CLINICAL TRIAL PROTOCOL

Induction of tolerance with immunoablation and autologous hematopoietic stem cell transplantation for systemic lupus erythematosus refractory to standard immunosuppressive therapy

AN OPEN-LABEL, PHASE II MULTICENTER COHORT STUDY OF IMMUNOABLATION WITH CYCLOPHOSPHAMIDE AND ANTITHYMOCYTE-GLOBULIN AND TRANSPLANTATION OF AUTOLOGOUS CD34-ENRICHED HEMAPOIETIC STEM CELLS VERSUS CURRENTLY AVAILABLE IMMUNOSUPPRESSIVE/IMMUNOMODULATORY THERAPY FOR TREATMENT OF REFRACTORY SYSTEMIC LUPUS ERYTHEMATOSUS

Acronym: ASSIST (Autologous Stem Cell Transplantation in Systemic Lupus Erythematosus Trial)

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Study Principal Investigator:
Prof. Dr. med. Falk Hiepe
Charité – University Medicine
Department of Rheumatology and Clinical Immunology
Charitéplatz 1
10117 Berlin
Tel.: +49 (0)30 450 513012
Email: falk.hiepe@charite.de

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1. TRIAL SYNOPSIS

STUDY TITLE	AN OPEN-LABEL, PHASE II MULTICENTER COHORT TRIAL OF IMMUNOABLATION WITH CYCLOPHOSPHAMIDE AND ANTITHYMOCYTE-GLOBULIN AND TRANSPLANTATION OF AUTOLOGOUS CD34-ENRICHED HEMAPOIETIC STEM CELLS VERSUS CURRENTLY AVAILABLE IMMUNOSUPPRESSIVE/IMMUNOMODULATORY THERAPY FOR TREATMENT OF REFRACTORY SYSTEMIC LUPUS ERYTHEMATOSUS.
SPONSOR	This study is sponsored by the Charité - University Medicine Berlin, Germany.
PRINCIPAL INVESTIGATOR	Prof. Dr. med. Falk Hiepe Department of Rheumatology and Clinical Immunology Charité - University Medicine Charitéplatz 1 10117 Berlin
OBJECTIVES	**Primary Objective:** Safety and efficacy of immunoablation and transplantation of autologous CD34-enriched hematopoietic stem cells compared to treatment with currently available immunosuppressive/immunomodulatory therapy in refractory SLE Primary endpoint is the number of patients in persistent clinical remission at month 24 after ASCT, defined as SLEDAI less than 3 in the absence of immunosuppressive therapy and prednisolone dosage ≤ 7.5mg daily. **Secondary Objectives:** - To assess durability of clinical response with respect subjects showing complete remission at Month 48, defined as SLEDAI less than 3 in the absence of immunosuppressive therapy and prednisolone dosage ≤ 7.5mg daily. - To assess time-point and incidence of SLE relapse, defined as increase in prednisolone dosage >10mg/d (for SLE treatment) or increase in SLEDAI by at least 3 compared to previous visit - To assess serological response including serum antibody titers for ANA, anti-dsDNA abs, anti-Cardiolipin abs and complement levels C3, C4 - To assess health related Quality of Life - To assess organ specific response parameters based on individual SLE manifestations

- To assess immune reconstitution and to characterize protective and pathogenic (autoreactive) immunologic memory before and after treatment
- To search for predictive factors favouring long-term remission

NUMBER OF CENTERS	In total, 8 centers will participate across Germany. Further centers may be included during the course of the study.
STUDY DESIGN	An open-label, phase II multicenter cohort trial.
TREATMENT	**GROUP A)** Transplantation of purified $CD34^+$ autologous hematopoietic stem cells mobilized with cyclophosphamide (CYC; $2g/m^2$) and granulocyte colony-stimulating factor (G-CSF; 10µg/kg/d) after immunoablation with cyclophosphamide (200mg/kg) and anti-thymocyteglobulin (ATG, Fresenius; 90mg/kg). **GROUP B)** Treatment with best currently available immunosuppressive/immuno-modulatory therapy. Treatment may include one or a combination of the following treatments: corticosteroids, azathioprine, methotrexate, cyclosporine, mycophenolate mofetil, IVIG, leflunomide or rituximab. **Treatment allocation** is made by the treating physician according to preference of individual patient. Any influence on the treatment decision by the study management is excluded for ethical reasons.
SAMPLE SIZE	Total enrolment of 30 patients in 2 years, aiming at 15 patients per group.
DURATION	Planned duration of the study is 6 years in total with an enrolment phase of 2 years. Follow-up time for each subject will be 4 years.
HYPOTHESIS	We postulate that immunoablative therapy eliminates or effectively reduces the level of autoreactive T and B lymphocytes and then regeneration of *de novo* immunity resets the autoreactive immune system into a self-tolerant, protective immune system resulting in prolonged and treatment-free remission.
INCLUSION CRITERIA	1. Diagnosis of SLE according to American College of Rheumatology (ACR) classification criteria for SLE 2. Age between 18 and 60 years, inclusive

3. Provision of informed consent by subject
4. Active disease, refractory to standard immunosuppressive therapy

defined as:

- BILAG level A and a SLEDAI-score of at least 10, despite treatment with high-dose corticosteroids and pulse intravenous CYC at doses of 500-1000mg/m^2 for at least 6 months or mycophenolate mofetil (MMF) at doses of at least 2g daily for at least 6 months for at least one of the following:
  - Lupus nephritis with renal biopsy performed within one year prior to screening showing glomerulonephritis WHO class III or IV
  - Parenchymal disease of heart or lung
  - Neuropsychiatric lupus
  - Autoimmune cytopenia

OR

- recurrence of disease activity (defined as BILAG level A and a SLEDAI of at least 10) within one year after successful induction therapy with cyclophosphamide or MMF in the presence of an adequate maintenance therapy with either cyclophosphamide (at least 500mg/m^2 monthly), mycophenolate mofetil (at least 2g daily), azathioprine (at least 1.5mg/kg/d), methotrexate (at least 15mg weekly), cyclosporine (at least 3mg/kg/d)

in patients with persistent anti-dsDNA antibodies

EXCLUSION CRITERIA

1. Severe concomitant disease or organ damage
   a) renal: renal insufficiency with glomerular filtration rate below 40ml/min
   b) cardiac: congestive heart failure, LVEF < 40% determined by echocardiogram, uncontrolled arrhythmia
   c) pulmonary: mean pulmonary arterial pressure >50mmHg, TLCO/VA < 40 % predicted
   d) gastrointestinal: liver cirrhosis (Child A, B or C), SGOT, SGPT greater than 2 x the upper limit of normal, unless due to active lupus
2. Ongoing cancer or history of malignancy within 5 years of screening
3. Women who are pregnant or breastfeeding or use non-reliable methods of contraception
4. Subjects with active systemic infection
5. Subjects with history of viral infection (CMV, EBV) within 6 months prior to screening, known HIV-infection or chronic Hepatitis B or Hepatitis C
6. History of allergic reaction to Cyclophosphamide, G-CSF or ATG
7. Use of immunosuppressive agents for indications other than SLE
8. Patients unable to give informed consent

9. Any comorbidity that in the opinion of the investigator would jeopardize the ability of the subject to tolerate therapy

SAFETY ASSESSMENTS

ICH guidelines will be applied to assess any adverse event and the seriousness of the event. Safety assessments include physical examination, vital signs, safety laboratory tests for blood and urine and electrocardiograms (ECG) at different time points.

EFFICACY ASSESSMENTS

Primary efficacy assessments

The primary efficacy endpoint is the number of patients showing a persistent complete remission at Months 24, defined as SLEDAI less than 3, in the absence of immunosuppressive therapy and prednisolone dosage ≤ 7.5mg daily.

Secondary efficacy assessments

Secondary analyses will be conducted for the following parameters at different time points:

1. Percentage and number of patients in complete remission at month 48, defined as SLEDAI less than 3 in the absence of immunosuppressive therapy and prednisolone ≤ 7.5mg daily
2. Time-point of relapse, defined as increase in prednisolone dosage >10mg/d (for SLE treatment) or increase in SLEDAI by at least 3 compared to previous visit
3. Changes in BILAG (British Isles Lupus Assessment Group) scale
4. SLICC-DI score (System Lupus International Collaborating Clinics - Damage Index)
5. Health related quality of life: SF-36 survey
6. Serologic response including autoantibody titers (ANA, anti-dsDNA abs, anti-cardiolipin, circulating immune complexes) and serum complement levels C3, C4
7. Assessment of immune reconstitution (phenotypic analysis of repopulating lymphocytes using multiparameter flow cytometry) and characterization of the protective and pathogenic (autoreactive) immunologic memory before and after treatment
8. Assessment of changes in organ specific parameters based on individual's lupus manifestations and clinical indication: pulmonary function test, cerebral magnetic resonance imagery scan, neuropsychiatric assessments, echocardiogram

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2. LIST OF ABBREVATIONS

Abs	Antibodies
ACA	Anticardiolipin Antibodies
ACR	American College of Rheumatology
AE (s)	Adverse Event(s), Adverse Experience(s)
ALT	Alanine Aminotransferase
ANA	Anti-nuclear antibodies
APSA	Antiphosphatidylserine antibodies
ASCT	Autologous Stem Cell Transplantation
AST	Aspartate Aminotransferase
ATG	Anti-thymocyteglobulin
BILAG	British Isles Lupus Assessment Group
bpm	Beats Per Minute
ß-hCG	Beta Human Chorionic Gonadotrophin
°C	Degree Celsius
CAG	Clinical Advisory Board
CBC	Complete Blood Count
CIC	Circulating Immune Complexes
CRF	Case Report Form
CRP	C-reactive protein
CYC	Cyclophosphamide
dsDNA	Double-stranded DNA
ECG	Electrocardiogram
ELISA	Enzyme-linked Immunosorbent Assay
ENA	Extractable nuclear antibodies
FACS	Fluorescence Activated Cell Sorter
GCP	Good Clinical Practices
GFR	Glomerular filtration rate
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonization
Ig	Immunoglobulin
IgA	Immunoglobulin type A
IgG	Immunoglobulin type G
IgM	Immunoglobulin type M
IRB	Institutional Review Board
LAC	Lupus anticoagulant

mAb	Monoclonal Antibodies
MCV	Mean Corpuscular Volume
mg	Milligram
ml	Milliliter
MMF	Mycophenolate Mofetil
mmHg	Millimeter of Mercury
NSAID(s)	Non Steroidal Anti-Inflammatory Drug(s)
PT	Prothrombin Time
RBC	Red Blood Cells Count
s	Second
SAE	Serious Adverse Event
SC	Subcutaneous
SLE	Systemic Lupus Erythematosus
SELENA SLEDAI	SELENA SLE Disease Activity Index
Sm	Smith Antigen
SLICC/ACR	The Systemic Lupus International Collaborating Clinics/American College Of Rheumatology Damage Index (SLICC/ACR)
WBC	White Blood Cell

3. INTRODUCTION

3.1. Background

Taken together, all patients with systemic lupus erythematosus have a mortality of approximately 1% per year (1;2). Among these, there are individual patients with higher risks with a 20% 1-year, 35% 5-year and 45% 10-year mortality (3). According to longitudinal studies, patients at high risk for lethal complications can be identified by renal disease, lung involvement, autoimmune cytopenia, antibodies to phospholipids and active disease demonstrated by a high activity index score despite therapy (4;5). The degree of disease activity, as judged by SLEDAI, is directly associated with mortality relative risk: this rises from 1.3 for those with a SLEDAI score below 5, to over 14 for a SLEDAI score of above 20 (6).

In addition, chronic morbidity and incapacity result from organ damage and drug toxicity, and the risks of malignancy and cardiovascular disease are significantly elevated in these patients (7;8). Taken together, persistent disease activity or severe and frequent flares despite immunosuppressive treatment can be used as prognostic variables to define a subgroup of patients that might benefit from immunoablative therapy.

3.2. Rationale for ASCT in severe autoimmune diseases

Peripheral blood hemopoietic stem cell transplantation (PBSCT) has been considered a potential therapy for autoimmune disease in view of several lines of evidence. First is the observation that patients with autoimmune disease who undergo allogeneic, and more recently autologous bone marrow transplant for hemopoietic or other malignancy, are reported to achieve remission of their autoimmune disease (9-12). Second is the evidence from disease susceptible strains of animals that autologous hemopoietic stem cells may cure the autoimmune disease and induce tolerance to the relevant antigen (13-15). Finally, the notion that immunosuppressive therapy acts with a dose response pattern (16).

For patients with severe disease, immunosuppression may be intensified to the point of myelosuppression or hematopoietic ablation. We hypothesize that this high-dose immunoablative chemotherapy eliminates or effectively reduces the level of autoreactive T and B lymphocytes. Subsequently, immunity may then be reconstituted *de novo* deriving from $CD34^+$ hematopoietic progenitor cells including the regeneration of central and peripheral tolerance. As a consequence, an autoreactive immune system may be reset into a self-tolerant, protective immune system resulting in prolonged disease remission.

3.3. Clinical outcome of phase I/II studies for SLE

Facing the poor prognosis in patients with severe and refractory SLE and the lack of available therapies we and others initiated clinical phase I/II studies to evaluate safety and long-term efficacy of ASCT in these patients (17-19).

The largest single-center trial has been performed in Chicago, USA were data on 50 patients with refractory SLE is available (20). Hemopoietic stem cells were mobilized with cyclophosphamide ($2g/m^2$) and G-CSF (10µg/kg/d), enriched *ex vivo* using $CD34^+$ selection and re-infused after immunoablation with cyclophosphamide (200 mg/kg), methylprednisolone (3mg/kg) and antithymocyte globulin (90mg/kg). With a median follow-up of 29 months the disease-free survival at time-point 5 years after ASCT was reported 50%. Treatment-related mortality was 4%.

The European Group for Blood and Marrow Transplantation and European League against Rheumatism (EBMT/EULAR) registry has collected retrospective data on 53 patients with SLE treated by ASCT in 23 centers (21). In summary, peripheral blood stem cells were mobilized with CYC and G-CSF in 93% of cases. *Ex vivo* CD34 stem cell selection was performed in

42% of patients. Conditioning regimes employed CYC (84%), antithymocyte globulin (76%) and lymphoid irradiation (22%). The mean follow-up after ASCT was 26 months (0-78). Remission of disease activity (SLEDAI<3) was achieved in 33/53 (66%) evaluable patients at 6 months, of which 10/31 (32%) subsequently relapsed. Relapse was associated with negative anti-dsDNA antibodies before ASCT. There were 12 deaths, of which seven (12%) were related to the procedure.

In Berlin, 7 patients with severe SLE have been treated since 1998 with a median follow-up of 64 months (range 36-108 months)(18). Mobilization and conditioning regimens are similar to the trial protocol used by Richard Burt in Chicago (20). All 7 patients have completed ASCT and achieved clinical and serological remission. One patient died due to transplantation related infection (aspergillosis) on d+90. Three patient reactivated SLE after being free of clinical symptoms (+18mo, +30mo, +80mo). The remaining three patients are in stable long-term clinical and serological remissions that are not reliant on further immunosuppression.

3.4. High-dose chemotherapy without stem cell rescue

Recently, a trial of high-dose cyclophosphamide (200mg/kg) without stem cell rescue was reported for the treatment of refractory SLE (22). In summary, treatment was generally well tolerated. 5/14 patients (36%) achieved a complete response, and an additional 6 patients (43%) had a partial response, both defined using the RIFLE. At a median follow-up of 32 months (range 17-43) all complete responses have been durable. In contrast to studies performed for high-dose chemotherapy with ASCT, enrolled patients in this study had only moderate-to-severe SLE that had been refractory to corticosteroids and only one additional immunosuppressive drug. Compared to high-dose immunoablative chemotherapy followed by ASCT, the application of this non-myeloablative regimen is the less aggressive and results in a lower toxicity as a consequence. However, in terms of the clinical outcome high-dose chemotherapy with stem cell support (ASCT) seems to be superior.

3.5. Definition of conditioning regimen

The effective eradication of autoreactive clones by the conditioning regimen seems to be a major prerequisite to achieve long-term clinical remission. Since SLE is a cyclophosphamide-responsive disease, a cyclophosphamide-based conditioning regimen was employed. However, the use of high-dose cyclophosphamide (200mg/kg) alone in the treatment of refractory SLE was reported to achieve only complete remissions in 36% of cases (22). We presume that the additional treatment with antithymocyte globulin (ATG) which aims to efficiently deplete surviving lymphocytes *in vivo* independent of the mitosis rate is a prerequisite to induce long-term clinical remissions. This notion aligns with the clinical results from the group of Richard Burt (23) as well as our findings both using cyclophosphamide (200mg/kg) plus antithymocyte globulin (90mg/kg). Although a few patients relapsed, this regimen has resulted in drug-free, clinical and serological remission of greater than 4 years (18;20;24).

There are several lines of evidence suggesting that depletion of lymphocytes in the course of stem cell selection is a key precondition to induce clinical remission. It has been postulated that the reinfusion of autoreactive clones within the graft may re-establish disease with autologous stem cell transplantation. Early recurrence or persistence of autoimmune diseases is described in the treatment of five patients with autoimmune diseases (CREST syndrome, myasthenia gravis and Hashimoto's Thyreoiditis, systemic lupus erythematosus, atopic dermatitis, and rheumatoid arthritis) who underwent autologous bone marrow (n = 1) or peripheral blood progenitor cell (n = 4) transplantation with unmanipulated graft (25). These observations should be regarded as a cautionary note concerning the efficacy of high-dose therapy followed by transplantation of unmanipulated autologous stem cells for treatment of severe autoimmune diseases. Contrary to expectations, relapse rates were not reported

reduced by *in vitro* graft manipulation in the retrospective EBMT/EULAR registry (21). However, this study compromised to a large extent a heterogonous group according to conditioning regimen and graft manipulation and has therefore limitations in interpretation of the beneficial use of graft manipulation.

3.6. Definition of mobilization regimen

Mobilization with G-CSF alone has been demonstrated to precipitate a flare of some autoimmune diseases (26). For this reason, peripheral blood stem cells were mobilized with cyclophosphamide (2.0g/m^2) followed 48-72h later by daily G-CSF (10µg/kg/d). This approach not only prevented disease exacerbation but induced partial amelioration of disease activity.

4. OBJECTIVES

4.1. Primary objective

Evaluation of safety and efficacy of immunoablative chemotherapy and autologous stem cell transplantation compared to treatment with currently available immunosuppressive/immuno-modulatory therapy in patients with refractory SLE. Primary endpoint is the number of patients showing a persistent clinical remission at month 24, defined as SLEDAI less than 3 in the absence of immunosuppressive therapy and prednisolone dose ≤7.5mg daily.

4.2. Secondary objectives

- To assess other efficacy parameters, including:
    - Serological response: assessment of autoantibody titers (ANA, anti-dsDNA abs, CIC, anti-cardiolipin abs) and complement levels of C3, C4
    - Organ specific response parameters based on individual's lupus manifestations and clinical indication
    - Health-related Quality of Life
    - SLICC-DI score (System Lupus International Collaborating Clinics - Damage Index)
- To evaluate immune reconstitution: phenotypic analysis of repopulating lymphocytes using multiparameter flow cytometry to evaluate the origin and kinetics of repopulating lymphocytes, to characterize the residual protective and pathogenic (autoreactive) immunologic memory and its impact on relapse development post-transplantation
- To evaluate durability of clinical response with respect to percentage of subjects showing complete remission (referred to as SLEDAI less than three in the absence of immunosuppressive therapy and prednisolone dose ≤7.5mg daily) at 48 months after ASCT and assessment of time point of relapse (referred to as an increase in SLEDAI by at least three or an increase in prednisolone to more than 10mg daily for the treatment of SLE).

5. STUDY DESIGN

ASSIST is an open-label, phase II multicenter cohort clinical trial of immunoablation and autologous hematopoietic stem cell transplantation versus treatment with best currently available therapy for SLE refractory to standard treatment.

This study consists of two treatment groups. Patients are either treated with immunoablation and transplantation of CD34-selected autologous hematopoietic stem cells (treatment group, Group A) or with currently available immunosuppressive/immunomodulatory treatments as the control group (control group, Group B).

For ethical reasons there will be no randomization, as we would compare the efficacy of an experimental therapy with a “failed therapy” in the control arm. Instead, treatment allocation is made by the treating physician according to the preference of the individual patient. All eligible patients will be offered a treatment with immunoablation and autologous stem cell transplantation. Only patients that consent to the treatment will undergo ASCT. Remaining patients will be asked to participate in this trial serving as the control population. Patients from both treatment groups will be evaluated post-treatment with same means.

The control arm (Group B) for this study reflects the best current available treatment options for SLE. Investigators may choose from commonly used and currently available immunosuppressive/immunomodulatory treatments based on the individual’s lupus manifestation and treatment history. Treatment may include one or a combination of the following treatments: corticosteroids, azathioprine, methotrexate, cyclosporine, mycophenolate mofetil, IVIG, leflunomide or rituximab.

Treatment may be changed as frequently as necessary and can consist of one or a combination of medication. As new drugs may become available and a part of the usual medication for the treatment of SLE, they may be approved for use in this study. Note, that any influence on the treatment decision by the study management is excluded for ethical reasons.

A crossover for patients from the control group to the treatment group is possible at any time, if subjects are still eligible according to inclusion criteria.

6. PATIENT ELIGIBILITY

6.1. Inclusion Criteria

1. Diagnosis of SLE according to American College of Rheumatology (ACR) classification criteria (27)
2. Age between 18 and 60 years
3. Provision of informed consent by subject
4. Active disease, refractory to standard immunosuppressive therapy defined as:
    - BILAG level A and a SLEDAI of at least 10, despite treatment with high-dose corticosteroids and pulse intravenous CYC (500-1000mg/m^2) for 6 months or mycophenolate mofetil (MMF) at doses of 2g/d for at least 6 months for at least one of the following:
        - Lupus nephritis with renal biopsy performed within one year prior to screening showing glomerulonephritis WHO class III or IV
        - Parenchymal disease of heart or lung
        - Neuropsychiatric lupus
        - Autoimmune cytopenia

    OR

    - recurrence of disease activity (defined as BILAG level A and a SLEDAI of at least 10) within one year after successful induction therapy with cyclophosphamide or MMF in the presence of an adequate maintenance

therapy with either cyclophosphamide (at least 500mg/m^2 monthly), mycophenolate mofetil (at least 2g/d), azathioprine (at least 1.5mg/kg/d), methotrexate (at least 15mg weekly), cyclosporine (at least 3mg/kg/d)

in patients with persistent anti-dsDNA antibodies

6.2. Exclusion Criteria

1. Severe concomitant disease or organ damage
    a) Renal: chronic renal insufficiency with creatinine-clearance <40ml/min or serum creatinine concentration >3mg/dl
    e) Cardiac: congestive heart failure, LVEF < 40% determined by echocardiogram, uncontrolled arrhythmia
    f) Pulmonary: mean PAP >50mmHg, TLCO/VA <40 % predicted
    g) Gastrointestinal: liver cirrhosis (Child B or C), SGOT, SGPT greater than 2 x the upper limit of normal, unless due to active lupus
2. Ongoing cancer or history of malignancy within 5 years of screening
3. Women who are pregnant or breastfeeding or use non-reliable methods of contraception
4. Subjects with active systemic infection
5. Subjects with history of viral infection (CMV, EBV) within 6 months prior to screening, known HIV-infection or chronic Hepatitis B or Hepatitis C
6. History of an allergic reaction to cyclophosphamide or ATG
7. Use of immunosuppressive agents for other indications other than SLE
8. Patients unable to give informed consent
9. Any comorbidity that in the opinion of the investigator would jeopardize the ability of the subject to tolerate therapy

7. STATISTICAL CONSIDERATIONS

7.1. Planning size of trial

Based on the experience on 53 SLE patients treated with ASCT and collected in the EBMT/EULAR registry (28) we assume a remission rate of at least 66% (see 3.3.) in the ASCT-treatment arm (group A). In patients treated with conventional regimens in the control group (group B) a clearly lower rate has to be anticipated, assuming a rate of ≤10%.

A two-sided Fisher's exact test will then have a power of 84% to detect a significant difference in the primary endpoint between both groups when the sample size in each group is 15 and the alpha is set 0.05.

7.2. Analysis populations

7.2.1. Efficacy population

In this as-treated population all patients are analyzed who have at least one post-baseline efficacy assessment after having received either high-dose chemotherapy and transplantation

of hematopoietic stem cells (group A) or one dose of trial medication of conventional drugs (group B).

7.2.2. Safety population

All subjects who have at least one dose of the trial medication, including mobilization regimen in the treatment group A, will be included in the safety population.

7.3. Statistical analyses

7.3.1. Primary Endpoint

Two primary endpoints will be examined for this study in as-treated populations:

1. **efficacy**: patients achieving complete clinical remission (defined as a SLEDAI-score of less than 3 in the absence of immunosuppressive therapy and prednisolone dose ≤7.5mg/d) that continuously persists until month 24 from ASCT (group A) or baseline (group B)

   Patients that do <u>not</u> reach the primary endpoint are defined:

   - death
   - lost to follow-up
   - show persistent SLE activity, either:
     a) SLEDAI-score of continuously ≥ 3 or
     b) persistent use of immunosuppressive therapy, including prednisolone dosage >7.5mg/d

     from baseline to study visit 10 (follow-up at 24 months after ASCT)
   - suffer relapse of SLE, either:
     a) SLEDAI-score of ≥ 3 after having reached complete clinical remission (see definition above) or
     b) reintroduction of immunosuppressive therapy, including prednisone dosage >7.5mg/d, after discontinuation of treatment

     at any time from baseline to study visit 10 (follow-up at 24 months after ASCT)

   A two-sided Fisher's exact test will be applied to detect a statistical significance in the primary endpoint between groups.

2. **safety**: overall survival

   Overall survival will be analyzed in as-treated populations using the Kaplan-Meier method and log-rank test.

7.3.2. Secondary Endpoints

1. For **secondary efficacy parameters** (autoantibodies, complement levels, creatinine clearance, lung diffusion capacity, SLICC-score and HAQ) a Wilcoxon's signed-ranks test will be used for pairwise comparisons of pre- and post-ASCT variables. All p-values will be two-sided and the statistical significance set at alpha 0.05.

2. The statistical significance of **immunological changes** will be longitudinally evaluated. Wilcoxon's signed-ranks test will be applied for paired comparisons and the nonparametric

Mann-Whitney rank sum test for group comparisons between treatment groups and between treatment groups and healthy controls

3. For analysis of patients showing **long-term clinical remission** defined as:

- SLEDAI-score of less than 3 in the absence of immunosuppressive therapy and prednisolone dose ≤7.5mg/d that continuously persist until month 48 after ASCT (termination visit 14)

a two-sided Fisher's exact test will be applied to detect a statistical significance in the endpoint between groups (see primary efficacy endpoint).

4. Patients with **relapse of SLE** (definion above) at any time from baseline to termination study visit 14 (48 months after ASCT) will be analyzed in as-treated populations using the Kaplan-Meier method and log-rank test.

7.3.3. Preconditions for statistical analyses

To detect a significant difference in the primary endpoint between both groups, the study is powered for a group size of each 15 (see 7.1.). Since the study is conducted in a non-randomized fashion, we may face an unequal distribution of group sizes.

Provided that a group size of 15 is achieved in one treatment arm, the two-sided Fisher's exact test will still have a power of ≥ 81% to detect a significant difference in the primary endpoint between both groups (alpha set at 0.05) when the sample size of the other treatment arm is at least 13. If the sample size is lower, the power is not sufficient to see significant differences in the primary endpoint between groups.

7.3.4. Interim analyses

Interim analyses will be performed two and four years after initiation of the trial for safety reasons and efficacy comparisons. The data will be discussed within the Data Safety Monitoring Board. Unexpected severe adverse events may result in a premature termination of the study. Criteria for end of the study are provided in protocol section 10.2.

7.4. Statistical support

Power calculation and statistical analyses are supported by Dr. Joachim Listing at the Department of Epidemiology of the German Rheumatism Research Center (DRFZ) Berlin.

Contact:
Dr. Joachim Listing
Deutsches Rheuma-Forschungszentrum (DRFZ)
Epidemiologie
Charitéplatz 1
10117 Berlin
E-mail: listing@drfz.de
Tel.: +49 30 28460 623

8. SCHEDULE OF ASSESSMENTS AND PROCEDURES

8.1. Study Task Flow Chart

	Visit 1 Screening	**Visit 2 Mobilization**	**Visit 3 Baseline (ASCT)**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**
Procedures	-90 to -60 days	-60 to -14 days	day 0	Month 1 ± 7 days	Month 3 ± 7 days	Month 6 ± 7 days	Month 9 ± 7 days	Month 12 ± 7 days
Informed Consent	✓							
Eligibility Criteria	✓							
Medical History, ACR criteria	✓							
Previous and Concomitant Medications	✓	✓	✓	✓	✓	✓	✓	✓
Physical Examination	✓	✓	✓	✓	✓	✓	✓	✓
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓
AE	✓	✓	✓	✓	✓	✓	✓	✓
Safety laboratory assessment[1]	✓	✓	✓	✓	✓	✓	✓	✓
Serum pregnancy test[2]	✓	✓	✓					
Hepatitis serology[3]	✓							
ECG	✓		✓					
SLE disease activity indices (BILAG, SLEDAI)	✓	✓	✓	✓	✓	✓	✓	✓
SLICC/ACR-DI	✓		✓					✓
SF-36 Survey	✓		✓			✓		✓
Diffusion capacity	✓		✓					✓
SLE urine analysis[4]	✓		✓			✓		✓
Echocardiogram[5]	✓		✓					
Cognitive testing[6]	✓		✓					
cMRI[7]	✓							
SLE Serology Assessments[8]	✓	✓	✓	✓	✓	✓		✓
Immunology Assessments[9]	✓	✓	✓		✓	✓		✓

	Visit 9	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14 Termi-nation**	**Unscheduled Visit**
Procedures	Month 18 ± 7 days	Month 24 ± 7 days	Month 30 ± 7 days	Month 36 ± 7 days	Month 42 ± 7 days	Month 48 ± 7 days	(any time during study)
Informed Consent							
Eligibility Criteria							
Medical History, ACR criteria							
Previous and Concomitant Medications	✓	✓	✓	✓	✓	✓	✓
Physical Examination	✓	✓	✓	✓	✓	✓	✓
Vital signs	✓	✓	✓	✓	✓	✓	✓
AE	✓	✓	✓	✓	✓	✓	✓
Safety laboratory assessment[1]	✓	✓	✓	✓	✓	✓	✓
Serum pregnancy test[2]							
Hepatitis serology[3]							
ECG		✓				✓	✓
SLE disease activity indices (BILAG, SLEDAI)	✓	✓	✓	✓	✓	✓	✓
SLICC/ACR-DI		✓		✓		✓	
SF-36 Survey		✓		✓		✓	
Diffusion capacity		✓		✓		✓	
SLE urine analysis[4]		✓		✓		✓	
Echocardiogram[5]		✓				✓	
Cognitive testing[6]		✓				✓	
cMRI[7]		✓				✓	
SLE Serology Assessments[8]		✓	✓	✓	✓	✓	✓
Immunology Assessments[9]		✓		✓		✓	

1. Safety laboratory assessments include hematology, serum chemistry, and urine analysis (see Section 8.3.3.).
2. Serum pregnancy test must be performed for women of childbearing potential at screening, mobilization and baseline visit before ASCT.
3. Hepatitis serology includes HbsAg, anti-Hbs, anti-Hbc and anti-HCV.
4. SLE urine analysis includes microscopy for active sediment and assessment of protein in 24h urine. As contamination by menstrual blood will interfere with the results, whether or not the patient is menstruating will be recorded on the CRF.
5. Echocardiogram must be performed for all patients at screening and baseline visit. Only for patients with cardiovascular or pulmonary lupus manifestation or pathologic findings during screening or baseline visits, echocardiogram has to be performed during follow-up and termination visit.
6. Cognitive function tests must only be performed for patients with cerebral involvement. Cognitive testing during follow-up and termination visit will only be necessary for patients with impaired cognitive function assessed at the screening visit. (see Section 8.4.6.)

7. Cerebral magnetic resonance imaging (cMRI) must only performed in patients with cerebral involvement. cMRI at screening is necessary unless recent imaging within 6 months prior to enrolment. cMRI must only performed during follow-up and termination visit in case of pathologic findings at the screening visit.
8. SLE serology assessments include ANA, ENA, anti-dsDNA, anti-Cardiolipin abs, circulating immune complexes; and serum complement C3 and C4. (see Section 8.4.5.)
9. Immunology assessments include immune phenotypic analyses on immune reconstitution (see Section 8.4.7.) and analyses to characterize the protective and pathogenic (autoreactive) immunologic memory (see Section 8.4.8.) before and after treatment

8.2. Screening examination and Eligibility Screening Form

A signed, informed consent must be obtained from each subject before any screening assessments are performed. At the screening visit, the subject's demographic information, medical history, and prior and current medications will be recorded.

Contraception methods will be discussed. Women of childbearing potential using a non-reliable method of contraception are not eligible. It is recommended that study treatment should not be initiated until a negative pregnancy test has been obtained.

8.3. Safety Assessments

The following assessments are planned to investigate the safety and tolerability of autologous stem cell transplantation:

Type of Assessment	Analysis
Safety and Tolerability	
AEs	Incidence and frequency
Safety Laboratory tests	Descriptive statistics of laboratory measurements Change from baseline
ECG	Descriptive statistics of measurement Change from baseline Incidence and frequency of potentially clinically significant values
Vital signs	Descriptive statistics of measurement Change from baseline Incidence and frequency of potentially clinically significant values
Physical examination	Descriptive statistics of abnormalities Change from baseline
Tolerability	Incidence and frequency of AEs

8.3.1. Physical Examination

A full physical examination, including all body systems and vital signs (oral temperature, pulse and blood pressure) will be performed at all scheduled and unscheduled visits.

8.3.2. Adverse Events

An AE is defined as any untoward medical occurrence (sign, symptom or laboratory finding), in a patient or clinical trial subject and which does not necessarily have a causal relationship with this treatment.

Adverse Events (AEs) will be monitored throughout the course of the study, collected on the basis of spontaneous reporting by subject or investigator. Adverse events persisting at the

time of study completion will be followed by the investigator through contact with the subject until a clinically acceptable resolution or stabilization has occurred.

The intensity or severity of an AE is characterized as:

- Mild: AE which is easily tolerated
- Moderate: AE sufficiently discomforting to interfere with daily activity
- Severe: AE which prevents normal daily activities

The relationship to the study treamtent of an AE is characterized as:

TERM	DEFINITION	CLARIFICATION
Unrelated	This category applies to those AEs which, after careful consideration, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.)	
Unlikely	In general, this category can be considered applicable to those AEs, which, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study drug.	An AE may be considered unlikely related if or when at least 2 of the following apply: ▪ It does not follow a reasonable temporal sequence from the administration of the study drug.. ▪ It could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. ▪ It does not follow a known pattern of response to the study drug.. ▪ It does not reappear or worsen when the study drug. is re-administered.
Possibly	This category applies to those AEs for which, after careful medical consideration at the time they are evaluated, a connection with the study drug.administration appears unlikely but cannot be ruled out with certainty.	An AE may be considered possibly related if or when at least 2 of the following apply: ▪ It follows a reasonable temporal sequence from administration of the study drug.. ▪ It could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. ▪ It follows a known pattern of response to the study drug..
Probably	This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the study drug..	An AE may be considered probably related if or when at least 3 of the following apply: ▪ It follows a reasonable temporal sequence from administration of the study drug.. ▪ It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors or other modes of therapy administered to the subject. ▪ It disappears or decreases on cessation

TERM	DEFINITION	CLARIFICATION
		or reduction in dose. There are important exceptions when an AE does not disappear upon discontinuation of the study drug, yet study drug-relatedness clearly exists. ▪ it follows a known pattern of response to the study drug.

A serious adverse event (SAE) is defined as any AE occurring at any dose that results in any of the following outcomes:

- Fatal
- A life-threatening illness
- Requires or prolongs hospitalization
- Results in persistent or significant disability or incapacity
- A congenital abnormality or birth defect
- A medically important event or one which required medical intervention to avoid one of the above outcomes

Any SAE, whether deemed treatment-related or not, must be reported to the Local Medical Director by telephone as soon as possible after the investigator or coordinator has become aware of its occurrence.

The investigator must be prepared to supply the Medical Director with the following information:

A. Investigator Name and Site Number
B. Subject number
C. Subject initials
D. Subject demographics
E. Clinical Event
    1. Description
    2. Date of onset
    3. Severity
    4. Treatment (including hospitalization)
    5. Relationship to study drug (causality)
    6. Action taken regarding study drug
F. If the AE was fatal or life threatening
    1. Cause of death (whether or not the death was related to study drug)
    2. Autopsy findings (if available)

Additional information about any SAE should be forwarded by the site within 24 hours of the information becoming available.

8.3.3. Safety Laboratory Tests

Safety Laboratory test will be performed at the site's laboratory. The following laboratory tests will be performed at every study visit:

Safety laboratory tests list:

- Hematology and Coagulation:
  - CBC
  - Prothrombin Time (INR and %)
  - Partial Thromboplastin Time (PTT)
  - Erythrocyte sedimentation rate (ESR)
- Clinical Chemistry:
  - Alanine aminotransferase (ALT/SGPT)
  - Aspartate aminotransferase (AST/SGOT)
  - gamma- glutamyl transpeptidase (GGT)
  - Total Bilirubin
  - Total Immunoglobuin G
  - Lactate Dehydrogenase (LDH)
  - Creatine Kinase (CK)
  - Creatinine
  - Urea
  - Glucose
  - Electrolytes: potassium and calcium
  - CRP
- Urinalysis
  - Glucose
  - Ketones
  - Blood, Leukocytes, Erythrocytes.
  - Specific gravity
  - pH
  - Nitrite
  - Bilirubin
  - Urobilinogen

Hepatitis serology (Screening visit only):

- Hepatitis B surface antigen (HBsAg), anti-HBs, anti-HBc
- Anti-HCV

8.3.4. Electrocardiogram (ECG)

ECG will be performed at screening, baseline, and study visit 10 (Month 24), visit 14 (Termination Visit) and during any unscheduled visit.

The ECG will be a standard 12-lead tracing performed at the investigational site, assessed by a qualified physician and retained as a source document. The ECG will be evaluated by the investigator at time of performance and the printout should be kept in the source documentation file. When potentially clinically significant findings are detected by the Site Investigator, a cardiologist should be consulted for a definitive interpretation. All communications and diagnoses should be filed in the source documentation file.

8.4. Efficacy Assessments

8.4.1. SLEDAI

The SLE Disease activity index (SLEDAI) assesses disease activity within the last 10 days (29). Sixteen clinical manifestations and eight laboratory items are scored for 9 organ systems, and summed to a maximum of 150 points. See Appendix 1.

8.4.2. BILAG

The BILAG Index is a comprehensive index for measuring clinical disease activity in SLE (30). It was developed according to the principle of the 'physician's intention to treat'. The index allocates separate alphabetic scores to each of eight organ-based systems: General, Mucocutaneous, Neurological, Musculoskeletal, Cardiovascular and Respiratory, Vasculitis, Renal and Haematological system.

A BILAG assessment consists of 86 questions; some based on the patient's history, some on examination findings and others on laboratory results. Each system can be score as follows: A (disease that requires urgent, disease modifying therapy), B (intermediate disease activity), C (mild, stable disease activity), D (inactive disease) and E (no activity ever). See Appendix 2 for the assessment form and Appendix 3 for symptoms meeting A and B criteria.

8.4.3. SLICC/ACR-DI

The SLICC/ACR-DI (Systemic Lupus International Collaborating Clinics/American Collage of Rheumatology Damage Index) assesses damage without discriminating between damage related to disease and damage related to treatment(31). Twelve organs are assessed, with a variable number of components in each, and summed to a maximum of 46 points. At diagnosis the SLICC/ACR-DI score is considered to be zero. Higher scores are a predictor of increased mortality. See Appendix 4.

8.4.4. Quality of life, SF-36®-survey

A standard SF-36 health survey will be completed by subjects during selected clinic visits. A copy of the survey form can be found in Appendix 5.

A 36-item medical outcome short-form (SF-36) was constructed to survey health status in clinical practice and research, health policy evaluations, and general population surveys. The SF-36 includes one multi-item scale that assesses eight health concepts: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions. The survey was constructed for self-administration by persons 14 years of age and older, and for administration by a trained interviewer in person or by telephone.

8.4.5. Assessment of serological response

For evaluation of serological response after ASCT, autoantibody titres and complement levels will be assessed. For analysis of autoantibody titres, centers will be asked to send a serum aliquot (1ml) to the reference laboratory in the Charité – University medicine.

Contact data:
Rheumatologisch-Immunologisches Labor
Charité Universitätsmedizin Berlin
Tucholskystraße 2
10117 Berlin
Tel.: 030 / 450 - 513 173

- Autoantibody titres: ANA, ENA (anti-Ro, anti-La, U1RNP, anti-Sm, anti-Centromer), anti-dsDNA (ELISA and Crithidia luciliae), anti-Nucleosome, anti-Cardiolipin, anti-beta2-glycoprotein, APSA, circulating immuncomplexes

8.4.6. Assessment of organ specific response parameters

As immune ablation and ASCT is employed in patients with multiple organ involvement, a special point of interest is the evaluation of changes in organ-specific response parameters.

- Renal: serum creatinine, urine sediment microscopic analysis, and 24h urine protein (mg/l and mg/d).
- Respiratory: diffusion capacity (DLCO-SB, DLCO/VA), echocardiography including assessment of pulmonary artery pressure (PAP).
- Cardiac: echocardiography and ECG.
- Cerebral: cognitive function tests and cerebral magnetic resonance imaging (cMRI) for patients with neuropsychiatric manifestations of SLE.

8.4.7. Assessment of immune reconstitution

Routine complete blood counts and differential white blood cell counts will be obtained at study visits and analyzed at the sites research laboratories. Peripheral blood mononuclear cells (PBMCs) are collected at mobilization visit, at baseline prior to high-dose chemotherapy and at Months 3, 6, 9, 12, 24, 36, 48.

The expression of a large panel of surface markers will be examined on T and B cell subsets and NK cells on freshly isolated PBMC by direct multiparameter flow cytometry using a FACSCalibur analyser (Becton Dickinson).

The following conjugated monoclonal antibodies are recommended for usage: CD3 FITC, CD4 APC and PerCP, CD8 PE and PerCP, CD16+56 PE, CD19 APC and PerCP, CD20 PE, CD25 APC, CD27 Cy5, CD31 PE, CD45 PerCP, CD45RA FITC, CD45RO APC, CD57 FITC, FoxP3 PE, IgD FITC.

The monoclonal antibodies will be used with following combinations:

- CD45/CD3/CD4/CD8
- CD45/CD3/CD16+56/CD19
- CD19/IgD/CD20/CD27
- CD4/CD27/CD45RA/CD45RO
- CD4/CD31/CD45RA/CD45RO
- CD4/CD25/FoxP3/CD45RA

- CD8/CD27/CD45RA/CD45RO
- CD8/CD57/CD27/CD45RA
- CD19 /CD1c/CD11c/CD14
- BDCA-2/CD123/CD11c

Results are presented as the frequency and absolute count for each lymphocyte subset.

Table 1: Characterization of lymphocyte subsets by expression of surface antigens

CD45	Pan lymphocytes
CD3	Pan T lymphocytes
CD16+56 $CD3^-$	NK cells
CD16+56 $CD3^+$	NKT cells
CD4	T helper cells (Th cells)
CD4 $CD45RA^+$ $CD31^+$	Thymic naïve Th cells
CD4 $CD45RA^-$ $CD27^+$	Central memory Th cells
CD4 $CD45RA^-$ CD27-	Effector memory Th cells
CD4 $CD25^{++}$ $Foxp3^+$	Regulatory T cells (Tregs)
CD8	Cytotoxic lymphocytes (CTL)
CD8 $CD45RO^+$ $CD27^+$	Central memory CTL
CD8 $CD45RA^+$ $CD27^-$	Effector memory CTL
CD8 $CD57^+$	Terminally differentiated CTL
CD19	B cells
CD19 $CD27^+$ IgD^-	Memory B cells (class switched)
CD19 $CD27^+$ IgD^+	Memory B cells (class unswitched)
CD19 $CD27^-$ IgD^+	Naïve B cells
CD19 $CD27^{++}$ $CD20^-$	Plasmablasts
$CD19^-$ $CD1c^+$ $CD11c^+$	Myeloid dendritic cells
BDCA-2^+ $CD123^{++}$ $CD11c^-$	Plasmacytoid dendritic cells

8.4.8. Characterization of protective and pathogenic (autoreactive) immunologic memory before and after treatment

(A) Short-term stimulation of peripheral blood (50ml) will be performed *in vitro* in the presence of infection/vaccine-specific antigens (CMV, EBV, Tetanus toxoid, Measels, Escherichia coli, Candida albicans) and autoantigens (Histone peptides, Nucleosomes, Netting neutrophils, circulating microparticles). As readout serve: (i) cytokine secretion (Interferon gamma, Tumour necrosis factor alpha, Interleukin-2), (ii) activation markers (CD40L, CD69), (iii) chemokine receptors, Ki-67 expression and phospo-STAT5/Foxo-1 in CD4 and CD8 T cells with flow cytometry. In case of rare frequencies, the Antigen-Reactive T Cell Enrichment (ARTE) technique for direct, high-resolution analysis (CD40L magnetic separation) will be performed. In a similar manner, the frequency and phenotype of autoantigen-specific B cells (anti-Ro-

specific B cells) will be analysed. Time-points of analyses: before and at months 3, 6, 12, 24, 36, 48 months after treatment.

(B) To characterize the fate of kidney-infiltrating T cells in lupus-nephritis, T cells isolated from urine samples will be investigated using flow cytometry (before and at months 3, 6, 12, 24, 36, 48 months after treatment) to assess their number, phenotype (CD3, CD4, CD8, CD45RA, CCR7), activation status (CD69, HLA-DR, CD38) and tissue homing potential (surface chemokine receptor CXCR3).

(C) Autoantibodies are secreted by both short-lived and long-lived plasma cells, the latter being harboured at dedicated niches in the bone marrow. To investigate their fate, bone marrow aspirates will be performed before and at 1 month after treatment in consenting patients. Their number, phenotype (CD19, CD27, CD38, CD138, HLA-DR) will be investigated with flow cytometry. If numbers allow, their specificity will be investigated with ELISpot. Pooled microbial antigens (vaccine-specific: Tetanus-Toxoid, Diphteria-Toxoid, Haemophilus influenzae Typ b-Polysaccharide, Pertussis-Toxoid (PT), inactivated Polio, Measels, Mumps, Rubella antigen) will be used to characterize the protective immunologic memory plasma cells and a mixture of autoantigens (HEp2 cell lysate) to analyse the autoreactive memory plasma cells. In addition, bone marrow aspirates will be analysed for the number, phenotype and specificity of T and B cells (see section 8.4.8. A).

(D) We also want to characterize the composition of the protective and pathogenic autoreactive immunologic memory that is mobilized from the bone marrow (after cyclophosphamide and G-CSF treatment). Here, the CD34-negative fraction of the leukapheresis product (after CliniMACS®) will be investigated with flow cytometry (similar to 8.4.8. A). In addition, FACS-sorted $CD4^+$ and $CD8^+$ T and $CD20^+$ B cells ($1x10^6$ cells) will be investigated for their specificity using TCR/BCR Next Generation deep sequencing (NGS) from isolated mRNA. To identify overlapping clones from peripheral blood before and after HSCT, FACS-sorted $CD4^+$ and $CD8^+$ T and $CD20^+$ B cells ($1x10^6$ cells), obtained from peripheral blood directly before mobilization and at months 12 and 24 post-transplantation, will be investigated with NGS.

(E) To investigate, how much immunologic memory resides after HSCT, vaccination studies will be performed, where defining the antigen-specific T/B cell responses will help to estimate the precursor frequency of residual vaccine-specific memory cells. To this end, we want to analyze the humoral and cellular responses to vaccination with the recall antigens Tetanus Toxoid/Diphtheria (e.g. with Td pur®, GlaxoSmithKline) at 1 year after transplantation (in patients with vaccine titters below protection limit as recommended by Robert-Koch-Institute and regarded as uncritical at 1 year after HSCT (*Robert Koch Epidemiologisches Bulletin Nov 2005)*) investigating whether patients after HSCT mount a primary or secondary immune response; specific antibody production with avidity/isotype testing and antigen-stimulated T/B cell proliferation and activation (CD38/HLA-DR expression) will serve as read-outs. This approach also allows identifying resting memory T cells and memory plasma cells that exclusively reside in the bone marrow, which under steady state conditions are not contained within the blood but can be mobilized from the bone marrow during immunization. Vaccination against Hepatitis A (as neoantigen) will serve as control (Havrix 1440®, GlaxoSmithKline). Hepatitis A vaccinations will only be performed in seronegative patients in whom vaccination is recommended according to the vaccination commission of the Robert-Koch-Institute (*Robert Koch Epidemiologisches Bulletin August 2016)*.

9. STUDY TREATMENT

9.1. Treatment Group (Group A): Immunoablation and ASCT

Patients in the treatment group (Group A) will receive the experimental therapy consisting of immunoablative chemotherapy and autologous stem cell transplantation. Initially, patients undergo mobilization, a process of shifting hematopoietic stem cells from the bone marrow into the peripheral blood, following collection of these stem cells by leukapheresis. Subsequently, high-dose chemotherapy (conditioning) will be applied before transplantation of CD34-selected hematopoietic autologous stem cells. This procedure will only be performed once during the study period.

9.1.1. Mobilization

Peripheral blood hematopoietic stem cells are mobilized with cyclophosphamide ($2g/m^2$) intravenously followed 48-72h later by daily G-CSF administration (subcutaneously, 10µg/kg/d). G-CSF will be given for about 4 to 7 days.

9.1.2. Stem cell harvest and graft purification

Leukapheresis will be performed with Cobe® Spectra Apheresis System when peripheral blood CD34-count in patients has reached > 10/µl. Leukapheresis will be repeated until a stem cell count of > 4.0 x 10^6 per kg body weight is achieved in apheresis product. Enrichment of $CD34^+$ autologous peripheral blood stem cells will be performed using the CliniMACS® cell selection system (Miltenyi Biotec GmbH, Bergisch-Gladbach, Germany) yielding a stem cell product of 2.0 - 10.0 x 10^6 $CD34^+$ per kg body weight. The CD34-selected autologous stem cell graft will be cryopreserved in DMSO.

9.1.3. Conditioning regimen and stem cell transplantation

Conditioning regimen consists of treatment with 50mg/kg/d cyclophosphamide intravenously for 4 days (total dose 200mg/kg), followed by intravenous application of antithymocyte globulin (ATG, Fresenius) at 30mg/kg daily over 10h on 3 consecutive days (total dose 90mg/kg). In addition, methylprednisolone (1g) will be administered intravenously on each day of ATG-treatment.

Prior to ATG-treatment, a test dosage will be administered intracutaneously. To avoid differences in ATG efficacy, ATG will be descended from the identical product-charge.

Following the conditioning regimen, 2.0 - 10.0 x 10^6 $CD34^+$ autologous hematopoietic stem cells per kg body weight will be transfused. The absolute number of $CD3^+$ T cells re-infused within the graft must not exceed 1.0 x 10^4 per kg body weight.

9.1.4. Supportive care

Patients receiving high-dose immunoablative chemotherapy are susceptible for infections, especially during the first months after treatment. To minimize the risk of severe infections, patients receive prophylactic medication in addition to standardized hygienic procedures.

All patients receive ciprofloxacine (500mg twice daily) beginning at day 0 after ASCT until leukocyte engraftment (3 days >1.0/nl). In cases with a history of tuberculosis an additional treatment with isoniacid and pyridoxine (Isocid comp. 300/60) is recommended. Anti-viral prophylaxis is performed using acyclovir starting day 0 after ASCT in a dose of 3x5mg/kg intravenously or 3x400mg orally. Prophylaxis is continued until leukocyte engraftment (3 days >1.0/nl). In single cases anti-viral prophylaxis can be supplemented with CMV-active drugs (e.g. gancylovir). From day 0 after ASCT an oral prophylaxis with Amphotericin B or Nystatin is

recommended. In case of Candida albicans infection in the patient's history a prophylaxis with fluconazole (200mg daily) is applied until leukocyte engraftment (3 days >1.0/nl). In patients who are continued to receive high doses of immunosuppressive drugs the prophylaxis can be continued.

Prophylaxis against infection with Pneumocystis carinii is achieved with either systemic application of cotrimoxazole or as inhalation with pentamidine. Systemic prophylaxis should be continued until +d180 or discontinuation of immunosuppressive therapy.

9.1.5. Maintenance therapy after ASCT

As patients with different SLE disease activity and different backgrounds regarding lupus manifestation and treatment history are included into the trial, there will be no rigid schema provided for steroid tapering. Overall, tapering may be continued in a prescribed manner to achieve a dose equivalent of 7.5 mg/d of prednisolone or less by one year post-transplant.

Immunosuppressive/immunomodulatory drugs other than steroids are intended to be discontinued after ASCT. For patients with clinical remission (defined as SLEDAI less than 3) during follow-up no immunosuppressants must be applied. After the end of study, further treatment strategies will be decided by the treating rheumatologist.

9.1.5. Treatment of relapse after ASCT

As flares of disease may occur following ASCT, immunosuppressive treatment might need to be restarted in individual cases. Given the limited available data on response rates to immunosuppressive agents in disease flares following ASCT the relapse treatment will be decided by the treating physician depending on the individual's disease activity and organ involvement.

9.2. Control Group (Group B): currently available therapy for SLE

Patients in the control group (Group B) will receive immunosuppressive/immunomodulatory therapy as prescribed by the study rheumatologist, based on the treatment history and the organ system affected.

Study treatments may consist of corticosteroids, cyclophosphamide, azathioprine, methotrexate, cyclosporine, mycophenolate mofetil, intravenous immunoglobulin (IVIG), leflunomide and rituximab.

Treatment can be changed as frequently as necessary and can consist of one or a combination of medication. The following dosages are recommended:

Cyclophosphamide: 500-1000mg/m^2 monthly intravenous

Azathioprine: 1-2 mg/kg/day orally

Cyclosporine: 5 mg/kg/day orally

Mycophenolate: 2 g/day orally

Methotrexate: 15 mg weekly orally or subcutaneously or intravenously

Leflunomide: 20 mg/day orally

IVIG: 0.5 g/kg intravenously administered every 3 to 4 weeks

Rituximab: either as 2 infusions of 1g (2 weeks apart) or as 4 infusions (1 week apart) of 500mg

10. WITHDRAWAL OF SUBJECTS AND CRITERIA FOR END OF STUDY

10.1. Withdrawal of subject from study

Subjects have the right to withdraw from the study at any time for any reason without prejudice. The investigator also has the right to withdraw subjects from the study if it is in the best interest of the subject. Subjects may be withdrawn if they have entered the study in violation of the protocol, if they require the use of an unacceptable concomitant medication, if they develop a condition during the study that violates the inclusion/exclusion criteria, if they are non-complaint with protocol procedures, or if they experience an adverse event that warrants withdrawal from the study.

In addition, subjects will be withdrawn if:

- they require treatment with immunosuppressive therapy for indications other than SLE
- they experience allergic reactions to G-CSF, cyclophosphamide or ATG that will lead to interference with the protocol treatment in treatment group A
- stem cell harvest fails to achieve a stem cell count of $>2x10^6$ $CD34^+$ hemopoietic stem cells during mobilisation in treatment group A

Withdrawal of subjects or treatment decisions (e.g. immunosuppressive therapy) that will lead to withdrawal of subjects must be discussed with the CAB.

An excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of subjects should be avoided. Should a subject decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible. These subjects should be treated off-study as deemed appropriate by the investigator.

10.2. Criteria for end of study

During the study unexpected events or conditions may occur that require a premature end of the trial for either ethical reasons or inability to achieve primary endpoints.

Regarding safety, the study will be terminated if the mortality rate is higher than expected. With respect to the retrospective data collected from the EBMT for the use of ASCT in SLE, treatment related mortality (TRM) is reported 12% (21). According to our protocol fifteen patients are scheduled to receive ASCT in the treatment group A. The study will be prematurely terminated if the number of deaths related to ASCT is greater than two (2/15 would have a TRM of 13%).

In addition, unexpected severe adverse events may under the personnel review of the Data Safety Monitoring Board lead to the premature termination of the study. Interim safety analyses will be performed 2 and 4 years after initiation of the study (see section 7.3.4.).

Regarding efficacy, we are assuming a remission rate of 66% after ASCT according to data from the retrospective registry survey by the European Blood and Marrow Transplant and European League Against Rheumatism (EBMT/EULAR) (32). If we fail to induce clinical remission after ASCT (SLEDAI < 3) in > 50% of patients the study will be terminated prematurely.

While conducting the trial, new data may become available that for ethical reasons oblige the Clinical Advisory Board to prematurely terminate the study.

Premature termination of the study may also be inevitable if the primary endpoint is most likely not to be achieved. This may include:

- patients lost to follow-up
- difficulties in patients recruitment

11. DOCUMENTATION

11.1. Study File and Site Documents

Prior to the initiation of the study, the following documents must be received by the sponsor from the study site:

1. Signed protocol amendment and notifications (if applicable) pages by the principal investigator.
2. The Principal Investigator curriculum vitae and where required current medical license.
3. Signed Clinical Study Agreement
4. EC/IRB membership list or an official statement that the EC/IRB is in compliance with 21 CFR part
5. EC/IRB written opinion for the protocol, amendments, informed consent, subject information sheet (if applicable), advertisements (if applicable).

11.2. Site Documents/Equipment Supplied by the Sponsor

Prior to the initiation of the study, the sponsor will supply the Site Investigator with the following items, in addition to the protocol:

- Investigator Site File
- Template Informed Consent
- Documentation files
- Insurance Certificate

11.3. Maintenance and Retention of Records

It is the responsibility of the Site Investigator to maintain a comprehensive and centralized filing system of all relevant documentation. Site Investigators will be instructed to retain all study records required by the sponsor and regulatory authorities in a secure and safe facility.

11.4. Data handling

Data will be entered at the site by the site investigator in the patient's file which is kept as a source document. In addition data will be entered in special documentation files which will be provided by the sponsor. Laboratory test results, ECG strips and all other source documents should be maintained and kept at the study site in the subject source binder.

Source data should include:

- Demographic information
- Evidence supporting the diagnosis/condition for which the subject is being studied
- General information supporting the subject's participation in the study
- Medical history and physical findings
- Hospitalization or Emergency Room records (if applicable)
- Each study visit by date, including any relevant findings/notes by the Site Investigator(s); occurrence (or lack) of AEs; and changes in medication usage, including the date the study drug was commenced and completed
- Any additional visits during the study
- Any relevant telephone conversations with the subject regarding the study or possible AEs
- Original, signed informed consent forms for study participation

12. STUDY PERSONNEL

A complete list of contact details of all study personnel and sites will be supplied in the Regulatory Binder.

12.1. Study Principal Investigator

The Study Principal Investigator is the head of the Clinical Steering Committee (CSC) and, as such, acts as the primary consultant on issues of safety, protocol adherence, study conduct and special cases regarding subject eligibility. He/she also motivates sites regarding recruitment.

12.2. Site Principal Investigator

The Site Principal Investigator fulfils the same functions as the Study Principal Investigator, for his/her particular center.

12.3. Investigative Site Personnel

At each study site, the staff will consist of a minimum of investigator and a clinical coordinator (who can be a nurse or a physician). The investigator can be an Internist/Rheumatologist/Hematologist. He/she will be responsible to oversee the accrual of appropriate subjects, the conduct of the study in accordance with the trial's protocol, communication with the EC/IRB and the collection of required data.

12.4. The Sponsor

12.4.1. Local Clinical Management

The local clinical management is responsible for the local day-to-day activities of the study and to ensure that the Sponsor supplies adequate resources to provide high-quality study management, monitoring and data management.

12.4.2. Global Clinical Safety Director

The Global Clinical Safety Director will be responsible for all safety aspects of the study. He will ensure that the safety of the subjects is appropriately assessed and maintained according to the study protocol, objectives and goals. He/she will assist in the approval and preparation of safety data as required.

12.4.3. Sponsor´s subcontractor facilities

For monitoring and data management, the sponsor cooperates with the Coordination Center for Clinical Trials – KKS of the Charité University Medicine. Contact person:
Roswitha Bussar-Maatz
Augustenburger Platz 1
13353 Berlin
Tel.: +49 30 450 553 016
Fax: +49 30 450 553 937
E-Mail: kks@charite.de

13. STUDY COMMITTEES

13.1. Clinical Advisory Board

The CAB will be responsible for the clinical development plan of the study including all clinical issues regarding study design and conduct. Refer to Operation Manual for list of CAB members.

The committee's responsibilities will include involvement in:

- design of the clinical development plan
- design of study protocols
- interpretation of results analysis upon study completion
- review of each individual case prior to treatment

13.2. Clinical Steering Committee

The CSC members will consist of all Site Principal Investigators and will be responsible for day-to-day study conduct issues in their sites:

- Assist in selection of qualified and experienced sites
- Assist in design of protocol, CRF and other documents
- Review subject eligibility criteria if needed
- Follow-up enrollment rate
- Assist sites for protocol adherence
- Assist in regulatory submissions
- Assist in review of publication

13.3. Data Safety Monitoring Board

An independent DSMB will be responsible for periodically reviewing safety data collected during the study. The Global Director of Clinical Safety will serve as a liaison for bi-directional communication to and from the Sponsor. The list of DSMB members appears in the Operations Manual.

14. USE OF INFORMATION AND PUBLICATIONS

14.1. Confidential Information

All information supplied by the sponsor in association with this study and not previously published, is considered confidential information. This information includes, but is not limited to, the Investigator's Brochure, clinical protocol and other scientific data. Any data collected during the study are also considered confidential.

The information developed during the conduct of this clinical study is also considered confidential, and will be used by the sponsor in connection with the evaluation of safety and efficacy of ASCT. The information obtained during this study may be made available to other Investigators who are conducting similar studies.

14.2. Publication

After termination of the study, the sponsor will publish the data in cooperation with all participating centers. Should the sites principal investigators wish to publish the results of this study, the PSI agrees to provide the sponsor with a manuscript for review prior to submission for publication.

15. REGULATORY AND ETHICAL ISSUES

15.1. Compliance with Regulations Applicable to Clinical Trials

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and will be consistent with International Conference on Harmonization Good Clinical Practice (ICH GCP) and applicable regulatory requirements.

This study will be conducted in compliance with the protocol. The protocol and any Amendments and the subject informed consent will receive Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval opinion prior to initiation of the study.

15.2. Informed Consent

The principles of informed consent, according to Declaration of Helsinki 1964 and all its updates, the International Conference on Harmonization (ICH) step 5 guidelines on Good Clinical Practice (GCP), 21 CFR part 50 of the FDA Regulations and/or EU Directives, will be followed. A subject should not enter a clinical study or perform any study-related procedures until he/she has been properly informed, has been given time to contemplate participation, and has freely given his/her consent by signing and dating the EC/IRB approved informed consent form.

The proposed consent form and any other documents relevant to the consent process must be submitted to the EC/IRB together with the protocol and must be approved prior to study start.

A signed copy of the consent form will be given to the subject and the original will be maintained at the site following the signing and dating by the person administering the consent and witness (where appropriate).

Freely given written informed consent must be obtained from every subject or their legally acceptable representative prior to clinical trial participation, including informed consent for any screening procedures conducted to establish subject eligibility for the trial.

Subjects unable to give their written consent may only be enrolled in the study with the consent of their legally acceptable representatives. The subject must also be informed about the nature of the study to the extent compatible with the subject's understanding, and should they become capable, personally sign and date the consent, who is capable of forming an opinion and assessing this information to refuse participation, or too be withdrawn from, the clinical trial should be considered by the investigator.

15.3. Ethics Committee (EC) or Institutional Review Board (IRB)

The study must have unconditional approval in writing, by an appropriate Ethics Committee/Institutional Review Board (EC/IRB). A copy of the Letter of Approval from the EC/IRB, which contains specific identification of the documents approved, must be received by the sponsor prior to site initiation.

Any substantial amendments to the protocol or subsequent changes to the informed consent form as a result of changes to the protocol that is approved by the sponsor must also be sent to the EC/IRB and written opinion has to be provided to the sponsor. Records of the EC/IRB review and opinion of all documents pertaining to this study must be kept on file by the investigator and are subject to regulatory authority and/or sponsor inspection during or after completion of the study.

Serious Adverse Events (SAEs) must also be reported to the EC/IRB by the investigator or the sponsor.

Periodic status reports must be submitted to the EC/IRB as required, as well as notification of completion of the study and a final report where applicable. A copy of all reports submitted to the EC/IRB must be sent to the sponsor.

15.4. Protocol Amendments

Changes to the protocol should only be made by an approved protocol amendment. Protocol amendments must be approved by the Sponsor and each respective site's EC/IRB prior to implementation.

For clinical trial sites located in EU member states, the procedures outlined in Directive 2001/20/EC, Article 10(a), are applicable. Elsewhere, the country regulations apply.

15.5. Declaration of the End of the Clinical Trial

For clinical trial sites located in EU member states, a declaration of the end of the clinical trial will be made according to the procedures outlined in Directive 2001/20/EC, Article 10(c). Elsewhere, the country regulations apply.

15.6. Subject Confidentiality

All subject data will be identified only by a subject identification number, subject initials and date of birth.

After obtaining the subject's consent the investigator will permit the Study Monitor, independent auditor or regulatory agency personnel to review that portion of the subject's

medical record that is directly related to the study. This shall include all study relevant documentation including subject medical history to verify eligibility; laboratory test result reports; admission/ discharge summaries for hospital admissions occurring while the subject is in the study; and autopsy reports for deaths occurring during the study (where available).

15.7. Liability and Insurance

A Certificate of Clinical Trials Insurance will be provided to the study sites by the sponsor, where required.

16. SIGNATURES

_____	_____
Date	Prof. Dr. med. Falk Hiepe Study Principal Investigator
_____	_____
Date	Dr. Joachim Listing Study statistical support

17. REFERENCES

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18. APPENDIX

Appendix 1: SLEDAI Assessment Form

SLEDAI 2K DATA COLLECTION FORM (SLEI)

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	Descriptor	Definition	SLEDAI Score
1	Seizure	Recent onset. Exclude metabolic, infectious or drug causes	☐ **0, 8**
2	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes	☐ **0, 8**
3	Organic brain syndrome	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features. Inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes	☐ **0, 8**
4	Visual disturbance	Retinal changes of SLE, include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid or optic neuritis. Exclude hypertension, infection or drug causes	☐ **0, 8**
5	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves	☐ **0, 8**
6	Lupus headache	Severe persistent headache; may be migrainous, but must be non-responsive to narcotic analgesia	☐ **0, 8**
7	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis	☐ **0, 8**
8	Vasculitis	a. Ulceration, gangrene ☐ b. Tender finger nodules ☐ c. Periungual infraction ☐ d. Splinter hemorrhages or biopsy or angiogram proof of vasculitis ☐	☐ **0, 8**
9	Arthritis	≥ 2 joints with pain and signs of inflammation (i.e., tenderness, swelling or effusion)	☐ **0, 4**
10	Myositis	a. Proximal muscle aching/weakness, associated with ☐ b. Elevated creatine phosphokinase/aldolase or ☐ c. Electromyogram changes or ☐ d. A biopsy showing myositis ☐	☐ **0, 4**
11	Urinary casts	Heme-granular or red blood cell casts	☐ **0, 4**
12	Hematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause	☐ **0, 4**
13	Proteinuria	>0.5 gram/24 hours	☐ **0, 4**
14	Pyuria	>5 white blood cells/high power field. Exclude infection	☐ **0, 4**

SLEDAI 2K DATA COLLECTION FORM (SLEI)

	Descriptor	Definition	SLEDAI Score
15	Rash	Inflammatory type rash	☐ **0, 2**
16	Alopecia	Abnormal, patchy or diffuse loss of hair	☐ **0, 2**
17	Mucosal ulcers	Oral or nasal ulcerations	☐ **0, 2**
18	Pleurisy	a. Pleuritic chest pain with ☐ b. Pleural rub or ☐ c. Effusion or ☐ d. pleural thickening ☐	☐ **0, 2**
19	Pericarditis	a. Pericardial pain with at least one of the following ☐ b. Rub or ☐ c. Effusion or ☐ d. Electrocardiogram confirmation ☐	☐ **0, 2**
20	Low complement	Decrease in CH50, C3 or C4 below the lower limit of normal for testing laboratory	☐ **0, 2**
21	Increased DNA binding	Increased DNA binding by Farr assay above normal range for testing laboratory	☐ **0, 2**
22	Fever	>38°C Exclude infectious cause	☐ **0, 1**
23	Thrombocytopenia	<100,000 platelets / $x10^9$/L, exclude drug causes	☐ **0, 1**
24	Leukopenia	<3,000 white blood cells / $x10^9$/L, exclude drug causes	☐ **0, 1**

☐
SLEDAI 2K
Total Score
OP (Not for Data Entry)

Appendix 2: BILAG - Worksheet

All features must be attributable to active SLE and refer to last 4 weeks compared with prior disease activity

Indicate features which are present: 1) *Improving*
2) Same
3) Worse
4) New

Or Y/N or value (where indicated)

GENERAL			47. Aseptic Necrosis	*Y/N*	( )
1. Pyrexia (documented)		( )			
2. Weight loss - unintentional > 5%		( )	**CARDIOVASCULAR & RESPIRATORY**		
3. Lymphadenopathy/splenomegaly		( )	48. Pleuropericardial pain		( )
4. Fatigue/malaise/lethargy		( )	49. Dyspnoea		( )
5. Anorexia/nausea/vomiting		( )	50. Cardiac failure		( )
			51. Friction rub		( )
MUCOCUTANEOUS			52. Effusion (pericardial or pleural)		( )
6. Maculopapular eruption -severe, active		( )	53. Mild or intermittant chest pain		( )
(or discoid/bullous)		( )	54. Progressive cxr changes-lung fields	*Y/N*	( )
7. Maculopapular eruption - mild		( )	55. Progressive cxr changes-heart size	*Y/N*	( )
8. Active discoid lesions – generalised or			56. ECG evidence of pericarditis or		
extensive		( )	myocarditis	*Y/N*	( )
9. Active discoid lesions - localised			57. Cardiac arrhythmias including tachycardia		
Including lupus profundus		( )	> 100 in absence of fever	*Y/N*	( )
10. Alopecia (severe, active)		( )	58. Pulmonary function fall by > 20%	*Y/N*	
11. Alopecia (mild)		( )	59. Cytohistological evidence of		
12. Panniculitis (severe)		( )	inflammatory lung disease	*Y/N*	( )
13. Angio-oedema		( )			
14. Extensive mucosal ulceration		( )	**VASCULITIS**		
15. Small mucosal ulcers		( )	60. Major cutaneous vasculitis incl.ulcers		( )
16. Malar erythema		( )	61. Major abdominal crisis due to vasculitis		( )
17. Subcutaneous nodules		( )	62. Recurrent thromboembolism (excluding		( )
18. Perniotic skin lesions		( )	strokes)		
19. Peri-ungual erythema		( )	63. Raynaud's		( )
20. Swollen fingers	*Y/N*	( )	64. Livido reticularis		( )
21. Sclerodactyly	*Y/N*	( )	65. Superficial phlebitis		( )
22. Calcinosis	*Y/N*	( )	66. Minor cutaneous vasculitis		
23. Telangiectasia	*Y/N*	( )	(nailfold vasculitis, digital vasculitis,		
			purpura, urticaria)		( )
NEUROLOGICAL			67. Thromboembolism (excl. stroke)		
24. Deteriorating level of consciousness		( )	- 1st episode	*Y/N*	( )
25. Acute psychosis or delirium or confusional state		( )			
26. Seizures		( )	**RENAL**		
27. Stroke or stroke syndrome		( )	68. Systolic blood pressure (mm Hg)	*value*	( )
28. Aseptic meningitis		( )	69. Diastolic blood pressure (mm Hg)	*value*	( )
29. Mononeuritis multiplex		( )	70. Accelerated hypertension	*Y/N*	( )
30. Ascending or transverse myelitis		( )	71. Urine dipstick protein (+ = 1, ++ = 2,	*value*	( )
31. Peripheral or cranial neuropathy		( )	+++ = 3)		
32. Disc swelling/cytoid bodies		( )	72. 24 hour urinary protein (g)	*value*	( )
33. Chorea		( )	73. Newly documented proteinuria > 1g/d	*Y/N*	( )
34. Cerebellar ataxia		( )	74. Nephrotic syndrome	*Y/N*	( )
35. Headache severe, unremitting		( )	75. Creatinine (plasma/serum)	*value*	( )
36. Organic depressive illness		( )	76. Creatinine clearance/GFR ml/min	*value*	( )
37. Organic brain syndrome including		( )	77. Active urinary sediment	*Y/N*	( )
pseudotumor cerebri		( )	78. Histological evidence of active nephritis		
38. Episodic migrainous headaches		( )	- within 3 months	*Y/N*	( )
MUSCULOSKELETAL			**HAEMATOLOGY**		
39. Definite myositis (Bohan & Peter)		( )	79. Haemoglobin g/dl	*value*	( )
40. Severe polyarthritis - with loss of		( )	80. Total white cell count x 10^9/l	*value*	( )
function		( )	81. Neutrophils x 10^9/L	*value*	( )
41. Arthritis		( )	82. Lymphocytes x 10^9/L	*value*	( )
42. Tendonitis		( )	83. Platelets x 10^9/L	*value*	( )
43. Mild chronic myositis		( )	84. Evidence of active haemolysis	*Y/N*	( )
44. Arthralgia		( )	85. Coomb's test positive	*Y/N*	( )
45. Myalgia		( )	86. Evidence of circulating anticoagulant	*Y/N*	( )
46. Tendon Contractures and Fixed Deformity	*Y/N*	( )			

Appendix 3: BILAG - Glossary

A. INSTRUCTIONS

- only record features that are attributable to SLE disease activity and not due to damage, infection, or other conditions
- assessment refers to manifestations occurring in the last 4 weeks compared with the previous 4 weeks
- activity refers to disease process which is reversible while damage refers to permanent process/scarring (irreversible)
- damage due to SLE should be considered as a cause of features that are fixed/persistent (SLICC/ACR damage index uses persistence ≥ 6 months to define MOST damage items)
- in some manifestations, it may be difficult to differentiate SLE from other conditions as there may not be any specific test and the decision would then lies with the physician's judgement on the balance of probabilities

B. GUIDANCE FOR RECORDING ITEMS:

(4) NEW

- manifestations are recorded as new when it is a new episode occurring in the last 4 weeks (compared to the previous 4 weeks) which has not improved and this includes new episodes (recurrence) of old manifestations
- new episode occurring in the last 4 weeks but also satisfying the criteria for improvement (below) would be classified as improving instead of new

(3) WORSE

- this refers to manifestations that have deteriorated in the last 4 weeks compared to the previous 4 weeks

(2) SAME

- this refers to manifestations that have been present for the last 4 weeks and the previous 4 weeks without significant improvement or deterioration (from the previous 4 weeks)
- this also applies to manifestations that have improved over the last 4 weeks compared to the previous 4 weeks but do not meet the criteria for improvement

(1) IMPROVING

- definition of improvement:

  (a) the amount of improvement is sufficient for consideration of reduction in therapy and would not justify escalation in therapy

  (b) improvement must be present currently and ≥ 2 weeks of the last 4 weeks

(0) NOT PRESENT

C. ADDITIONAL COMMENTS

If a lupus manifestation can be recorded as a mild or a severe item (depending on glossary definition), and is recorded as the severe item, the corresponding mild item should be

recorded as well. When the feature improves and changes to mild, just the mild item is recorded (but it will not be new, it will be improving).

If a mild item deteriorates and becomes severe, the severe item is new, and the mild item is recorded as worse.

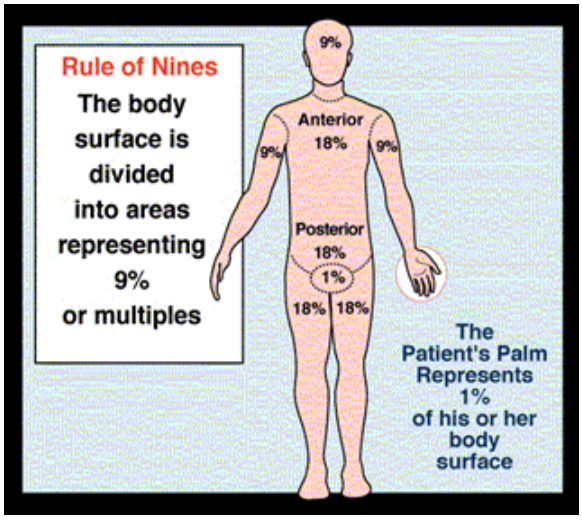
General System:

Item	Definition
1. Pyrexia	Temperature of > 38.0° C documented (infection excluded)
2. Weight loss	Unintentional weight loss >5% in one month (due to lupus, not diet or co-morbid disease)
3. Lymphadenopathy	Palpable lymph nodes > 1 cm in diameter usually vary in size with time
4. Fatigue/malaise/weakness	Sufficiently severe to affect normal activities and tends to fluctuate with time (in contrast to chronic fatigue syndrome or fatigue of fibromyalgia which tends to be constant and present all the time)
5. Anorexia/nausea/vomiting	Lupus- related (excludes symptoms due to drug side-effects, infection etc)

Mucocutaneous system:

Item	Definition
6. Maculopapular eruption – severe	Active maculopapular or bullous eruption. This must be extensive, (> 2/9 (18%) of body surface area), scarring, or causing disability (rule of 9s – see below)
7. Maculopapular eruption – mild	Limited to ≤2/9 (18%) or less of body surface area, non-scarring, non-disabling
8. Active discoid lesions – generalized or extensive	>2/9 (18%) of body surface area
9. Active discoid lesions – localized	Limited to ≤2/9 or less of body surface area, includes lupus profundus
10. Alopecia – severe, active	Abnormal diffuse hair loss which is clinically detectable with scalp inflammation
11. Alopecia – mild	Limited, relatively inactive; abnormal diffuse hair loss with little or no detectable scalp inflammation
12. Panniculitis	Extensive, painful, erythematous subcutaneous nodules associated with an overlying discoid skin lesion.
13. Angio-oedema	Potentially life-threatening, e.g. stridor (NOT SUITABLE AS Entry Criterion for trial requiring A level disease as usually short-lived and requires emergency treatment)

Item	Definition
14. Extensive mucosal ulceration	Severe, deep and extensive disabling ulcers
15. Small mucosal ulcers	More than 1 aphthous ulcer, painful or painless
16. Malar erythema	Classical “butterfly” type erythematosus rash due to lupus but may only be small areas and may occur on other parts of the face as well as cheeks and nose, but spares naso-labial folds
17. Subcutaneous nodules	As in rheumatoid arthritis
18. Perniotic skin lesions	Also called chilblain lupus- red-purple patches and plaques on toes, fingers, heels, calves, elbows, knees, nose with or without fissuring, often in response to cold & may be associated with discoid lesions
19. Peri-ungual erythema	
20. Swollen fingers	Do not record if damage
21. Scerodactyly	Do not record if damage
22. Calcinosis	Do not record if damage
23. Telangiectasia	Do not record if damage



Neurological system:

Item	Definition
24. Impaired level of consciousness	Acute deteriorating level of consciousness by any accepted clinical criteria (exclude drugs, infection, co-morbid disease)

Item	Definition
25. Acute psychosis or delirium or confusional state	Acute severe disturbance in the perception or reality characterized by delusions, hallucinations, incoherence, marked illogical thinking, bizarre or catatonic behavior (exclude drugs, substance abuse, primary psychotic disorder)
26. Seizures	independent description of seizure by reliable witness
27. Stroke or stroke syndrome	Attributable to acute lupus inflammation;exclude atherosclerosis, emboli, hypoglycaemia, cerebral sinus thrombosis, vascular malformation, tumour, abscess
28. Aseptic meningitis	criteria: acute/subacute onset, headache, with fever and abnormal CSF (raised protein, lymphocytes predominant but negative cultures ie without evidence of infection or bleed) +/- photophobia, neck stiffness, signs of meningeal irritation
29. Mononeuritis multiplex	Multiple (>1) nerves affected by inflammatory process
30. Ascending or transverse myelitis	acute onset of rapidly evolving paraparesis or quadriparesis and/or sensory level (exclude intramedullary and extramedullary space occupying lesion)
31. Peripheral or cranial neuropathy	Acute symmetrical distal peripheral or cranial sensory and/or motor deficit
32. Disc swelling/cytoid bodies	(exclude diabetic retinopathy etc)
33. Chorea	Exclude drug-induced
34. Cerebellar ataxia	in isolation of other CNS features (not brainstem stroke)-usually subacute presentation
35. Headache, severe and unremitting	Continuous disabling headache lasting $\geq$3 days, not relieved by narcotic analgesia (exclude intracranial space occupying lesion and CNS infection)
36. Organic depressive illness	Attributable to lupus and associated with somatic symptoms and severe enough to merit treatment with anti-depressive medication
37. Organic brain syndrome	Impaired orientation, memory or other intellectual function in the absence of metabolic, psychiatric, or pharmacological causes ➢ Clinical features develop over a short period (usually hours to days) and tend to fluctuate over the course of the day ➢ Clouding of consciousness with reduced capacity to focus and sustain attention to environment

Item	Definition
	➢ Perceptual disturbance-misinterpretations, illusions, or hallucinations. ➢ Incoherent speech ➢ Insomnia or daytime drowsiness ➢ Increased or decreased psychomotor activity ➢ Disorientation and recent memory impairment
38. Episodic migrainous headaches	Recurrent lupus related headaches, lasting 4 - 72 hours, may be preceded by neurological aura (lasting up to 1 hour)

Musculoskeletal system:

Item	Definition
39. Myositis	At least 3 of the following Bohan & Peter criteria-acute proximal muscle weakness, elevated muscle enzymes (CK), positive biopsy, and abnormal EMG
40. Polyarthritis with loss of function	Active joint inflammation in at least 2 joints with clinically significant loss of the functional range of movement of the involved joints, unresponsive to NSAIDS, prednisolone 10 mg daily and/or cytotoxic agents.
41. Arthritis	Active joint inflammation in 1 or more joints (tenderness, warmth or swelling without loss of functional range of motion)
42. Tendonitis	Inflammatory not mechanical
43. Mild chronic myositis	2 or 3 Bohan & Peter criteria or sub-acute (not damage)
44. Arthralgia	Inflammatory joint pain with morning stiffness on history and with no signs of inflammation (exclude OA, mechanical problems, fibromyalgia)
45. Myalgia	Inflammatory muscle pain without weakness or elevated CPK (exclude fibromyalgia)
46. Tendon contractures and fixed deformity	(damage, so should not be recorded)
47. Aseptic necrosis	(damage, so should not be recorded)

Cardiorespiratory system:

Item	Definition
48. Pleuropericardial pain	Localised sharp or dull pain in the chest aggravated by respiration (on inspiration) without chest wall tenderness

49.	**Dyspnoea**	on exertion (but not orthopnoea alone, and exclude angina, infection, asthma, chronic bronchitis etc)
50.	**Cardiac failure**	cardiac failure due to lupus myocarditis or non-infective inflammation of endocardium or cardiac valves (endocarditis)- exclude other causes
51.	**Friction rub**	Pleural or pericardial (exclude chronic fibrosis)
52.	**Effusion (pericardial or pleural)**	Clinically detectable
53.	**Mild intermittent chest pain**	Non-specific (not clearly pleuritic, pericardial, musculoskeletal, or angina)
54.	**Progressive CXR changes – lungs**	Due to lupus
55.	**Progressive CXR changes – heart**	Due to lupus
56.	**ECG evidence of pericarditis or myocarditis**	
57.	**Cardiac arrhythmias including tachycardia > 100 in absence of fever**	Due to lupus
58.	**Pulmonary function fall >20%**	>20 % fall since last assessment or >20% below lower limit of normal if not measured before in lung volumes and/or transfer factor corrected for lung volumes (must be associated with change in symptoms to suggest acute inflammatory disease not co-morbid lung conditions or infection)
59.	**Cyto-histological evidence of inflammatory lung disease**	Due to lupus

Vasculopathy (vasculitis) system:

Item		Definition
60.	**Major cutaneous vasculitis including ulcers**	Extensive gangrene and/or ulceration
61.	**Major abdominal crisis due to vasculitis**	small or large bowel, gall bladder etc with supportive imaging &/or biopsy findings
62.	**Recurrent thromboembolism (excluding stroke)**	
63.	**Raynaud's Phenomenon**	
64.	**Livedo reticularis**	
65.	**Superficial phlebitis**	
66.	**Minor cutaneous vasculitis**	Includes nailfold vasculitis, digital vasculitis, purpura, ulcers, leukocytoclastic/ hypersensitivity Vasculitis
67.	**Thromboembolism (excluding stroke) 1st episode**	

Renal system (original- see below for 2004 revision):

Item	Definition
68. Systolic BP mmHg	
69. Diastolic BP mmHg	
70. Accelerated hypertension	BP rising to > 170/110 (5^{th} phase) within 1 month, if accompanied by Grade IV retinal changes (i.e. haemorrhage, exudates)
71. Dipstick (+ = 1, ++ = 2, +++ = 3)	Proteinuria (exclude infection if positive)
72. 24 h urine protein (g)	
73. New documented proteinuria of > 1g/24h	
74. Nephrotic syndrome	heavy proteinuria (>50 mg/kg/day or > 3.5 g/day), hypoalbuminaemia and oedema
75. Creatinine (plasma/serum)	Record value and units
76. Creatinine clearance/GFR (ml/min)	Record value
77. Active urinary sediment	Uncentrifuged specimen with pyuria (> 5 wbc/hpf), hematuria (> 5 rbc/hpf), or red cell casts in the absence of infection **or any other cause**
78. Histological evidence of active nephritis (within 3 months)	Histological evidence of active nephritis according to WHO criteria. Sclerosis alone (without inflammation) will not be regarded as evidence of active nephritis

Hematological system:

Item	Definition- record values and
79. Hemoglobin (g/dL)	Indicate if abnormal value not due to lupus (eg iron deficiency anaemia, drugs etc)
80. Total white cell count x 10^9/L	Indicate if abnormal value not due to lupus (eg iron deficiency anaemia, drugs etc)
81. Neutrophils x 10^9/L	Indicate if abnormal value not due to lupus (eg iron deficiency anaemia, drugs etc)
82. Lymphocytes x 10^9/L	Indicate if abnormal value not due to lupus (eg iron deficiency anaemia, drugs etc)
83. Platelets x 10^9/L	Indicate if abnormal value not due to lupus (eg iron deficiency anaemia, drugs etc)
84. Evidence of active hemolysis	positive Coomb's test & evidence of haemolysis (raised bilirubin or raised reticulocyte count or reduced haptoglobulins)
85. Coombs test positive	Isolated without evidence of haemolysis (exclude infection)
86. Evidence of circulating anticoagulant	Evidence of circulating lupus anticoagulant, anti-cardiolipin or other antiphospholipid antibody

RENAL GLossary for BILAG 2004

Systolic blood pressure	
Diastolic blood pressure	
Accelerated hypertension	blood pressure rising to > 170/110 mm Hg within 1 month with grade 3 or 4 Keith-Wagener-Barker retinal changes (flame-shaped haemorrhages or cotton-wool spots or papilloedema
Urine dipstick	record if 0, 1+, 2+ or 3+
Urine albumin-creatinine ratio	on freshly voided urine sample
Urine protein-creatinine ratio	on freshly voided urine sample
24 hour urine protein	g/l

Appendix 4: BILAG - Scoring System

General: Category Scoring

Category A
Pyrexia recorded as 2 (Same), 3 (Worse) or 4 (New) **Plus** 2 others recorded as 2 (Same), 3 (Worse) or 4 (New)
Category B
Pyrexia recorded as 2 (Same), 3 (Worse) or 4 (New) **Or** 2 others recorded as 2 (Same), 3 (Worse) or 4 (New)
Category C
Any one criterion recorded as 1 (Improving), 2 (Same), 3 (Worse), or 4 (New)
Category D
Previous General System involvement, currently active
Category E
No previous General System involvement

Mucocutaneous: Category Grading

Category A
Any one of the following recorded as 2 (Same), 3 (Worse), or 4 (New): Severe maculopapular, discoid or bullous eruption i.e. active facial and/or extensive (>2/9), scarring Angio-oedema Extensive mucosal ulceration
Category B

Any one of the following recorded as 2 (Same), 3 (Worse), or 4 (New): Malar erythema Severe active alopecia Mild maculopapular eruption Subcutaneous nodules Panniculitis Perniotic skin lesions Localised active discoid lesions inc. lupus profundus
Category C
Any Category A or Category B criteria recorded as 1 (Improving) **or** Any one of the following recorded as 1 (Improving), 2 (Same), 3 (Worse), or 4 (New): Peri-ungual erythema Sclerodactyly Swollen fingers Mild alopecia Calcinosis Small mucosal ulceration Telangiectasia
Category D
Previous mucocutaneous involvement, currently inactive
Category E
No mucocutaneous involvement

Neurological: Category Grading

Category A
Any one of the following recorded as 3 (Worse) or 4 (New): Impaired level of consciousness Psychosis, delirium,or confusional state Grand mal seizure Stroke or stroke syndrome Aseptic meningitis Mononeuritis multiplex Ascending or transverse myelitis Peripheral or cranial neuropathy Chorea Cerebellar ataxia
Category B

Any one of the following recorded as 3 (Worse) or 4 (New): Headache (severe unremitting) Organic depressive illness Chronic brain syndrome including pseudotumor cerebri Disc swelling or cytoid bodies or **Or Any of the following recorded as 1 (Improving) or 2 (Same):** Impaired level of consciousness Pychosis, delerium or convulsional state Grand mal seizure
Category C
Episodic migrainous headaches **recorded as**: 1 (Improving), 2 (Same), 3 (Worse), or 4 (New): **Or any one of the following recorded as 1 (Improving) or 2 (Same):** Stroke or stroke syndrome Aseptic meningitis Mononeuritis multiplex Ascending or transverse myelitis Peripheral or cranial neuropathy ChoreaCerebellar ataxia Headache (severe unremitting) Organic depressive illness Chronic brain syndrome (incl. pseudotumor cerebri) Disc swelling or cytoid bodies
Category D
Previous CNS disease, currently inactive
Category E
No previous CNS disease

Cardiorespiratory: Category Grading

Category A

cardiac failure recorded as 2 (Same), 3 (Worse), or 4 (New) **plus** two other criteria listed below recorded as 2 (Same), 3 (Worse), or 4 (New):
Or
Symptomatic effusion recorded as 2 (Same), 3 (Worse), or 4 (New) **plus** two other criteria listed below 2 (Same), 3 (Worse), or 4 (New):
Or
Four of the criteria listed below each recorded as 2 (Same), 3 (Worse), or 4 (New):

Pleuropericardial pain
Dyspnea
Friction rub
Progressive chest x-ray changes – lung fields
Progressive chest x-ray changes – heart size
ECG evidence of pericarditis or myocarditis
Cardiac arrhythmias including tachycardia - >100 in absence of fever
Deteriorating lung function: <20% of expected or >20% fall
Cytohistological evidence of inflammatory lung disease

Category B
Two of the criteria listed below each recorded as 2 (Same), 3 (Worse), or 4 (New): Pleuropericardial pain Dyspnea Friction Rub Progressive chest x-ray changes – lung fields Progressive chest x-ray changes – heart size ECG evidence of pericarditis or myocarditis Cardiac arrhythmias including tachycardia - >100 in absence of fever Deteriorating lung function: <20% of expected or >20% fall Cytohistological evidence of inflammatory lung disease
Category C
One of the criteria listed below each recorded as 1 (Improving), 2 (Same), 3 (Worse), or 4 (New): Mild intermittent chest pain Pleuropericardial pain Dyspnea Friction Rub Progressive chest x-ray changes – lung fields Progressive chest x-ray changes – heart size ECG evidence of pericarditis or myocarditis Cardiac arrhythmias including tachycardia - >100 in absence of fever Deteriorating lung function: <20% of expected or >20% fall Cytohistological evidence of inflammatory lung disease
Category D
Previous Cardiovascular / Respiratory disease involvement, currently inactive
Category E
No previous Cardiovascular / Respiratory disease involvement

Vasculitis: Category Grading

Category A
Major cutaneous vasculitis (including ulcers), accompanied by infarction occuring in the past 4 weeks, recorded as 2 (Same), 3 (Worse), or 4 (New) **Or** Major abdominal crisis due to vasculitis, recorded as 2 (Same), 3 (Worse), or 4 (New) **Or** Recurrent thromboembolism (excluding strokes), recorded as 2 (Same), 3 (Worse), or 4 (New)
Category B
Minor cutaneous vasculitis, recorded as 2 (Same), 3 (Worse), or 4 (New) **Or** Superficial phlebitis, recorded as 2 (Same), 3 (Worse), or 4 (New) **Or** Thromboembolism (excluding strokes), first episode, recorded as 2 (Same), 3 (Worse), or 4 (New)
Category C
Any Category A or Category B criteria recorded as 1 (Improving) **Or** Raynaud's Phenomenon, recorded as 1 (Improving) 2 (Same), 3 (Worse), or 4 (New) **Or** Livedo reticularis, recorded as 1 (Improving) 2 (Same), 3 (Worse), or 4 (New)
Category D
Previous Vasculitis involvement, currently inactive
Category E
No previous Vasculitis involvement

Renal: Category Grading

Category A

Two or more of the following providing one of 1, 4 or 5 is included:

1. Proteinuria defined as
   a) Urinary dipstick increased by 2 or more levels; or
   b) 24-hour urine protein rising from < (0.20 grams to > 1 gram, or
   c) 24-hour urine protein rising from > 1 gram by 100%, or
   d) Newly documented proteinuria of > 1 gram

2. Accelerated hypertension

3. Deteriorating renal function, defined as
   a) plasma creatinine ≥130 μmol/l and having risen to >130% of previous value; or
   b) creatinine clearance having fallen to < 67% of previous value; or
   c) creatinine clearance < 50 ml/min, and last time was ≥ 50 ml/min or was not measured

4. Active urinary sediment (on uncentrifuged specimen): pyuria (>5 wc/hpf), hematuria (>5 rbc/hpf) or red cell casts in the absence of infection or other cause

5. Histological evidence of active nephritis by WHO criteria within last 3 months (or since previous assessment if seen less than 3 months ago; Sclerosis without inflammation is not counted)

Category B

One of the following:
One of the category A criteria (above)

(a) 1) urine dipstick which has risen by 1+ or more to at least 2+, OR
2) 24 hour urinary protein rising from > 1g by >50% but <100%
OR
(b) Plasma creatinine > 130 μmol/l **and)** having risen to 115% of previous value.

Category C

O*ne of the following:*
(a) 24 hour urine protein > 0.25g
(b) Urine dipstick 1+ or more
(c) Rising blood pressure,defined as (a) systolic rise of ≥ 30mm **and** (b) diastolic rise of ≥15mm (providing the recorded values are > 140/90)

Category D

Previous renal disease, currently inactive

Category E

No evidence of any renal disease ever

Hematological: Category Grading

Category A

One of the following*:* Hemoglobin < 8g/dl White cell count < 1000/µl Platelet count < 25/µl
Category B
One of the following: Hemoglobin < 11g/dl White cell count < 2500/µl Platelet count < 100/µl Coombs Test positive **and** evidence of active hemolysis, e.g.raised bilirubin +/- increased Reticulocyte Count
Category C
One of the following: White cell count < 4000/µl Platelet count < 150/µl Lymphocyte count < 1500/µl Coombs Test positive (no active hemolysis) Evidence of circulating lupus anticoagulant **or other antiphospholipid antibody**
Category D
Previous Hematological disease involvement, currently inactive
Category E
No previous Hematological disease involvement

Appendix 5: SLICC/ACR Damage Index

SLICC (Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index) Scoring system:

Organ	Item	Points
Ocular (either eye by clinical assessment)	Any cataract ever	1
	Retinal damage *or* optic atrophy	1
Neuropsychiatric	Cognitive impairment (e.g. memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance level) *or* major psychosis	1
	Seizures requiring therapy for 6 months	1
	Cerebrovascular accident ever (score 2 if more than 1)	1 or 2
	Cranial or peripheral neuropathy (excluding optic)	1

	Transverse myelitis	1
Renal	Estimated or measured glomerular filtration rate < 50%	1
	Proteinuria ≥ 3.5 g per 24 hours, *or*	1
	End-stage renal disease (regardless of dialysis or transplantation)	3
Pulmonary	Pulmonary hypertension (right ventricular prominence or loud P2)	1
	Pulmonary fibrosis (physical and radiograph)	1
	Shrinking lung (on radiograph)	1
	Pleural fibrosis (on radiograph)	1
	Pulmonary infarction (on radiograph)	1
Cardiovascular	Angina or coronary artery bypass	1
	Myocardial infarction ever (score 2 if more than 1)	1 or 2
	Cardiomyopathy (ventricular dysfunction)	1
	Valvular disease (diastolic murmur or systolic murmur > 3/6)	1
	Pericarditis for 6 months or pericardiectomy	1
Peripheral vascular	Claudication for 6 months	1
	Minor tissue loss (pulp space)	1
	Significant tissue loss ever (e.g. loss of digit or limb resection) (score 2 if more than one site)	1 or 2
	Venous thrombosis with swelling, ulceration or venous stasis	1
Gastrointestinal	Infarction or resection of bowel below duodenum, spleen, liver or gallbladder ever, for any cause (score 2 if more than 1 site)	1 or 2
	Mesenteric insufficiency	1
	Chronic peritonitis	1
	Stricture or upper gastrointestinal tract surgery ever	1
	Pancreatic insufficiency requiring enzyme replacement, or pseudocyst	1
Musculoskeletal	Muscle atrophy or weakness	1
	Deforming or erosive arthritis (including reducible deformities excluding avascular necrosis)	1
	Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)	1
	Avascular necrosis (score 2 if more than 1)	1 or 2
	Osteomyelitis	1
Skin	Scarring chronic alopecia	1
	Extensive scarring or panniculum other than scalp and pulp space	1
	Skin ulceration (excluding thrombosis) for more than 6 months	1

Other	Premature gonadal failure	1
	Diabetes (regardless of treatment)	1
	Malignancy (exclude dysplasia) (score 2 if more than 1 site)	1 or 2

Glossary of terms:

Term	**Definition**
Damage	Nonreversible change, not related to active inflammation, occurring since diagnosis of lupus, ascertained by clinical assessment and present for at least 6 months unless otherwise stated. Repeat episodes must occur at least 6 months apart to score 2. The same lesion cannot be scored twice.
Cataract	A lens opacity (cataract) in either eye ever, whether primary or secondary to steroid therapy, documented by ophthalmoscopy.
Retinal damage	Documented by ophthalmoscopic examination. May result in field defect, legal blindness.
Optic atrophy	Documented by ophthalmoscopic examination.
Cognitive impairment	Memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance level, documented on clinical examination or by formal neurocognitive testing.
Major psychosis	Altered ability to function in normal activity due to psychiatric reasons. Severe disturbance in the perception of reality characterized by the following features: delusions, hallucinations (auditory, visual), incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized or catatonic behavior.
Seizures	Paroxysmal electrical discharge occurring in the brain and producing characteristic physical changes including tonic and clonic movements and certain behavioral disorders. Only seizures requiring therapy for 6 months are counted as damage.
Cerebrovascular accident (CVA)	Cerebrovascular accident resulting in focal findings such as paresis weakness etc. or surgical resection for causes other than malignancy.
Neuropathy	Damage to either cranial or peripheral nerve, excluding optic nerve, resulting in either motor or sensory dysfunction.
Transverse myelitis	Lower extremity weakness or sensory loss with loss of rectal and urinary bladder sphincter control.
Renal	Estimated or measured glomerular filtration rate < 50% proteinuria ≥ 3.5 g per 24 hours or end-stage renal disease (regardless of dialysis or transplantation).
Pulmonary	Pulmonary hypertension (right ventricular prominence or loud P2), pulmonary fibrosis (physical and radiograph), shrinking lung (radiograph), pleural fibrosis (radiograph), pulmonary infarction (radiograph), resection for cause other than malignancy.
Cardiovascular	Angina or coronary artery bypass, myocardial infarction (documented by electrocardiograph and enzyme studies) ever, cardiomyopathy (ventricular dysfunction documented clinically), valvular disease (diastolic murmur or systolic murmur > 3/6), pericarditis for 6 months or pericardiectomy.

Peripheral vascular	Claudication persistent for 6 months by history, minor tissue loss such as pulp space ever, significant tissue loss such as loss of digit or limb or resection ever, venous thrombosis with swelling, ulceration or clinical evidence of venous stasis.
Gastrointestinal	Infarction or resection of bowel below duodenum by history resection of liver spleen or gallbladder ever for whatever cause, mesentric insufficiency with diffuse abdominal pain on clinical examination, chronic peritonitis with persistent abdominal pain and peritoneal irritations on clinical examination, esophageal stricture on endoscopy upper gastrointestinal tract surgery such as correction of stricture, ulcer surgery etc. ever by history, pancreatic insufficiency requiring enzyme replacement or with a pseudocyst.
Musculoskeletal	Muscle atrophy or weakness demonstrated on clinical examination, deforming or erosive arthritis including reducible deformities (excluding avascular necrosis) on clinical examination, osteoporosis with fracture or vertebral collapse (excluding avascular necrosis) demonstrated radiographically; avascular necrosis demonstrated by any imaging technique, osteomyelitis documented clinically and supported by culture evidence, tendon ruptures.
Skin	Scarring, chronic alopecia documented clinically, extensive scarring or panniculum other than scalp and pulp space documented clinically; skin ulceration (excluding thrombosis) for more than 6 months.
Premature gonadal failure	Secondary amenorrhea prior to age of 40.
Diabetes	Diabetes requiring therapy but regardless of treatment.
Malignancy	Documented by pathologic examination excluding dysplasia.

Appendix 6: SF-36

INSTRUCTIONS: This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is: (circle one)

Excellent 1
Very good 2
Good 3
Fair 4
Poor 5

2. Compared to one year ago, how would you rate your health in general now? (circle one)

Much better now than one year ago 1
Somewhat better now than one year ago 2
About the same as one year ago 3
Somewhat worse now than one year ago 4
Much worse now than one year ago 5

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? (circle one number on each line)

ACTIVITIES	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing several flights of stairs	1	2	3
e. Climbing one flight of stairs	1	2	3
f. Bending, kneeling, or stooping	1	2	3
g. Walking more than a mile	1	2	3
h. Walking several blocks	1	2	3
I. Walking one block	1	2	3
j. Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? (circle one number on each line)

	YES	NO
a. Cut down on the amount of time you spent on work or other activities	1	2
b. Accomplished less than you would like	1	2
c. Were limited in the kind of work or other activities	1	2
d. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? (circle one number on each line)

	YES	NO
a. Cut down on the amount of time you spent on work or other	1	2

activities		
b. Accomplished less than you would like	1	2
c. Didn't do work or other activities as carefully as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups? (circle one)

Not at all 1
Slightly ……..2
Moderately..... 3
Quite a bit 4
Extremely 5

7. How much bodily pain have you had during the past 4 weeks? (circle one)

None 1
Very mild 2
Mild 3
Moderate 4
Severe 5
Very severe 6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (circle one)

Not at all 1
A little bit..... 2
Moderately..... 3
Quite a bit 4
Extremely 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks.

For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks. (circle one number on each line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
a. Did you feel full of pep?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6

d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6
f. Have you felt downhearted and blue?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
I. Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?
(circle one)

All of the time 1
Most of the time..... 2
Some of the time 3
A little of the time..... 4
None of the time..... 5

11. How TRUE or FALSE is each of the following statements for you? (circle one number on each line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
a. I seem to get sick a little easier than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5