ and organ system of a human body.

SLE affects women more frequently than men and is more common among Afro-Caribbean and Asian compared to Caucasian subjects. Incidence rates in Europe vary, but are generally between 2 to 4.7 per 100,000 per year and prevalence rates range from 20 to 150 cases per 100,000 in the overall population. While SLE is generally thought to affect primarily women in the third and fourth decade of life, the peak incidence seems to be later among patients of European descent. In about 15%-20% of cases, disease onset occurs during childhood and tends to be more severe with faster and more severe damage accrual.

The aetiology is considered multifactorial, with genetic, hormonal and environmental factors playing important parts. So far, no single abnormality of the immune system is viewed as solely responsible for the development of the disease. Activation of autoreactive B-cells, production of numerous autoantibodies and immune complex formation causing tissue injury and organ damage, are believed to play a central role in the pathogenesis. The interplay of a number of other factors including T-cells, antigen-presenting cells, cytokines, the complement system and apoptosis has also been considered important.

Currently there are no internationally validated diagnostic criteria for systemic lupus, however revised classification criteria published by the American College of Rheumatology (ACR) are used to make the diagnosis. These classification criteria require four or more of the eleven clinical and immunological criteria to be present at some time-point and as such, tend to identify more severe disease of longer duration.

The SLICC classification consists of seventeen criteria and for the SLE classification requires: 1) fulfilment of at least four criteria with at least one clinical criterion and one immunologic criterion; or 2) lupus nephritis as the sole clinical criterion in the presence of anti nuclear antibody (ANA) or anti-ds DNA. These criteria were shown to have higher sensitivity but less specificity than ACR revised criteria.

SLE is clinically a heterogeneous condition in terms of symptoms and signs, organ system involvement, clinical course and treatment response. In general, SLE has a waxing and waning course, where

periods of relatively stable disease are followed by flares that can ultimately lead to irreversible damage.

Lupus nephritis is the most common severe systemic manifestation of SLE affecting up to 50% of adult patients during the course of their disease. Morphologically the disease comprises a spectrum of vascular, glomerular and tubulointerstitial lesions. According to the WHO classification (defined in 1982 and revised in 1995) lupus nephritis can be divided into five classes based on biopsy. This classification is superseded by the Renal Pathology Society Working Group and the International Society of Nephrology Working Group (ISN/RPS Criteria from 2003) classification where six classes of lupus nephritis are described: Class I minimal mesangial glomerulonephritis, Class II mesangial proliferative lupus nephritis, Class III focal lupus nephritis, Class IV diffuse segmental or global lupus nephritis, Class V membranous lupus nephritis, Class VI advanced sclerosing lupus nephritis. Mortality is highest amongst patients with proliferative renal involvement and progression to renal failure is strongly predictive of mortality. This poor prognosis is related to both unspecific risk associated with the development of chronic renal disease, as well as manifestations of more severe forms of systemic disease.

Anti-malarials, non-steroidal anti-inflammatory drugs and local agents are widely used for the treatment of mild manifestations of lupus. For patients with moderate or severe disease, glucocorticoids are the mainstay of therapy in the acute phase. Additional immunosuppressive or immunomodulatory drugs alone or in combination can be used for the reduction and control of disease activity. Biologic therapies have recently been added to the SLE treatment armamentarium.

Randomised controlled trials to assess efficacy and safety of new treatments in patients with SLE have been particularly challenging; this may be related to disease heterogeneity arising from high levels of both inter- and intra-individual variability in disease manifestations, a lack of specific or sensitive instruments, a lack of predictive biomarkers or surrogate endpoints, and high numbers of patients receiving background therapy with glucocorticoids.

Although recent improvements in treatment regimens and medical care have reduced mortality and morbidity, many patients still have incompletely controlled disease and progress to end-stage organ involvement. Standard treatment regimens that are commonly used target inflammation non-specifically and cause immune suppression giving rise to increased risks of debilitating side effects. The future goals for clinical management of this disease are set towards better targeted, more effective and less toxic treatments.

2. Scope

This Guideline provides assistance for the development and evaluation of medicinal products for the chronic treatment of systemic lupus erythematosus in adult and juvenile onset forms. It also addresses the development of medicinal products for the treatment of patients with lupus nephritis. Whilst other subsets of SLE such as central nervous system (CNS) lupus and secondary antiphospholipid syndrome are not specifically covered by this guideline in view of either the difficulty in making a diagnosis and/or the absence of validated efficacy assessment tools, it is encouraged to include patients with these conditions in the trials. Results from systemic lupus could in principle be generalised to these conditions at least where anti-inflammatory activity is concerned. The ability of the investigational medicinal product to cross the blood brain barrier would also need to be considered in the case of lupus involving the CNS. Due to limited regulatory experience, cutaneous lupus is not under the scope of this guideline.

3. Legal basis and relevant guidelines

These Guidelines have 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 adopted European and ICH guidelines.

- Note for Guidance on Dose Response Information to Support Drug Registration - CPMP/ICH/378/95 (ICH E4);
- Note for Guidance on Statistical Principles for Clinical Trials - CPMP/ICH/363/96 (ICH E9);
- Note for Guidance on Choice of the control group in clinical trials - CPMP/ICH/364/96 (ICH E10);
- Guideline on the Choice of the Non-Inferiority Margin (CHMP/EWP/2158/99);
- Guideline on Missing Data in Confirmatory Clinical Trials - CPMP/EWP/1776/99 Rev.1-;
- Note for Guidance on Population Exposure: The Extent of Population Exposure to assess Clinical Safety - CHMP/ICH/375/95 (ICH E1);
- Note for Guidance on Ethnic Factors in the Acceptability of Foreign Clinical Data - CPMP/ICH/289/95 (ICH E5);
- Guideline on Missing data in Confirmatory Clinical Trials (CPMP/EWP/1776/99)
- Pharmacokinetic Studies in Man- EudraLex vol. 3C C3A;
- Note for Guidance on the Investigation of Drug Interactions - CPMP/EWP/560/95;
- Note for Guidance on Clinical investigation of medicinal products in the paediatric population - CPMP/ICH/2711/99 (ICH E11);
- Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population (EMA/CHMP/EWP/147013/2004)
- Note for Guidance on Studies in Support of Special Populations: Geriatrics (ICH Topic E 7) and the Questions and Answers - EMA/CHMP/ICH/604661/2009;
- Reflection Paper on the Regulatory Guidance for the Use of Health-Related Quality of Life (HRQL) Measures in the Evaluation of Medicinal Products (EMA/CHMP/EWP/139391/2004);

4. Patient selection/diagnostic criteria

4.1. Systemic Lupus

Participating patients should have a definite diagnosis of SLE based on generally accepted classification criteria, i.e. the revised American College of Rheumatology classification criteria or the SLICC SLE classification criteria. It is advisable to adhere to one classification set throughout the clinical development programme. Considering that SLE can have a wide range of manifestations and affected patient populations can be diverse, it is encouraged that a broad spectrum of patients compatible with the objectives of the planned clinical trial should be enrolled unless a specific subset or subsets of SLE patients is planned to be targeted (e.g. renal lupus).

In all cases, demographics and baseline disease characteristics including duration of the disease, disease manifestations, previous and concomitant therapies (including those not directly aimed at SLE, but which could for example alter the extent of organ damage, e.g. drugs associated with photosensitivity, thrombocytopenia etc.), should be carefully recorded at the beginning of the study.

The serologic markers such as positivity for ANA, anti-dsDNA and complement levels should additionally be considered at study entry.

Patients should also be characterised with respect to disease activity and the severity of the disease. In order to demonstrate a significant reduction in disease activity it is recommended that patients have a clinically important and sufficient level of disease activity despite prior treatment, at least moderate to severe active disease defined by e.g. baseline SLEDAI >6. Care should be taken to distinguish disease activity at enrolment from the level of damage and functional disability reached by the patient due to the course of the disease prior to baseline. Therefore, it should be clear how the activity and severity of disease has been measured and the primary data collected should be carefully recorded.

In addition to the level of disease activity at enrolment, documentation of the frequency of flares, e.g. the number of well documented flares for a period of 6-12 months prior to enrolment, should be recorded.

It should be ensured that different study arms are balanced for patients' characteristics and prognostic factors, including baseline disease activity, ethnicity and background therapy (e.g. glucocorticoid use above a given dose). If any baseline factors may in themselves significantly influence prognosis, prior stratification according to these factors should be considered.

Additionally, if certain medication is not allowed, a drug free interval should be specified. In the case that a prerequisite for enrolment is a discontinuation of certain medications, the reason for discontinuation e.g. lack of efficacy, intolerance or adverse reactions, and the necessary wash out intervals should be clearly defined and justified in the protocol.

4.2. Lupus nephritis

Clinical trials assessing renal outcomes should include patients with active lupus nephritis. Diagnosis of lupus nephritis should be in accordance with generally accepted criteria (i.e. ACR or SLICC classification criteria). It is advisable to select and adhere to one classification set throughout the clinical development programme. Active nephritis should be properly documented by increments in the total protein to creatinine ratio (UPCR), the presence of sediment and/or a significant decrease in renal function. Testing for the presence of serologic autoantibodies, i.e. anti-dsDNA, should be done at study entry. If patients with systemic lupus disease are included, these should be appropriately characterised with respect to the activity and severity of the general manifestations.

Clinical (i.e. nephritic/nephrotic) symptoms need to be classified by pathological assessment of renal biopsy, specifying both glomerular and non-glomerular lesions, e.g. Classes of LN, such as proliferative glomerulonephritis (ISN/RPS 2003 Class III or IV) or membranous nephritis (ISN/RPS 2003 Class V); the Activity/Chronicity Indexes, such as defined by NIH Activity and Chronicity Indexes. The biopsy should be of sufficient quality to allow clear diagnosis and ideally be performed as close to the start of the investigational therapy as possible and optimally within 6 months before randomisation. Combinations of different classes of glomerulonephritis, including important histopathological variants, such as additional tubulointerstitial and vascular involvements in one patient can occur. This should be recorded and taken into consideration in the analysis of results.

Patients should be stratified at randomisation by relevant baseline characteristics e.g. histological class of lupus nephritis, level of proteinuria, and/or creatinine clearance; while other ~~risk factors~~ ~~relevant for intended claim?~~ ~~should be reported and the most important~~ factors should be identified beforehand and taken into consideration by inclusion of these factors into the analysis model.

An increased risk for renal disease, different responses to treatment, worse prognosis, and increased mortality have been observed among Afro-Caribbean and Hispanic patients compared with other racial groups. Care should therefore be taken that both study arms include comparable numbers of patients of different ethnic background.

Concomitant medication that can affect renal outcome (e.g. anti-hypertensives including ACE-inhibitors, cholesterol lowering treatment) needs to be well documented in the protocol and taken into consideration during the analysis of results.

5. Efficacy assessment

5.1. Primary outcomes in SLE

The selection of the primary endpoint will depend on the objective of the clinical study and may be generally aimed at the control of disease activity and/or prevention of long-term damage. Given the heterogeneity of SLE manifestations, supportive evidence derived from secondary endpoints is of particular interest in this clinical setting to fully characterise the treatment effect.

5.1.1. Control of the disease activity

5.1.1.1. Reduction of the level of disease activity

The therapeutic goal of any given treatment intended for chronic use is to induce a clinically relevant reduction in the activity of the disease that is maintained in the long term.

Several validated scales of disease activity are available. Thus far, SLEDAI and BILAG have been shown to be sensitive in clinical trials. However, in view of the complexity of SLE, measurement of disease activity by a single index alone is considered insufficient to fully describe the therapeutic effect in individual patients. It should be demonstrated that an effect on reduction in global disease activity is not offset by worsening in any specific organ system. Therefore, it is recommended to assess the effect on disease activity preferably through validated composite indexes, (i.e., SLE Responder Index [SRI] or BILAG-based Composite Lupus Assessment [BICLA]), which both include a measure of global disease activity (by SELENA-SLEDAI), specific organ system involvement (BILAG) and overall subject's condition (Physician's Global Assessment).

The preferred main analysis should rely on the differences in the rate of responders. Responder criteria should be pre-defined, e.g. the target outcome could be remission, or a major clinical response, as defined by SLEDAI score of ≤ 2 or SIS ≤ 4 , BILAG score of C, PGA of improvement, with or without specific laboratory tests where relevant. Complete clinical remission is defined by complete absence of disease activity measured by disease activity indices in patients who do not require any ongoing lupus specific therapy. For patients on steroids, including steroid dependent patients, the goal of treatment is steroid-free or at least to achieve a low-steroid dose to maintain remission.

If partial response is targeted, defined as a clinically relevant response not fulfilling criteria for major response, this should be accompanied by a favourable safety profile, and/or a significant reduction of steroid use (see section 5.2.1). The clinical relevance of response criteria should be adequately justified, chosen before the study is initiated and thresholds should be thoroughly predefined.

The results should also be presented by both the absolute and the percentage change of the selected index/ composite between baseline and the end of the trial when possible, depending on nature of the index/composite.

There are several other scales available or under development to assess disease activity in SLE. Other scales should not be used as a primary endpoint, unless they are fully validated and generally accepted. It is recommended to seek scientific advice prior to the studies if there is deviation from the SLI as primary endpoint.

Patients should be followed up and assessed regularly in order to evaluate the response trends and establish the start of the effect, the peak and maintenance of effect.

The time point chosen for the evaluation of the effect on disease activity will depend on the time it takes the study drug to achieve an optimal effect, on the severity of the disease and whether it is intended for acute or chronic use. In some cases a response, informed by pharmacodynamic properties, may be considered achievable within 4 to 8 weeks from the start of treatment. However, for drugs intended for chronic use, control of disease activity should be determined over the longer term, i.e. at least 1 year.

5.1.2. Prevention of flares

The aim of any study drug intended for chronic use is to maintain the clinical response previously achieved by demonstrating an effect on the prevention of flares (decrease frequency/severity). Therefore, this should be measured either as a primary endpoint or as a key secondary endpoint.

Criteria for flares should be predetermined in the protocol. The characteristics of the flare include a clinically significant measurable increase in disease activity in one or more organ systems. It is most commonly a temporary event and usually there would be at least consideration of initiation or increase in treatment.

The flare is reflected by a clinically meaningful increase in an accepted disease activity score, for example an increase in SLEDAI-2K score ≥ 4 points, an increase in SELENA-SLEDAI score of ≥ 3 points or 1 new category A or 1 or 2 new category B items on the BILAG score. Other tools and/or definitions can be used if generally accepted and well justified.

Either, the time to a new flare or the frequency/annual rate of flares according to accepted criteria should be measured. If the time to a new flare has been chosen as a primary endpoint, the rate of flares over appropriate time points should be included as a secondary endpoint. An evaluation of the frequency of flares should normally be made over a period of at least one year. The protocol should establish the requirements to consider changes in disease activity as a new flare and not part of the previous episode. In addition, maintenance of response, i.e. defined by differences in the proportion of patients in different study arms who remain flare free over at least 12 months is considered as a relevant primary or secondary endpoint.

A study duration of at least 1 year is usually needed to demonstrate the effect on flares.

5.1.3. Prevention of long term damage

Accumulated multi-system chronic organ damage as measured by the SLICC/ACR damage index is suitable to use in studies enrolling patients particularly those with short duration of disease and without pre-existing damage, as it is more difficult to evaluate differences in damage accrual if the population enrolled has highly variable baseline damage. As the evaluation of damage accrual will be clearer in those with low baseline damage, it is recommended to stratify by baseline damage.

Manifestations should be recorded as damage only if they develop at or after the diagnosis of lupus, provided they fulfil the list of definitions, and irrespective of whether they are considered to be directly

attributable to the disease. Damage accrual is usually recorded if present over 6 months or associated with immediate pathological change indicative of damage. Therefore the clinical trial should be long enough (at least 12 months) for damage to occur and persist for 6 months. Using a SLICC/ACR damage index may be problematic when a new study drug is associated with toxicities not listed in the Damage Index used to. In this event, other instruments to assess damage could potentially be used, however this should be discussed with relevant regulatory authorities prior to commencing trials. For a therapy that has efficacy in reducing disease activity, long-term follow-up of patients in a controlled extension would be required to demonstrate efficacy for reduction of damage.

5.2. Other relevant secondary endpoints for SLE

When a composite endpoint that consists of multiple indices (e.g SLE Responder Index) is used as a primary outcome measure to assess the efficacy of the drug, components of this composite endpoint should be analysed separately as secondary outcomes and described alongside the result for the composite outcome. Relevant endpoints not selected as primary should be included as key secondary endpoints.

5.2.1. Decrease in steroid dose

The concept of steroid-sparing is a key variable to consider in trials assessing add-on and maintenance effect during which the aim is to reduce the dose or even discontinuing steroids without precipitating a flare. The timing of altered doses in relation to the final outcomes needs to be considered. In the protocol it should be clear at which time point dose changes within predefined limits would be allowed. The protocol should also specify if administration of other forms of steroid including parenteral, intra-muscular or intra-articular steroids are allowed.

The efficacy evaluation for steroid tapering should be based on the percentage of patients whose average prednisone (equivalent) dose can either be discontinued while maintaining control of disease activity or at least reduced by a clinically relevant magnitude according to different stringent pre-specified criteria, e.g. subjects whose prednisone equivalent dose was 15 mg/day at baseline and reduced to ≤ 7.5 mg/day., without any flares for at least the final 3 months in a trial lasting one year. Reductions should have meaningful clinical implications

5.2.2. Patients and investigators reported outcomes

Quality of life

Health related quality of life (HRQoL) is known to be compromised in lupus patients and appears to be an independent outcome measure that does not necessarily correlate strongly with disease activity or organ damage. Given the fact that HRQoL is an independent outcome in Lupus patients, it is therefore important to consider assessing the impact of the condition on the patient's HRQoL to have a complementary source of information beyond what is captured by measures of disease activity and organ damage.

Medical Outcome Study Short Form 36 (SF-36) has widely been used to assess physical, psychological and social impact of chronic disease like lupus. An additional tool available to assess the impact of disease on the patients includes the Work Productivity and Activity Impairment Lupus score.

Lupus specific instruments include the Lupus Quality of Life (Lupus QoL), SLE symptom checklist and SLE Quality of Life (SLE QoL). As these instruments have not been validated in clinical trial settings and their correlation with SF-36 is variable, it is prudent to use these instruments together with SF-36.

Fatigue is a major concern for adults with SLE affecting more than 90 percent of the lupus patient population. Many instruments have been developed to measure fatigue severity and its impact in SLE, including the fatigue severity scale (FSS) which is most commonly used and correlates moderately with the 8 scales of SF-36, the FACIT fatigue or the Brief Fatigue Inventory (BFI). Other alternatives might be used provided they are validated and generally accepted.

Changes in physical function by e.g. ADL may also be of interest.

5.2.3. Biomarkers

Although a large number of novel biomarkers have been studied in lupus, none of them have been rigorously validated in longitudinal studies and in different ethnic cohorts. Furthermore, a candidate biomarker or combinations of them will unlikely substitute for conventional clinical parameters for monitoring the disease course. However, such biomarkers when used in combination with clinical parameters may improve efficiency of confirmatory trials with respect to patient selection, dose optimisation, and identification of drop outs with the future aim of developing more targeted treatments. It is therefore advised that identification and inclusion of biomarkers is incorporated as an integral part of the drug development programme.

5.3. Organ specific outcomes: Lupus nephritis

5.3.1. Primary outcomes in Lupus nephritis

Studies conducted in patients with lupus nephritis should be aimed for the control of renal activity. So, primary outcomes should focus on renal specific endpoints. If patients with SLE are included, it should be ensured that any benefit in renal functioning is not offset by a deleterious effect on other organs. Therefore, this should be assessed either as a component of a co-primary endpoint or as a key secondary endpoint.

- a) Induction of major/complete renal response: demonstrated as clinically significant improvement of renal function during induction phase e.g. by improvement of eGFR and reducing renal injury, primarily protein excretion and findings in active urinary sediment. It is expected that primary endpoints should be contextualised by reference to clinically meaningful values for major/complete response, such as normalisation/return to baseline of measured GFR or proteinuria of <0.5 g/24-h. A partial response, i.e. not full recovery but renal response able to maintain an eGFR within pre-specified margins with respect to baseline values, could only be accepted as primary endpoint if prospectively defined and relevance is well justified. Results for complete remission should be presented separately.
- b) Maintenance of major/complete renal response and prevention of renal flares [in terms of both decreased incidence proportions and their severity grades, specifying the type of renal flares (both nephritic and/or proteinuric ones) and classified correspondingly to the baseline conditions]
- c) prevention of long-term damage, i.e. slowing progression of chronic kidney disease (CKD) (please refer to other EU guidance options, including scientific advice)

Study endpoints must be appropriate to show efficacy for the indication sought.

5.3.2. Secondary specific LN outcomes

- Partial response, defined as a clinically meaningful improvement or stabilisation of GFR without full recovery to normal or baseline values.
- Clinical indices of systemic SLE: presence of extrarenal SLE manifestations, assessment of overall SLE activity
- Laboratory indices, showing either activity of the renal disease or chronic damage: such as active urinary sediment, proteinuria and renal function, including clinically relevant change in serum creatinine and GFR values
- Histological results of renal biopsy (such as changes in Activity and Chronicity indices over at least a 6 month period) should be collected where possible.
- Long term renal outcomes: development of end stage renal disease (ESRD, CKD 5D) with requirement of chronic renal replacement therapy and/or transplantation

6. Strategy and Design of Clinical Studies

6.1. Exploratory studies

6.1.1. Pharmacokinetics

The pharmacokinetic properties of the medicinal product should be thoroughly investigated in accordance with relevant guidelines regarding interactions, special populations (elderly and paediatric, renal and hepatic patients), and specific quality aspects (locally applied drugs, proteins and monoclonal antibodies).

6.1.2. Dose response studies

For dose response studies, ICH E4 guidance Dose-Response Information to Support Drug Registration should be considered. Evaluation of multiple doses is recommended. Should specific indications targeted at specific patients be sought, efforts should be made to find different doses and treatment intervals according to the respective patient characteristics (i.e. severity, organ involvement). For products being investigated in 2 or more autoimmune diseases extrapolation of dose-finding across indications could be acceptable subject to adequate justification.

Placebo controlled, randomised, double blind and parallel group design is recommended. Duration of the dose finding study depends on the lupus patient profile (e.g. severity of organ manifestations), chosen endpoints and mode of action of the medication.

6.1.3. 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 (e.g. glucocorticoids, immunosuppressants, NSAIDs) should be evaluated.

6.2. Therapeutic Confirmatory Studies

6.2.1. Systemic Lupus

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 of the test drug.

Although SLE has a fluctuating course, induction and maintenance therapy are not considered as separate treatment modalities of SLE treatment in clinical practice -this in contrast to lupus nephritis, where treatment of acute flares is separated from chronic maintenance treatment.

Double blind, parallel group, randomised trial design is recommended. Superiority trial design against an active comparator or placebo is preferred. Non-inferiority studies could only be accepted provided that the selected comparator could be justified on the basis of a well-established efficacy, and an appropriately justified non-inferiority margin could be predefined. Such comparative studies must have assay sensitivity. Alternative designs might be considered but it is recommended to discuss the design and planned data analysis methods with regulatory authorities before initiating the studies.

Placebo controlled trials are acceptable provided that placebo is given in add-on to standard of care therapy, unless otherwise justified. In placebo controlled add-on design setting the background treatment becomes of particular relevance. In order to avoid sub-optimal treatment in the control group of SLE patients, predefined adjustments in the background treatment should be planned, allowed and presented in the protocol. Escape provisions to an alternative standard-of-care regimen for patients who worsen during the study can be included and should be predefined.

The possibility of including an active comparator in the study design could be considered and predefined in the protocol. The three-arm placebo- and active-controlled study would aim to demonstrate that the test product is superior to placebo and allow putting results into perspective; It will address the real contribution of the new substance and could give clues for its suitability as first line treatment in some patients.

Possible primary endpoints include clinically relevant sustained reduction in disease activity. Alternatively, efficacy in the control of disease activity can be demonstrated by a significant effect in the prevention of moderate-severe flares. Considering the fluctuating nature of SLE, the duration of a trial aimed for the control of disease activity should be at least 12 months.

Other clinical trial designs that provide enhanced information to understand long-term efficacy and persistence of effect might be considered, e.g. a randomised withdrawal against placebo once short-term efficacy has been shown.

6.2.2. Lupus Nephritis

Double blind, parallel group, randomised trial design is recommended. Superiority trial design against an active comparator or placebo is preferred. Placebo controlled trials are acceptable provided that placebo is given in add-on to standard of care therapy.

Non-inferiority studies could only be accepted provided that the selected comparator could be justified on the basis of a well-established efficacy, and an appropriately justified non-inferiority margin could be predefined. Such comparative studies must have assay sensitivity.

Contrary to SLE, a clear distinction between induction and maintenance is generally accepted for lupus nephritis. The minimum optimal duration for assessing outcomes in clinical trials of Class III to V LN

should be 3 to 6 months for induction of partial response. A longer period might be needed for induction of complete renal remission, i.e. 1 year. For an agent used for both induction and maintenance an additional 1 year is needed after achieving the response for observing the maintenance of the effect. For a maintenance only claim a 1 year period is reasonable. Tapering the immunosuppressant after induction and/or maintenance period should be predefined and assessed thoroughly during development, if applicable.

6.2.3. Background medication

Changes in background medications that are used to treat patients with SLE can obscure detection of a treatment effect with the study drug. Therefore, background therapy should be standardised and stable as far as possible without compromising optimisation. Patients' needs during the trial should be addressed appropriately. Certain common practice modifications of background therapy could be allowed; these modifications should be well defined and carefully documented in the protocol (this includes also non-SLE medication, e.g. ACE inhibitors). If medication changes are substantial based on uncontrolled disease, then patients can be rescued and considered for the purpose of the primary efficacy endpoint as treatment failures.

The trial should include predefined escape conditions to allow switching to "rescue medication" when the patient fails to improve or the condition worsens. The choice and terms of rescue medication should be predefined in the protocol.

7. Juvenile-onset SLE

Although direct comparison with adult-onset disease is sparse due to the low incidence of juvenile-onset SLE (less than 1/100,000), there is evidence to suggest that juvenile-onset SLE patients (disease onset before 18 years) display some differences in their disease profile. Compared with adult-onset SLE populations there is an increased male-to-female ratio, a higher prevalence of nephritis and CNS involvement and faster accrual of damage in juvenile-onset SLE. This would often necessitate aggressive treatment and sustained need for steroids. Therefore specific instruments to assess disease outcome are needed that would on the one hand take into consideration disease course and aggressive therapy and on the other hand take into consideration the growing and developing paediatric patient whose perception of disease can be very different from adults and depend on the age group. Patient Reported Outcome (PRO) measures may require validated adaptations for use in paediatric subjects, such as incorporating symbolic visual anchors and/or age-appropriate text in symptom rating scales.

The Paediatric Rheumatology International Trials Organization (PRINTO), has developed a core set of five domains for the evaluation of overall response to therapy in juvenile-onset SLE. These domains include the following:

- Physician's global assessment of disease activity;
- A global disease activity measure (e.g. European Consensus Lupus Activity Measure (ECLAM), Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), Systemic Lupus Erythematosus Activity Measure (SLAM), British Isles Lupus Assessment Group (BILAG), or other global disease activity measures deemed appropriate for clinical trials)
- 24-hour proteinuria. Alternatively the spot urine protein: creatinine ratio on first morning void urine sample is considered a valid measurement.
- Patient's/Parent's global assessment of the overall patient's wellbeing
- Health-related quality of life assessment (Child Health Questionnaire physical summary score)

According to the PRINTO/ACR criteria patients are classified as responders if they demonstrate at least 50% improvement from baseline in any 2 among 5 core set measures with no more than 1 of the remaining worsening by more than 30%. The PRINTO/ACR criteria can be applied to all subtypes of juvenile SLE including trials specially designed for patients with renal involvement. Other composite indices that account for both improvement and worsening of disease manifestations in different organ systems, such as the SRI or BICLA, as well as time to SLE flare may also be acceptable primary efficacy endpoints.

Paediatric adjusted parameters (e.g GFR, blood pressure adjusted to the age, sex and height of the patient) should be used when evaluating clinical activity of the disease

In long term follow up the accrual of damage caused by the disease could be evaluated using SLICC/ACR damage index.

Pharmacokinetic, dose finding and where relevant vaccination/immune response studies should be performed in children from 5 to less than 12 years old. Where possible dosing for adolescents may be extrapolated from adults. There is no need for development of medicines for SLE in children under 5 years of age as the disease is extremely rare in that age group.

Safety may not be fully extrapolated from adults: however it is not realistic to accumulate sufficient information on safety in pre authorisation studies in children. Long term post authorisation studies or establishment of patient registries are necessary.

8. Elderly

While onset of SLE is generally between the ages of 15-45 years, the improved survival of patients with SLE over the last 20 years and in addition cases of late onset SLE means that older patients should be included in clinical trials of adult SLE. Study data should be reported separately for patients aged 65-74, 75 and older where available.

9. Clinical Safety Evaluation

Specific adverse events to be monitored

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. These specific adverse effects might occur after drug discontinuation and should be evaluated and documented for an appropriate period post study.

As the risk of malignancy, infection and cardiovascular events is greater in SLE patients, this should be specifically monitored. As the kidney is an important target organ for SLE, potential impact of the new agent on renal function or, in turn, any influence of renal impairment on drug elimination should be adequately monitored. Adverse events related to common organs/systems involved in SLE should also be closely monitored. Long term follow-up data must be available.

The extrapolation of data from the general safety database for organ specific conditions should be thoroughly justified.

Long-term safety

SLE is a chronic disease and most systemic 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 applicable to long-term treatments. Importantly, a risk management plan should be submitted that includes measures for provision of long term data post authorisation to assess the development of related malignancies.

For further identification of rare adverse events associated with new therapies, intensive safety evaluation during randomised trials might contribute but long-term follow-up in a large population will be needed.