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

Draft

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Executive summary

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

Patients with a diagnosis of SLE, according to the American College of Rheumatology revised classification criteria or SLICC SLE 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 should be used in order to assess efficacy. These endpoints include reduction of disease activity/induction of remission parameters; decrease of the cumulative steroid dose, prevention of flares/increased time intervals between flares (maintenance of remission) and prevention of long term damage. Points that should be considered for inclusion and exclusion criteria and the required efficacy readouts for cutaneous lupus, 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

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory connective tissue 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 generally fall between 2 and 4.7 x 10^5 per year. 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 has been considered solely to be 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, complement system and apoptosis has also been considered important.

Currently there are no internationally validated diagnostic criteria for systemic lupus, however revised classification criteria that have been 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. These criteria have a preconceived outlook towards more severe and longer durational disease.

More recently the Systemic Lupus International Collaborating Clinics (SLICC) revised and validated the SLICC classification criteria for SLE. 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 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.

Skin involvement is common in lupus and includes a variety of conditions. Lesions can be divided into lupus specific and lupus non-specific. The lupus specific cutaneous manifestations are classified as acute cutaneous lupus (malar/butterfly rash or generalized maculopapular eruption), subacute cutaneous lupus and chronic cutaneous lupus (discoid lupus, lupus panniculitis and chilblain lupus). Lupus tumidus has been recently added as a separate entity of intermittent cutaneous lupus. The risk for a patient with primarily cutaneous disease to develop systemic conditions is smaller in localised discoid lupus (1.3%), but considered higher in disseminated forms (around 20%). The most common lupus non-specific lesions include vasculitis, livedo reticularis and non-scarring alopecia.

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. For disease modification in the induction and maintenance phase, various immunosuppressive or immunomodulatory drugs alone or in combination are used. Biologic therapies have been used to treat moderate-to-severe SLE. More recently Belimumab gained regulatory approval as the first biologic therapy for SLE treatment.

Randomized controlled trials to assess efficacy and safety of new treatments in patients with SLE have been particularly challenging, this may be related to wide heterogeneity of the disease (both inter- and intra-individual variability in disease manifestations is large), the lack of specific or sensitive instruments, the lack of predictive biomarkers or surrogate endpoints, or high background therapy with glucocorticoids.

Although recent improvements in treatment regimens and medical care have dramatically 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 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 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 cutaneous lupus and lupus nephritis. Central nervous system lupus and secondary antiphospholipid syndrome are not specifically covered by this guideline; however these patients are not excluded from the trials.

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);
- 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 (EMEA/CHMP/EWP/147013/2004)
- Reflection Paper on the Regulatory Guidance for the Use of Health-Related Quality of Life (HRQL) Measures in the Evaluation of Medicinal Products (EMEA/CHMP/EWP/139391/2004);
- Guideline on the Choice of the Non-Inferiority Margin (CHMP/EWP/2158/99);

4. Patient characteristics for clinical trials selection

4.1. Definition and specifications of the disease

4.1.1. General considerations

Participating patients should have a definite diagnosis of SLE based on the revised American College of Rheumatology classification criteria. Alternatively SLICC SLE classification criteria can be used. Considering that SLE can have a wide range of manifestations and affected patient populations can be

diverse, it is encouraged that a broad a spectrum of patients compatible with the objectives of the planned clinical trial should be enrolled. Nevertheless, study population characteristics including demographics, duration of the disease, previous and concomitant therapies (including those not directly aimed at SLE, but which could for example alter the extent of organ damage), should be predefined in detail and carefully recorded at the beginning of the study. All specific diagnostic actions taken by physicians before including patients into a clinical trial (e.g. screening for latent tuberculosis) should be described in the selection criteria part of the study protocol. In the case that a specific patient cohort with certain organ manifestation is planned to be studied, the measures of how the organ involvement has been diagnosed and severity of manifestations should be well described. Patients whose disease is limited to specific organ system only (e.g. cutaneous lupus), should undergo additional tests including serological analysis for autoantibodies and antiphospholipid antibodies. This baseline information is useful following treatment in order to compare those who seroconvert and who go on to develop systemic features in each arm of the trial.

4.1.2. Cutaneous lupus

Lupus-specific cutaneous disease should be diagnosed based on clinical, histopathological and immunohistological findings. Alternative diagnoses such as drug-induced cutaneous lupus need to be excluded. As smoking is a possible exacerbating factor for cutaneous lupus, smoking status should be taken into consideration.

4.1.3. Lupus nephritis

Clinical trials assessing renal outcomes should include patients whose clinical (i.e. nephritic/nephrotic) symptoms are proven with pathological assessment of renal biopsy, specifying both glomerular and non-glomerular lesions, e.g. Classes of LN, such as proliferative glomerulo-nephritis (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 within 6 months of randomization. Combination of different classes of glomerulo-nephritis, 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.

4.2. Inclusion and exclusion criteria

4.2.1. General considerations

All inclusion and exclusion criteria that can affect the trial outcome should be clearly defined, specified at baseline and recorded.

In order to demonstrate a reduction disease activity (induction of clinical response) patients need to have a clinically important and sufficient level of disease activity prior to treatment in order to demonstrate a significant change. Care should be taken to distinguish disease activity at the enrolment phase 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 collected primary data should be carefully recorded. Activity of the disease should be assessed by means of validated indices and considering several aspects of the disease.

In order to demonstrate prevention or reduction of flares (maintenance of clinical response) patients will need to have evidence of well documented flares for a period of 6-12 months prior to enrolment.

The use of composite scores such as BILAG, ECLAM, LAI, SLEDAI and SLAM, ideally a combination of these, is considered appropriate and may be complemented with global patient assessments of the disease with visual analogue scales and health related quality of life. The serologic markers such as positivity for anti-dsDNA and complement levels should additionally be considered at study entry.

The age group of enrolled patients and duration of the SLE can be of importance, as disease manifestation, outcome and complications from the disease and previous treatments can vary widely and could influence the end result. Ethnic diversity of SLE and its impact on clinical manifestations is well known and should be taken into consideration to avoid unequal distribution in the study arms. It should be ensured that different study arms are balanced in respect of patients' characteristics, including baseline disease activity, ethnicity and background therapy (e.g. glucocorticoid use).

4.2.2. Cutaneous lupus

The accurate diagnosis of the CLE subtype(s) included in the trial, together with the extent of active disease and damage at baseline, should be recorded. For an investigational therapy for a second line indication that is for systemic use, subjects should have failed or have been poorly tolerant to previous adequate trials of topical therapies and/or hydroxychloroquine, despite adequate UV-protection and smoking cessation advice. For an investigational therapy for first line therapy then comparison with hydroxychloroquine is recommended.

Subjects must have active inflammation and have disease of sufficient severity to warrant inclusion and the degree of activity used as an inclusion criterion should be justified. For example, a baseline score for Cutaneous Lupus Area and Severity Index Activity Score (CLASI) of 10-20 is classified as moderate severity, and a CLASI score of 21-70 as severe, but as the CLASI overall score includes scores for activity and damage, a significant component to the score should be activity, thereby enabling demonstration of efficacy for active lesions.

Exclusion criteria for subjects with only cutaneous lupus and no systemic disease should include topical or any local therapy known to affect CLE within 4 weeks of baseline and use of concomitant DMARDs except in the case of add-on trials to hydroxychloroquine.

Of note is that some patients can have more than one type of CLE, and for these subjects information on each subtype should be provided.

4.2.3. Lupus nephritis

Patients should be stratified for randomization by relevant baseline characteristics pertinent for risk profiling e.g. histological class of lupus nephritis, level of proteinuria, and/or serum creatinine for ability to achieve remission; while other risk factors relevant for intended claim (e.g. ability to achieve remission, renal relapses or progression of renal failure) 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.

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

In the case that patients with end stage renal disease are excluded from the trial, this should be recorded in the protocol and GFR should be given.

Exclusion of patients with certain concomitant pathologies in addition to renal involvement (e.g. haematological abnormalities, liver involvement) should be clearly defined and the cut-off values of the laboratory indices given. If certain SLE non-related pathologies are excluded then this should be clearly stated in the protocol.

4.3. Concomitant medication

4.3.1. General considerations

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 standardized and stable as far as possible without compromising optimization. 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)

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. It should also be made clear, how the use of rescue medication is going to be analyzed. Comparative analysis of final background treatments in the responder and non-responder groups including "drop-out patient groups due to protocol violation" could add additional value to interpret the results and help in future study design.

Glucocorticoids are the accepted treatment for moderate to severe SLE. The dose of steroid depends on the disease severity in the affected organ system and can vary widely. In a clinical trials setting, the steroid dose for induction and maintenance should be restricted to within pre-defined clinically justified limits. It should also be clear what the duration of the permissible dose is. The protocol should also specify if administration of other forms of steroid including parenteral, intra-muscular or intra-articular is allowed (see section 5.2.1).

Additionally, if certain medication is not allowed, a drug free interval should be specified. In the case that the prerequisite to 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.

4.3.2. Cutaneous lupus

Care should be taken to avoid the addition of medications which are associated with high rates of cutaneous adverse drug reactions. The addition of new medications during the trial, such as drugs associated with cutaneous lupus induction or drugs with known photosensitizing potential should be avoided.

Therapy, including topical steroids should be balanced between the arms of the trial and stratification by systemic or topical treatment should be performed where possible.

Pre-defined escape conditions to allow rescue medication should be included. For subjects who have systemic disease in addition to CLE, the principles outlined in the main guidelines pertain.

4.3.3. Lupus nephritis

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 endpoints will depend on the objective(s) of the clinical study and may be generally aimed at induction and/or maintenance of response. More specifically, this might include a reduction of disease activity, the prevention of flares/increased time intervals between flares and prevention of long term damage.

In the case of induction of a major clinical response claim, the aim is to demonstrate a clinically relevant reduction in the activity of the disease. Efficacy should be demonstrated preferably through validated composite indexes in which the effect seen in an objective measure of reduction in global disease activity is not offset by worsening of the subject's condition overall or worsening in any specific organ system.

The aim of any study drug intended for maintenance of the response could demonstrate either the prevention of flares (decrease frequency and severity) and/or the reduction in the glucocortioid use while maintaining the control of the disease activity and/or the prevention of long term damage.

5.1.1. Reduction of disease activity ; induction of major clinical response or remission

In order to capture disease activity and subsequent damage, standardised disease activity indices (DAI) have been developed (SLEDAI, SLAM, BILAG, LAI, ECLAM, SIS and updated versions BILAG2004, SELENA/SLEDAI/2K and SLAM-R). SLEDAI and BILAG are extensively used in clinical practice and experience with these has also been gained from clinical trials.

The response criteria should be adequately justified, chosen before the study is initiated and thresholds should be thoroughly predefined. A major clinical response could refer to either no or minimal disease activity on the background of acceptable therapy (e.g. prednisone of ≤7.5mg/d and stable doses of immunosuppressant). Minimal disease activity could be measured as values of disease activity indexes (e.g. BILAG score of C, SLEDAI score of ≤2 or SIS ≤4), with or without specific laboratory tests where relevant. A partial clinical response could exemplify clinically significant improvement that is not sufficient for major clinical response/complete response. 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.

In the view of the complexity of SLE, measurement of disease activity by a single index alone is considered insufficient to describe the therapeutic effect in individual patients. It is recommended to assess the effect on disease activity by more than one single score, to ensure that the whole spectrum of the activity of the disease is captured and that results are consistent. Validated composite indices that combine multiple DAI are considered acceptable i.e. SLE Responder Index (SRI) and BILAG-based Composite Lupus Assessment (BICLA). Both SRI and BICLA are composite indices which include: measure of global disease activity (by SELENA-SLEDAI), specific organ system involvement (BILAG)

and overall subject's condition (Physician's Global Assessment). Investigators should be adequately trained to perform these scores in order to standardise their assessment.

The results should be presented by both the absolute and the percentage change of the selected index/ composite between baseline and the end of the trial. Analysis should take into consideration the baseline score from which the change has occurred.

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 proper timing for the evaluation of the effect on disease activity will depend on the time it takes the study drug to achieve its optimal stable effect, on the severity of the disease and its intended place in therapeutics. For induction of response the minimum would be 3 months –and in the maintenance phase 12 months is considered necessary (see section 5.1.2).

5.1.2. Maintenance of response: Prevention of flares/increased time intervals between flares

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 definition of flare should be the same at study entry and during the trial. Trials assessing flares should randomize clinically stable patients (e.g. stable SLEDAI score for at least two consecutive visits with a minimum interval between visits of 2 months). Patients, who have achieved remission during an induction phase of the study (as defined by BILAG C or better in all organ systems) and enter into the maintenance phase of the study, could also be recruited.

In terms of the instruments used to measure disease activity in SLE the SLEDAI-2K, BILAG, modified SLE Flare Index or SELENA-SLEDAI or a combination of them are recommended. The flare is reflected in an increase in the 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 2 new category B items on the BILAG score.

Either, the time to a new flare or the frequency/annual rate of flares according to the accepted criteria should be measured. The reduction in the frequency of flares is the preferred one. 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. Alternatively maintenance of response can also be met by expressing the differences in proportions of patients in different study arms who remain flare free over at least 12 months.

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 with short duration of disease and without pre-existing damage as it is hard to evaluate differences in damage accrual if the population enrolled has highly variable 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 attribution. Damage items are usually recorded if the clinical item has been present over 6 months or associated with immediate pathological

change indicative of damage. Therefore to measure the damage that has accrued during the clinical trial, the trial has to be long enough (for at least 18 months for damage to occur and remain present 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. This should be taken into consideration and addressed (other indices used) to overcome this difficulty. Other instruments to assess damage might also be used, however this should be discussed with relevant regulatory authorities prior to commencing trials. Please also see the organ-specific outcome section 5.3.

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, then components of this composite endpoint should be analyzed separately as secondary outcomes and described alongside the result for the composite outcome.

5.2.1. Decrease in cumulative steroid dose

The concept of steroid-sparing is a key variable to consider in trials assessing add-on and maintenance therapy during which the aim is to reduce the cumulative dose or even discontinuing steroids without precipitating a flare.

The efficacy evaluation for steroid tapering should be based on the percentage of patients whose average prednisone (equivalent) dose was reduced by a clinically relevant magnitude according to different stringent pre-specified criteria, i.e. subjects whose prednisone equivalent dose was >7.5 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, or the proportion of patients who discontinue glucocorticoids while maintaining disease activity controlled. Reductions should have meaningful clinical implications. If a patient's disease could not be controlled during tapering and subsequent predefined stable low dose (≤7.5 mg/day prednisone or equivalent), the patient by definition has failed to achieve the goal of steroid tapering.

5.2.2. Patients and investigators reported outcomes

Quality of life

Health related quality of life (HRQoL) is known to be impaired in lupus patients and appears to be an independent outcome measure.. As at the time of writing this Guideline, no single tool exists that measures all the aspects that influence health related quality of life (fibromyalgia, fatigue, cognitive dysfunction, depression, other co-morbidities and concomitant medication) in lupus. Therefore, although HRQoL is important to consider from patient's perspective, the measure does not necessarily correlate strongly with disease activity or organ damage. As QoL is of central relevance from the patient's perspective, particularly in cutaneous lupus, supportive data from QoL is strongly recommended.

Medical Outcome Study Short Form 36 (SF-36) has widely been used to assess physical, psychological and social impact of chronic disease like lupus. As the SF-36 in SLE patients with established disease changes little over a longer period (8 years), the SF-36 is more sensitive to change over short time periods and in cases of earlier disease where there is less damage.

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 and the scores of fatigue domain tend to be poor regardless of levels of disease activity and damage. Despite of its relative importance, consensus of which scale possesses the most suitable properties is lacking. Fatigue severity scale (FSS) is most commonly used and correlates moderately with the 8 scales of SF-36. Improvement/decrease of 15% in FSS should be considered important.

Physician's Global Assessment (PGA)

Physician's Global Assessment instruments should be used as secondary endpoints, .

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 subsequent inclusion of biomarkers is incorporated as an integral part of the drug development programme.

5.3. Organ specific outcomes

5.3.1. Cutaneous outcomes

The aim of treatment for CLE could include a reduction in disease activity and the extent of disease (i.e. induction of major clinical response or remission), reduction in the rate of development and number of new lesions, (maintenance of response, prevention of flares), prevention of long-term damage and improved quality of life.

When assessing cutaneous outcome in lupus, the tool should differentiate between active lesions and damage. It should also take into consideration the subtype of CLE and duration of the disease.

Therefore the response to treatment should include:

- macroscopic signs of active lesion (erythema and/or scale)
- presence of damage (scarring and/or hyperpigmentation)
- anatomical area involved
- patient reported outcome

Not all CLE subtypes result in scarring. Inclusion of patients with high activity and minimal scarring (where relevant) will enable clear evidence of efficacy for a therapy that leads to reduction in activity.

The CLASI has been systematically validated for the commonly occurring types of CLE (DLE, SCLE and tumid LE). The index distinguishes separately between activity and damage, with the total possible scores for activity and damage as 70 and 56 respectively. The separation of activity and damage is important because following effective therapy as the activity score decreases the resolving lesions may become hyperpigmented or scarred. Therefore both the CLASI total score and the CLASI activity score

should be used (Bonilla-Martinez), as use of the activity score will provide information on efficacy in active disease and use of the whole score will provide information on overall dermatology outcome.

The pre-defined reduction in CLASI should be justified to be clinically meaningful and is expected to be a 50% or greater reduction from baseline CLASI score. An alternative primary endpoint could be the proportion of patients achieving a complete response. For those with systemic disease it is recommended to use CLASI in conjunction with validated standardised global scores and to assess efficacy (systemic and skin-specific) as co-primary endpoints.

Suitable secondary endpoints include Physician's Global Assessment, patient's global assessment, patient's QoL and dermatology quality of life indices e.g. DQLI, patient's global assessment and VAS for itch and pain.

Input from experts in dermatology is required in order to ensure uniformity in scoring and to avoid misdiagnosis of non-lupus lesions as CLE. Misclassification of a non-lupus lesion as CLE may underestimate disease responsiveness to treatment via inaccurate and biased CLASI rating.

Additional endpoints should include the proportion of patients developing a cutaneous flare, the proportion of patients developing an increase CLASI damage score following treatment, the effect of therapy on autoantibody levels, development of new-onset systemic SLE features and, for those with concomitant systemic disease the main guideline pertains.

For disease activity the duration of efficacy needs to be demonstrated and rebound on withdrawal needs to be investigated in a randomized withdrawal phase.

For a therapy that has efficacy in reducing disease activity, long-term follow-up of patients in an open label extension will be required to demonstrate efficacy for reduction of damage.

5.3.2. Renal outcomes

Primary specific outcomes

Primary renal specific endpoints in a trial, conducted specifically among lupus nephritis patients, should include SLE endpoints as co-primary endpoints. It should be clearly stated what histopathological classes are included in the study, as the results obtained from certain classes cannot generally be extrapolated to the other classes.

- (a) Induction of major/complete renal response (demonstrated as clinically significant improvement of renal function during induction phase e.g. by improvement of GFR and reducing renal injury, primarily protein excretion and findings in active urinary sediment). It is expected that primary endpoints should be construed by clinically meaningful cut-off values for major/complete response, such as normalization/return to baseline of measured GFR or proteinuria of <0.5 g/24-h. The partial response should be assessed as the secondary endpoint only, but may serve as a main secondary one.

and/or

- (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]

with/without

- (c) prevention of long-term damage, i.e. slowing progression of CKD (please refer to other EU guidance options, including scientific advice)

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

Secondary specific outcomes

- Partial response in induction or maintenance of remission
- 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)
- Long term renal outcomes: development of ESRD (CKD 5D) with requirement of chronic renal replacement therapy and/or transplantation
- Frequency and severity adverse events associated with treatment

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 the dose response ICH E4 guidance *Dose-Response Information to Support Drug Registration* should be considered. Evaluation of multiple doses is recommended. Efforts should be made to find different doses and treatment intervals according to the respective patient characteristics (i.e. severity, organ involvement).

Placebo controlled, randomized, double blind and parallel group design is recommended. Duration of the phase II dose finding study depends on the SLE patient profile (e.g. severity of organ manifestations), chosen endpoints and mode of action of the medication, but it should not be shorter than 3 months.

For lupus nephritis patients separate appropriate dose finding needs to be undertaken for both the induction and maintenance phases. For the purpose of induction of the remission, study duration of at least 3 months in phase II should be necessary and at least an additional 6 months for the maintenance of the remission is advised.

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, immunosuppressant's, NSAIDs) should be evaluated.

6.2. Therapeutic Confirmatory Studies

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.

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. If non-inferiority study design is followed an appropriately justified non-inferiority margin and an overall favourable benefit-risk profile have to be demonstrated. Alternative designs might be considered but it is recommended to discuss the design and planned data analysis methods with regulatory authorities before initiating their studies.

Placebo controlled trials might be 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 readjustments 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 to ensure that no patient is denied potentially effective therapy.

Alternatively, the possibility of including an active comparator in the study design should be considered and predefined in the protocol. It will address the real contribution of the new substance and could give clues for its suitability as first line treatment in some patients.

Study design taking into account the clinical setting can be as follows:

Double blind, parallel group, randomized trial design is recommended. The selection of patients for confirmatory studies will depend on the type of drug and its intended aim in the treatment of lupus. The study design and potential primary outcomes will be discussed for each of the clinical settings defined:

A) New drugs intended to treat SLE disease: The aim of any new treatment in this setting could be either the induction of response and/or the maintenance of response.

A.1 Induction of major response or remission: Randomized controlled trial seeking to show superiority or at least non-inferiority versus an accepted comparator. Study duration 3 to 6 months. Based on the claim the maintenance of the effect and the absence of rebound should be addressed in the long term.

A.2. Maintenance of response: Efficacy could be demonstrated by either the prevention of flares and/or increased time interval between flares. Other targets may be the reduction in the glucocorticoids use while maintaining the control of the disease activity and/or the prevention of long term damage compared to the comparator arm.

A trial evaluating both induction followed by a maintenance of response can include a withdrawal phase in between, during which patients are randomly assigned to continue on new treatment or to receive placebo on top of standard of care therapy in a double-blind fashion.

Considering the fluctuating nature of SLE, the duration of a trial, where the prevention of a flare is the primary endpoint, should be at least 12 months with endpoint assessment at additional intermediate time points.

The minimum optimal duration for assessing outcomes in clinical trials of Class III to V LN should be 3 months to 6 months for induction of remission. A longer period might be needed for induction of complete renal response. **For an agent used for both induction and maintenance** an additional

1 year to 2 years are needed after achieving the remission for observing the maintenance of the effect. For the maintenance only claim a 1 year period is reasonable. Tapering the immunosuppression after induction and/or maintenance period should be predefined and assessed thoroughly during development, if so applicable.

Handling of withdrawals:

Handling of missing data should be in line with the Guideline on Missing data in Confirmatory Clinical Trials (CPMP/EWP/1776/99 Rev1). Additional statistical methods should be implemented to take into account the potential over dispersion due to the variability in exacerbation rates between subjects.

6.3. 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 are 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.

In an effort to standardize the conduct and reporting of clinical studies and to coordinate and facilitate future clinical trials the Paediatric Rheumatology International Trials Organization (PRINTO), in collaboration with the Paediatric Rheumatology Collaborative Study Group and with the support of the European Union and the US National Institutes of Health, 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:

1. Physician's global assessment of disease activity;
2. 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)
3. 24-hour proteinuria. Alternatively the spot urine protein:creatinine ratio on first morning void urine sample is considered a valid measurement.
4. Parent's global assessment of the overall patient's wellbeing
5. 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.

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 trials with longer duration than 1 year the accrual of damage caused by the disease should be evaluated using SLICC/ACR damage index.

Juvenile onset SLE shares many pathophysiological features with adult SLE allowing extrapolation of efficacy from adult studies to paediatric population. Such studies in adults that would be used for extrapolation purposes should include a spectrum of patients that corresponds with the paediatric population, i.e. including patients with renal and CNS involvement.

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 cannot be extrapolated, however it is not realistic to accumulate sufficient information on safety in pre authorisation studies in children. Long term post authorisation studies and establishment of patient registries are necessary.

6.4. 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. Available data should be reported separately for patients aged 65-74, 75 and older.

7. Clinical Safety Evaluation

7.1. Specific adverse events to be monitored

Safety database should be adequate to establish the overall safety profile associated with the medicinal product. Acknowledging the limitations of the database at the time of filling, the need for long term data, registries are of particular relevance in this setting.

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 SLE organ manifestation which may determine the course of disease, the impact of the new agent on renal function and potential renal damage should be adequately monitored. Events related with 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.

7.2. Extent of population exposure to assess clinical safety

The safety database to be submitted for assessing a new product should comply with the corresponding guidelines. For substance groups for which specific serious drug-related risks are known, a larger safety population may be needed. Special attention should be paid to the possible influence of concomitant medications in this often multi-drug treated patient population.

7.3. 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 on long-term treatments. Importantly, long term data to assess the development of related malignancies should be provided.

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

8. Abbreviations

ACLE	Acute cutaneous LE
ANA	Antinuclear antibody
CCLE	Chronic cutaneous LE
CLASI	Cutaneous Lupus Area and Severity Index Activity Score
CLE	Cutaneous lupus erythematosus
DLE	Discoid LE
LE	Lupus erythematosus
SCLE	Subacute cutaneous LE