Clinical Study Protocol

A 52-Week, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a 200-mcg Dose of IPP-201101 Plus Standard of Care in Patients With Systemic Lupus Erythematosus

Phase 3 Study IPP-201101/005

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Sponsor
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Authorized Representative (Signatory)
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INVESTIGATOR AGREEMENT

Clinical Study Protocol
A 52-Week, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a 200-mcg Dose of IPP-201101 Plus Standard of Care in Patients With Systemic Lupus Erythematosus

Investigator (Country): _____

Title: _____

Address of Study Center: _____

_____

_____

_____

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Cell: _____

I have read the protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined therein.

I will provide copies of the protocol and all information on the drug relating to the nonclinical and prior clinical experience, which were furnished to me by the sponsor, to all physicians and other study personnel responsible to me who participate in this study, and will discuss this material with them to ensure that they are fully informed regarding the drug and the conduct of the study.

I agree to keep records on all patient information (ie, case report forms and informed consent statements), study drug shipment and return forms, and all other information collected during the study, in accordance with local and national regulations.

_____

Investigator's Signature **Date**

SPONSOR'S MEDICAL EXPERT

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CLINICAL STUDY PROTOCOL SYNOPSIS

Sponsor: ImmuPharma SA

Investigational Product: IPP-201101

Title of Study: A 52-Week, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a 200-mcg Dose of IPP-201101 Plus Standard of Care in Patients With Systemic Lupus Erythematosus

Number of Centers Planned: Approximately 50 centers globally

Planned Study Period: 3rd quarter 2015 to 4th quarter 2017 **Phase of Development:** 3

Primary Objective: The primary objective of this study is to evaluate the efficacy of a 200-mcg dose every 4 weeks for 48 weeks of IPP-201101 compared with placebo in patients with active systemic lupus erythematosus (SLE) as assessed by the SLE responder index (SRI) at week 52. An SRI response is defined as a reduction from baseline in the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score of at least 4 points, no worsening in Physician's Global Assessment (PhGA) (with worsening defined as an increase in PhGA of more than 0.30 point from baseline), no new British Isles Lupus Assessment Group A (BILAG A) body system score, and no more than 1 new BILAG B body system score from baseline.

Secondary Objectives: The secondary efficacy objectives of the study are to evaluate the following:

- the SRI response at each visit during the study
- the reduction in the SLEDAI-2K total score by at least 4 points at each visit during the treatment period
- the effect of IPP-201101 on disease activity, as assessed by the BILAG-2004 disease activity index, at each visit during the treatment period
- the effect of IPP-201101 on the status of disease (PhGA scale) at each visit during the treatment period
- the reduction of the SLEDAI-2K total score by at least 5 points at each visit during the treatment period
- the reduction of the SLEDAI-2K total score by at least 6 points at each visit during the treatment period
- the SRI-5 response at each visit during the treatment period
- the SRI-6 response at each visit during the treatment period
- the effect of IPP-201101 on arthritis, as assessed by the 28-joint count examination for pain and tenderness at each visit during the treatment period
- the effect of IPP-201101 on the incidence of disease flares (ie, Safety of Estrogens in Lupus Erythematosus: National Assessment [SELENA] Flare Index [SFI] and SLEDAI-2K score of greater than 15) at each visit during the treatment period
- the effect of IPP-201101 on the occurrence of SLE–induced organ damage (eg, Systemic Lupus International Collaborative Clinics/American College of Rheumatology [SLICC/ACR] Damage Index (SDI) and adverse event inquiry) at visits at weeks 24 and 52 (or final assessment)
- the effect of IPP-201101 on health-related quality of life, as assessed by completion of the Medical Outcome Survey Short Form 36 (SF-36) at visits at weeks 12, 24, 36, and 52 (or final assessment)
- the effect of IPP-201101 on steroid dose over time throughout the study The exploratory efficacy objectives of the study are to determine the following:
- the effect of IPP-201101 on the following biologic markers of disease activity at each visit during the treatment period:
  anti–double-stranded deoxyribonucleic acid antibody (anti-dsDNA Ab) complement components (C3 and C4)
- the effect of IPP-201101 on the following biologic markers of disease activity at visits at weeks 4, 12, 24, 36, and 52 (or final assessment):
  - antinuclear antibody (ANA)
  - anti-uridine rich 70 kilodalton small nuclear ribonucleoprotein particle Ab (anti–U1-70K snRNP Ab)
  - anti-Smith antibody (anti-Sm Ab)
  - C-reactive protein (CRP)
  - immunoglobulin G (IgG), immunoglobulin M (IgM), and immunoglobulin E (IgE), immunoglobulin A (Ig A)
- the effect of IPP-201101 on fatigue using the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-Fatigue) scale at visits at weeks 12, 24, 36, and 52 (or final assessment)

- in vitro intracellular and secreted cytokine response

The safety and tolerability of IPP-201101 will be evaluated by the following:

- occurrence of adverse events throughout the study
- clinical laboratory (serum chemistry, hematology, and urinalysis) test results at each visit during the treatment period
- vital signs (systolic and diastolic blood pressures, pulse, temperature, and body weight) measurements at each visit during the treatment period
- 12-lead electrocardiogram (ECG) findings at week 52 (or final assessment)
- physical examination findings, including physical examination symptom directed findings, at specified time points at each visit during the treatment period
- evaluation for suicidality at each visit during the treatment period using the Columbia-Suicide Severity Rating Scale (C-SSRS)
- concomitant medication usage throughout the study

The immunogenicity of IPP-201101 will be assessed by the following:

- any presence of anti–IPP-201101 antibodies (anti–IPP-201101 Ab) at visits at weeks 2, 4, 12, 20, 28, 36, 44, and 52 (or final assessment)

Number of Patients Planned: It is anticipated that approximately 270 patients may be screened for participation in the study prior to completion of enrollment. Approximately 200 patients are planned to be enrolled in the study, to provide 100 evaluable patients per treatment group. To be evaluable for efficacy, a patient must be treated with at least 1 dose of study drug and must have all components of the SRI (baseline SLEDAI-2K total score, BILAG-2004 body system scores, and PhGA score) available.

Diagnosis and Criteria for Inclusion: Patients are included in the study if all of the following criteria are met:

(a) The patient is a man or woman between 18 and 70 years of age with an established diagnosis of SLE as defined by ACR Classification Revised Criteria. The diagnosis is fulfilled provided that at least 4 criteria are met.

(b) The patient has a positive test result for ANA at screening (titer must be at least 1:80 [by human epithelial cell tumor line (HEp-2) ANA assay]) **and/or** a positive test result for anti-dsDNA Ab at screening (value must be 30 IU/mL or more by enzyme-linked immunosorbent assay [ELISA]).

(c) Written informed consent is obtained.

(d) Women must be surgically sterile, 2 years postmenopausal, or, if of childbearing potential, using a medically accepted method of contraception, and must agree to continued use of this method for the duration of the study and for 30 days after discontinuation of study drug treatment. Acceptable methods of contraception include barrier method with spermicide, abstinence (when this is in line with the preferred and usual lifestyle of the subject), intrauterine device (IUD), or steroidal contraceptive (oral, transdermal, implanted, and injected) in conjunction with a barrier method.

(e) The patient has a SLEDAI-2K clinical score of at least 6 points **during screening**. A SLEDAI-2K clinical score is the calculated score without inclusion of the points that may be contributed by having a positive titer for anti-dsDNA Ab or decreased serum complement levels.

(f) The patient does not have an "A" score on the BILAG-2004 scale.

(g) If the patient is using oral corticosteroids, the weekly cumulative dose must not exceed 80 mg of prednisone equivalent; the weekly dose must be stable over the 4 weeks preceding the 1st dose of study drug.

(h) If the patient is using antimalarials, methotrexate, leflunomide, mycophenolate mofetil (MMF), or azathioprine, the start date must be at least 3 months prior to the 1st dose of study drug, and the daily dose must be stable over the 4 weeks preceding the 1st dose of study drug.

(i) If the patient is not currently using corticosteroids, antimalarials, methotrexate, MMF, or azathioprine, the last dose (in case of previous use) must be at least 4 weeks prior to the 1st dose of study drug. For leflunomide, the stop date must be at least 8 weeks before the 1st dose of study drug unless an adequate cholestryamine washout has been performed. If cholestyramine washout is performed, the last use of leflunomide must be at least 4 weeks before the 1st dose of study drug.

(j) The patient must be willing and able to comply with study restrictions, to remain at the study center for the required duration during each study visit, and to return to the study center for the final assessment as specified in this protocol.

Criteria for Exclusion: Patients are excluded from participating in this study if 1 or more of the following criteria are met:

(a) The patient has been treated with intramuscular or intravenous (iv) pulse steroids (ie, 250 to 1000 mg iv total daily dose of methylprednisolone) within 4 weeks of the 1st dose of study drug. The use of intra-articular steroids may be allowed after consultation with the medical expert.
(b) The patient has received tacrolimus, cyclosporin A, or iv immunoglobulins (IVIG) within 3 months of the 1st dose of study drug.
(c) The patient has received cyclophosphamide within 6 months prior to the 1st dose of study drug.
(d) The patient has been treated for SLE with agents such as fusion proteins, therapeutic proteins, or monoclonal antibodies or antibody fragments, within 6 months of the 1st dose of study drug.
(e) The patient has received B-cell depleting agents such as rituximab, belimumab or epratuzumab within one year of the 1st dose and has not yet normalized the B-cell count (ie, $CD20^+$ B-cell count is less than normal range and the absolute lymphocyte count [ALC] is less than normal range).
(f) The patient has New York Heart Association (NYHA) Class III or IV congestive heart failure.
(g) The patient has an estimated glomerular filtration rate (eGFR) of less than 30 mL/min/1.73 m^2 (via Modification of Diet in Renal Disease [MDRD] equation).
(h) The patient has an aspartate aminotransferase (AST) or alanine aminotransferase (ALT) value greater than 2 times the upper limit of the normal range (ULN) or a total bilirubin level greater than 1.5 times ULN.
(i) The patient has a planned immunization with a live or live attenuated vaccine within 3 months prior to administration of the 1st dose of study drug and for 3 months after administration of the last dose of study drug.
(j) The patient has any clinically significant abnormalities on ECG that are not related to SLE, as determined by the investigator. Patients with stable ECG changes without evidence of active cardiovascular disease may participate at the discretion of the investigator and medical monitor.
(k) The patient has an ongoing active systemic infection requiring treatment or a history of severe infection, such as hepatitis or pneumonia, in the 3 months prior to administration of the 1st dose of study drug. Less severe infections in the 3 months prior to administration of the 1st dose of study drug are permitted at the discretion of the investigator and medical monitor.
(l) The patient has any concomitant medical condition unrelated to SLE that may interfere with his or her safety or with evaluation of the study drug, as determined by the investigator.
(m) The patient has a history of a medical condition other than SLE that has required treatment with oral corticosteroids in excess of 80 mg of prednisone equivalent/week within 3 months of the 1st dose of study drug.
(n) The patient has a positive test result for hepatitis B surface antigen (HBsAg) or hepatitis C virus antibody (HCV Ab).
(o) The patient has a known positive history of antibodies to human immunodeficiency virus (HIV) or HIV disease or other immunosuppressive state (eg, agammaglobulinemia, etc).
(p) The patient has a history of alcohol or substance dependence or abuse (with the exception of nicotine),according to the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association, Fourth Edition, Text Revision (DSM-IV-TR), within 3 months of the screening visit or has current substance abuse.
(q) The patient has a history of severe allergic reactions to or hypersensitivity to any component of the study drug or placebo.
(r) The patient has undergone or is undergoing treatment with another investigational drug for the treatment of lupus within 6 months prior to the 1st dose of study drug or has received any other investigational drug for any other condition within 4 weeks prior to the 1st dose of study drug.
(s) The patient has previously participated in a ImmuPharma- or ImmuPharma-sponsored clinical study with IPP-201101.
(t) The patient is a pregnant or lactating woman. (Any women becoming pregnant during the study will be withdrawn from the study.)
(u) The patient is unlikely to comply with the study protocol or is unsuitable for any other reason, as judged by the investigator or medical monitor.

Study Drug Dose, Mode of Administration, and Administration Rate:
Investigational Product: IPP-201101 is a white to off-white, amorphous powder and is supplied in single-dose

glass vials as lyophilized product for reconstitution. Before reconstitution, vials of study drug must be stored under refrigerated conditions (2° to 8° C [36° to 46° F]) in a secure place and protected from light. Each vial contains a sterile formulation of 220 mcg of IPP-201101, mannitol (and acetic acid used for pH adjustment, if necessary). This product does not contain preservatives. The study center will receive box(es) with up to 13 vials per box. Each vial will be labeled with a 4-digit treatment number and each box will contain IPP-201101. Prior to administration, IPP-201101 should be reconstituted with 1.1 mL sterile water for injection (volume of injection of 1.0 mL). After reconstitution, the vial can be stored at controlled room temperature (20° to 25° C [68° to 77° F]) for up to 2 hours prior to administration and does not need to be protected from light. Patients randomly assigned to IPP-201101 will be administered a dosage of 200 mcg subcutaneously (sc) every 4 weeks for 48 weeks (a total of 13 doses will be administered).

Placebo: Placebo vials matching the single-dose vials of IPP-201101 will be supplied by ImmuPharma. Each vial contains a white to off-white, amorphous powder as a lyophilized sterile formulation of mannitol (and acetic acid used for pH adjustment, if necessary). Before reconstitution, vials of placebo must be stored under refrigerated conditions (2° to 8° C [36° to 46° F]) in a secure place and protected from light. The study center will receive box(es) with up to 13 vials per box. Each vial will be labeled with a 4-digit treatment number and each box will contain placebo vials. Prior to administration, placebo should be reconstituted with 1.1 mL sterile water for injection (volume of injection of 1.1 mL). After reconstitution, the vial can be stored at controlled room temperature (20° to 25° C [68° to 77° F]) for up to 2 hours prior to administration and does not need to be protected from light. Patients randomly assigned to placebo will be administered placebo sc every 4 weeks for 48 weeks (a total of 13 doses will be administered).

Method of Blinding: Patients will be randomly assigned to treatment through a qualified randomization service provider (eg, interactive response technology [IRT]). Patients and investigators will remain blinded to treatment assignment during the study. Study drug may not be administered by the same individual performing the SLEDAI-2K, BILAG-2004, or PhGA. Study drug should be administered at each study visit after all study visit procedures and assessments have been completed.

Duration of Participation: This study will consist of a screening period up to 2 weeks and a 48-week treatment period. Patients will return to the study center approximately 4 weeks after administration of the last dose of study drug (at 48 weeks) for the final assessment (week 52). Patients are expected to participate in the study for up to approximately 54 weeks.

General Design and Methodology: This is a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of a 200-mcg dose of IPP-201101 plus standard of care (SOC) compared with placebo plus SOC in patients with active SLE. The study consists of a 2-week screening period (visit 1), a 48-week treatment period beginning with a baseline visit in which randomization will be completed and study drug treatment will start (visit 2 and visits 4 through 14), and a final assessment 4 weeks after the last dose of study drug (visit 16 [week 52]). NOTE: If needed during the screening period, up to 14 additional days are permitted to confirm eligibility (eg, BILAG-2004, SLEDAI-2K, and PhGA central system assessment, laboratory results ….). In addition to the typical assessments obtained at the screening visit, such as obtaining medical, psychiatric, and medication history (medication history to be obtained from start of screening) and performing a physical examination and tests to determine the patients' health status and eligibility for participation in the study, procedures will include assessment of disease activity using the SLEDAI-2K and BILAG-2004 disease activity indices and the SFI, and disease marker testing (ie, at screening, anti-dsDNA Ab, C3, C4, and ANA only]). Eligibility will be confirmed by using a central system to validate the BILAG-2004, SLEDAI-2K, and PhGA assessments. Eligible patients will return to the study center at baseline and will be randomly assigned (stratified by region, SLEDAI-2K screening total score [6 to 9 or ≥10], and racial-ethnic group classification [black/Hispanic or others]) at baseline with an equal probability and in a blinded fashion to receive either IPP-201101 or placebo sc every 4 weeks for 48 weeks. Pretreatment assessments will be performed and the 1st dose of 200 mcg sc of IPP-201101 or placebo (sc) will be administered after all assessments have been completed. Patients will be monitored for systemic symptoms for at least 1 hour after the first 2 doses of study drug have been administered. For subsequent doses, patients will be monitored, at the discretion of the investigator, in the study center after study drug treatment. Patients will return to the study center 2 weeks after administration of the 1st dose of study drug for immunogenicity testing, and every 4 weeks for 48 weeks (weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48) to receive study drug. Patients may continue on their usual treatment for SLE (ie, SOC) as long as the inclusion and exclusion criteria regarding these treatments are met and the total weekly steroid dose does not exceed 80 mg of prednisone equivalent/week; the dosages for

immunosuppressive medications may change, if needed, only as directed in the protocol. Efficacy assessments include SLEDAI-2K, BILAG-2004, PhGA scale, SF-36 questionnaire, biologic markers of disease, SFI, SDI, FACIT-Fatigue scale, and change in steroid dose over time. Adverse events will be recorded throughout the study. Safety will also be assessed by evaluating clinical laboratory test results, vital signs measurements, 12-lead ECG findings, physical examination findings, assessment of suicidality using the C-SSRS, assessment for anaphylaxis using the Clinical Criteria for Diagnosing Anaphylaxis, and concomitant medication usage throughout the study. Immunogenicity will also be assessed at weeks 4, 12, 20, 28, 36, 44, and 52 by detection of any presence of anti–IPP-201101 Ab . In vitro intracellular and secreted cytokine response will be assessed at weeks 0, 4, 24 and 48 weeks to assess intracellular modification linked to the treatment. In addition to standard safety monitoring, an independent, external Data and Safety Monitoring Board (DSMB) will oversee the safety of the patients and monitor the occurrence of flare throughout the study. The DSMB will meet as specified in its charter. Blood samples for measurement of IPP-201101 plasma concentrations will be collected prior to and after study drug administration at weeks 0, 16, and 32 from patients at selected North American and Western European study centers. A blood sample for measurement of the concentration of IPP-201101 will also be obtained from all patients who have a serious adverse event and/or have an adverse event leading to withdrawal from the study. Patients who complete the 48-week treatment period will return to the study center at week 52 for final procedures and assessments. Patients who withdraw from the study before completion of the 48-week treatment period will have their final procedures and assessments performed at their last visit. Any patient with a positive test result for anti–IPP-201101 Ab at the final study visit will be followed with additional immunogenicity testing at 8-week intervals until the level returns to baseline value or the levels are judged by the investigator to be chronic, or the patient is lost to follow-up.

Primary Efficacy Variable and Endpoint: The primary efficacy variable for this study is the proportion of patients achieving a combined clinical response using the SRI at week 52. An SRI response is defined as a reduction from baseline in the SLEDAI-2K score of at least 4 points, no worsening in PhGA (with worsening defined as an increase in PhGA of more than 0.30 point from baseline), no new BILAG A body system score and no more than 1 new BILAG B body system score from baseline.

Secondary Efficacy Variables and Endpoints:

The secondary efficacy variables and endpoints for this study are as follows:

- proportion of patients achieving an SRI response at each visit during the treatment period
- proportion of patients achieving a reduction of at least 4 points in the SLEDAI-2K total score at each visit during the treatment period
- proportion of patients achieving a clinical SLEDAI-2K response at each visit during the treatment period, where the clinical response is defined as a reduction of at least 4 points in the SLEDAI-2K clinical score
- proportion of patients achieving a BILAG-2004 response at each visit during the treatment period (no new BILAG A body system score and no more than 1 new BILAG B body system score from baseline)
- proportion of patients achieving a BILAG-2004 clinical response at each visit during the treatment period (an improvement in at least 1 category from a B score to a C or D score, with no worsening in any other category)
- proportion of patients showing no worsening on a PhGA scale at each visit during the treatment period
- proportion of patients achieving a reduction of 5 points in the SLEDAI-2K total score at each visit during the treatment period
- proportion of patients achieving a reduction of 6 points in the SLEDAI-2K total score at each visit during the treatment period
- proportion of patients achieving an SRI-5 response at each visit during the treatment period
- proportion of patients achieving an SRI-6 response at each visit during the treatment period
- proportion of patients showing an improvement in tender and swollen joint counts using the 28-joint count examination for pain and tenderness at each visit during the treatment period
- SFI at each visit during the treatment period
  - time to first mild to moderate flare
  - incidence of mild to moderate flare
  - time to severe flare (NOTE: A severe flare leads to early withdrawal)
- changes in the SDI over time (assessed at screening and weeks 24 and 52 [or final assessment])
- absolute and relative changes in the SF-36 at weeks 12, 24, 36, and 52 (or final assessment)
- proportion of patients with changes in steroid dose over time throughout the study The exploratory efficacy

variables and endpoints for this study are as follows:

- changes in the biomarkers anti-dsDNA Ab, C3, and C4 at each visit during the treatment period
- changes in the following biomarkers at weeks 4, 12, 24, 36, and 52 (or final assessment):
  - ANA
  - anti–U1-70K snRNP Ab
  - anti-Sm Ab
  - CRP
  - IgG, (Ig A), IgM, and IgE
- absolute and relative changes in the FACIT-Fatigue at weeks 12, 24, 36, and 52 (or final assessment)
- in vitro intracellular and secreted cytokine response

Safety Variables and Endpoints: Safety measures and endpoints will include the following:

- occurrence of adverse events throughout the study
- clinical laboratory (serum chemistry, hematology, and urinalysis) test results at each visit during the treatment period
- vital signs (systolic and diastolic blood pressures, pulse, temperature, and body weight) measurements at each visit during the treatment period
- 12-lead electrocardiogram (ECG) findings at week 52 (or final assessment)
- physical examination findings, including physical examination symptom directed findings, at specified time points at each visit during the treatment period
- evaluation for suicidality at each visit during the treatment period using the C-SSRS
- concomitant medication usage throughout the study

Immunogenicity: The immunogenicity variable/endpoint for this study is as follows: any presence of anti–IPP-201101 Ab at visits at weeks 2, 4, 12, 20, 28, 36, 44, and 52 (or final assessment). Any patient with a positive test result for anti–IPP-201101 Ab at the final study visit will be followed with additional immunogenicity testing at 8-week intervals until the level returns to baseline value or the levels are judged by the investigator to be chronic, or the patient is lost to follow-up.

Pharmacokinetics/Pharmacodynamics: Blood samples (5 mL) for pharmacokinetics will be collected from patients at selected North American and Western European study centers via venipuncture or indwelling catheter prior to and 5 minutes and 1, 2, and 24 hours after study drug administration at weeks 0, 16, and 32 (visits 2, 7, and 11, respectively). A blood sample for measurement of the concentration of IPP-201101 will also be obtained from all patients who have a serious adverse event and/or have an adverse event leading to withdrawal from the study.

In vitro intracellular and secreted cytokine response: Blood samples (5 mL) will be collected from patients at selected study centers via venipuncture or indwelling catheter prior study drug administration at weeks 0, 4 24 and 48 (visits 2,4,9 and 15, respectively).

Statistical Considerations: The primary efficacy variable is the proportion of patients achieving a combined clinical response using the SRI at week 52. With 100 evaluable patients per group (200 total), this study will have a 90% or greater power to detect a 25% or greater difference or a 20% difference with a 80% power in the proportion of SRI responders between the IPP-201101 group and the placebo group. This projection using the Pearson Chi-square test (2-sided, alpha=0.05) is based on an anticipated placebo effect at week 52 of 40% to 45%. This range covers the placebo effect reported in the literature and in a Phase 2b, multicenter, randomized, double-blind, placebo-controlled dose-ranging study of IPP-201101 (study IP-004). The response rate under active is based on the Phase IIb study performed with the mannitol formulation outside the US. This study showed an absolute 25% response of active over placebo increasing to 40% in the interim analysis. Using a 80% or a 90%power leads to a sample size of 100 evaluable patients per group. The efficacy evaluation will be based on the full analysis set that includes all patients who received at least 1 dose of the study drug.. The statistical method to be used for the SRI is the logistic regression model with treatment and stratification factors as main factors. The SRI is linked to the model factors through the logit function. The likelihood-ratio–based Chi-square statistics will be used for testing the treatment difference between IPP-201101 and placebo in SRI at week 52 at the significance level 0.05. The odds ratio (active/placebo) and associated 95% confidence interval will be determined from the logistic regression model. As sensitivity analyses, the primary analysis will be repeated using another 3 imputation methods to estimate missing SRI at week 52 according to the reason for withdrawal. In the 1st method, patients who withdraw because of lack of efficacy will be classified as treatment failures assessed by SRI at week 52. For patients who withdraw

because of other reasons, their missing SRI at week 52 will be estimated using the multiple imputation method. The imputation values will be drawn from the categories formed by treatment group and randomization stratum to which the patient belongs. In the 2nd method, the missing SRI at week 52 will be imputed using the last observation carried forward (LOCF) method. In the 3rd method, patients who withdraw and those completers who used prohibited medication within 8 weeks from week 52 will be classified as nonresponders. Secondary efficacy variables will be summarized using the descriptive statistics by treatment group and time point. Safety evaluations will include all patients who took at least 1 dose of study drug. Descriptive statistics will be used to summary the safety variables.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Ab	antibody(ies)
ACR	American College of Rheumatology
ALC	absolute lymphocyte count
ALT	alanine aminotransferase (SGPT)
ANA	antinuclear antibodies
ANC	absolute neutrophil count
anti-dsDNA Ab	anti–double-stranded deoxyribonucleic acid antibody anti-Sm Ab anti-Smith antibody
anti–U1-70K snRNP Ab	anti–uridine rich 70 kilodalton small nuclear ribonucleoprotein particle antibody
AST	aspartate aminotransferase (SGOT)
BILAG-2004	British Isles Lupus Assessment Group 2004
BUN	blood urea nitrogen
C3	complement component 3
C4	complement component 4
CFR	Code of Federal Regulations
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CNRS	Centre National de la Recherche Scientifique
CRF	case report form
CRP	C-reactive protein
C-SSRS	Columbia-Suicide Severity Rating Scale
DAI	disease activity index
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
DSM–IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
ECG	electrocardiography, electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EU	European Union
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy–Fatigue
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
HBsAg	hepatitis B surface antigen
HCV Ab	hepatitis C virus antibody
HEp-2	human epithelial cell tumor line
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgE	immunoglobulin E
IgG	immunoglobulin G

IgM	immunoglobulin M
Ig A	immunoglobulin A
IL	interleukin
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISRB	Interim Safety Review Board
IU	International Unit
IUD	intrauterine device
iv	intravenous, intravenously
IVIG	intravenous immunoglobulins
LDH	lactate dehydrogenase
LOCF	last observation carried forward
Lupus QoL Questionnaire	Lupus Quality of Life Questionnaire
MDE	missing data estimation
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MMF	mycophenolate mofetil
NYHA	New York Heart Association
OTC	over-the-counter
P140	peptide 131-151 that has been phosphorylated at position 140
P131-151	peptide 131-151
PBL	peripheral blood leukocyte
PBMC	peripheral blood mononuclear cell
PhGA	Physician Global Assessment
PtGA	Patient Global Assessment
RBC	red blood cell
sc	subcutaneous, subcutaneously
SD	standard deviation
SDI	Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index
SDV	source document verification
SE	standard error
SELENA	Safety of Estrogens in Lupus Erythematosus: National Assessment
SF-36	Medical Outcome Survey Short Form 36
SFI	Safety of Estrogens in Lupus Erythematosus: National Assessment Flare Index
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
SLE	systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SLICC/ACR	Systemic Lupus International Collaborative Clinics/American College of Rheumatology

SOC	standard of care
SOP	standard operating procedure
SRI	systemic lupus erythematosus responder index
SUSAR	suspected unexpected serious adverse reactions
TACI/BlyS	transmembrane activator and calcium modulator and cyclophilin ligand interacter/B lymphocyte stimulator
ULN	upper limit of the normal range
US(A)	United States (of America)
VAS	visual analog scale
WBC	white blood cell
WHO	World Health Organization
WHO Drug	World Health Organization (WHO) drug dictionary

1 BACKGROUND INFORMATION

1.1 Introduction

Systemic lupus erythematosus (SLE) is a polygenic autoimmune disease characterized by B-cell hyperactivity leading to the occurrence of an array of autoantibodies, formation of immune complexes, and inflammation in different organs and tissues. In addition to the intrinsic hyperactivity of B cells, abnormalities also affect T-cell responses, the production of T-cell cytokines, and the B-T–cell dialogue. Current treatments for patients with SLE are based primarily on immunosuppressive drugs, such as corticosteroids and cyclophosphamide, which are often administered at high doses during acute exacerbation phases. Although these treatments can reduce mortality and significantly lengthen patients' life expectancies, numerous adverse effects may result because these treatments are aggressive. For example, they cause nonspecific immune suppression, and the adverse effects are sometimes worse than the disease itself (Cunningham 2007, Kang and Park 2003, Vasoo and Hughes 2005, Vial and Descotes 1995). More targeted immune suppression with monoclonal antibodies or other specific therapies is being developed to improve the benefit-risk balance ofSLE treatments. To avoid the long-term effects of immunosuppressive therapy, alternative strategies have been proposed on the basis of targeted molecular therapy, including antibodies against the B-cell–specific antigens CD20 or CD22 (rituximab and epratuzumab, respectively) or against the BlyS (transmembrane activator and calcium modulator and cyclophilin ligand interacter/B lymphocyte stimulator) pathway (atacicept and belimumab, respectively). These approaches require the identification of peptide sequences that can interfere with the final autoantibody production.

IPP-201101 for injection, also known as peptide 140, P140, CEP 3357 LUPUZOR™, rigerimod, and forigerimod (herein referred to as IPP-201101), was initially developed by ImmuPharma France SA for SLE. ImmuPharma has a collaboration agreement with a group at Centre National de la Recherche Scientifique (CNRS; Strasbourg, France), France's national scientific research institution, who identified the peptide 131–151 (P131–151) of the U1-70K snRNP self-protein as a potential candidate peptide antigen. After additional nonclinical development (see section 1.3.1), IPP-201101, a form of P131–151 where the Serine in position 140 has been phosphorylated (hence the name), was selected for further development as a potential targeted agent for SLE, and a clinical program was initiated in January 2006 (see section 1.3.2). In 2009, Cephalon acquired the worldwide rights to develop and market IPP-201101 which was reverted to ImmuPharma in 2011 (IND ownership transfer in March 2013)

This current Phase 3 study will evaluate the efficacy and safety of administration of subcutaneous (sc) IPP-201101 in patients with active SLE.

1.2 Name and Description of Investigational Product

The investigational Product is supplied in 2-mL vials containing 220 mcg of IPP-201101 as a sterile lyophilizate formulated with mannitol (and acetic acid used for pH adjustment, if necessary). Prior to administration (by sc injection), IPP-201101 is reconstituted with 1.1 mL of sterile water for injection (volume for injection of 1.0 mL).

Additional information on IPP-201101 is provided in section 3.4.

1.3 Findings From Nonclinical and Clinical Studies

1.3.1 Nonclinical Studies

1.3.1.1 Pharmacology Studies

Peptides that target specific autoreactive B and/or T cells are being actively pursued as alternatives to current treatment options for SLE.

A peptide corresponding to the sequence 131–151 of the spliceosomal U1-snRNP protein has been identified as containing an epitope recognized by T cells in SLE (Monneaux et al 2000). On exposure ex vivo to this peptide called P131–151, autoreactive $CD4^+$ T cells from lupus-prone mice undergo proliferation and secrete interleukin-2 (IL-2). Studies with P131–151 in mouse models of lupus have led to the identification of IPP-201101 (also referred to in the literature as P140), a form of P131–151 (in which the serine at position 140 is phosphorylated). The phosphorylated peptide exhibits a number of unique properties, which suggests that it may function as an immunomodulator.

In the MRL/lpr mouse model, lupus-like disease correlates with proteinuria (an indicator of renal failure) and high anti–double-stranded deoxyribonucleic acid antibody (anti-dsDNA Ab) serum levels, both of which can be attenuated by IPP-201101. Preautoimmune MRL/lpr mice were treated with either saline, or P131–151, or IPP-201101 (4 doses of 100 mcg intravenously [iv] at 4, 6, 8, and 12 weeks of age). By week 15, the control (saline) and P131–151 groups developed severe proteinuria and animals began to die. The first deaths in the IPP-201101–treated group were not observed until 22 weeks. At 38 weeks, 5 of 9 mice treated with IPP-201101 survived (p=0.02: IPP-201101 vs control), with 2 of 8 mice and 0 of 8 mice surviving in the P131–151 and control groups, respectively. Serum anti-dsDNA Ab titers and proteinuria were significantly lower in IPP-201101–treated animals (Monneaux et al 2003), demonstrating the ability of the phosphorylated form of P131–151 to reduce disease progression, severity, and mortality in a severe lupus-prone mouse model.

When incubated ex vivo with peripheral blood mononuclear cells (PBMCs) from patients with SLE, IPP-201101 did not stimulate T-cell proliferation but increased interleukin-10 (IL-10) secretion in approximately 50% of ambulatory lupus patients. . IPP-201101 had no effect on IL-10 secretion in PBMCs from healthy subjects, suggesting the ability of the phosphorylated peptide to potentially modify SLE progression (Monneaux et al 2005). On the basis of these findings (see section 1.1), IPP-201101 was selected for development as a potential treatment for

SLE. Determination of the mechanism of action of IPP-201101 in SLE has been an area of active investigation for several years, using the MRL/lpr mouse as a model system. Administration of IPP-201101 to 6-week-old MRL/lpr mice by the treatment regimen utilized for efficacy studies resulted in reduction of elevated peripheral blood leukocyte (PBL) levels in MRL/lpr mice compared with those of control CBA/J mice at 14 weeks of age (Page et al 2009; Schall et al, 2012). This effect resulted from induction of apoptosis of B cells, activated T cells and CD3+CD4-CD8-B220^{+} (double negative) T cells, which was demonstrated to be dependent on the presence of γδ T cells. Apoptosis of CD4^{+} and CD8^{+} T cells was also observed following ex vivo treatment of MRL/lpr PBLs with IPP-201101 in a process that was shown to be granzyme B- and caspase-dependent (Page et al, 2009). Experiments designed to identify the cellular receptor for IPP-201101 demonstrated binding of the peptide to the constitutively expressed chaperone protein HSPA8/HSC70 on the surface of cells (Page et al, 2009).

The consequences of the interaction of IPP-201101 with HSPA8 have recently been studied in greater detail (Page et al 2011). The expression of both HSPA8 and major histocompatibility (MHC) Class II molecules was shown to be elevated in splenic B cells from MRL/lpr mice compared with those isolated from CBA/J control mice. The levels of these proteins were decreased on treatment of the mice with IPP-201101. Since HSPA8 plays a role in autophagy and loading of endogenous peptides onto MHC class II molecules, the effect of IPP-201101 on autophagy was examined. Autophagy markers accumulated in MRL/lpr B cells treated with IPP-201101, suggesting that the peptide decreased macroautophagic flux. Later on it was demonstrated that the primary target of IPP-201101 is chaperone-mediated autophagy (CMA) with implication on macroautophagy processes (Macri et al 2015). CMA was found to be hyperactivated in MRL/lpr lupus mice and significantly attenuated after IPP-201101 in vivo treatment. As a working hypothesis, these results and notably the down regulation of excessive CMA process are interpreted to indicate that the mechanism of action of IPP-201101 involves a decrease in autoantigen processing in MRL/lpr antigen-presenting B cells, resulting in a decrease in MHCII expression followed by a reduction of autoreactive T-cell priming and signaling. Past studies have effectively shown that compared to T cells from untreated mice, CD4+ T cells from P140-treated MRL/lpr mice reacted poorly with peptides containing self-T cell epitopes (Monneaux et al., 2007). As a matter of consequence, this effect on T helper cells leads to much weaker activation of B cells that will no longer maturate into plasma cells that secrete deleterious antibodies (Macri et al. 2015; Schall et al, article submitted). A remarkable observation is that P140-treatment had no effect on T- or B-cell reactivity to non-self (for example viral) peptides (Monneaux et al. 2007, Schall et al. article submitted). Based on these data, IPP-201101 is therefore proposed to have immunomdulatory effects on antigen presenting cells, B and T cells, resulting in the observed therapeutic effect.

1.3.1.2 Toxicology Studies

The local tolerance of repeated sc administration of IPP-201101 was evaluated in 2 studies performed in rats (study 19397/05) and dogs (study 19509/05). Both studies did not reveal any significant local intolerance reactions. Histopathologic results at the injection site did not reveal any abnormal findings deemed to be related to treatment with IPP-201101.

The subchronic toxicity of IPP-201101 was evaluated in 3 repeated-dose studies performed in

rats (study 19397/05), dogs (study 19509/05), and monkeys (study CRNS UPR 9021). In these 3 studies, the administration of IPP-201101 subcutaneously (sc) for a 2-week duration did not result in overt signs of toxicity.

The chronic toxicity of IPP-201101 evaluated in rats (155 days) and dogs (239 days) when administered every 15 days for a total of 12 injections in rats and 18 injections in dogs did not result in any overt signs of toxicity.

The effects of IPP-201101 on the reproduction and embryofetal development were evaluated in 3 reproductive toxicology studies performed in mice (study CRNS UPR 9021), rats (study 20060523TR), and rabbits (study 20060524TL). In these studies, there was no evidence of teratogenicity or arbortifacient effects of IPP-201101. There were no increases in prenatal mortality and no evidence of adverse effects on the embryofetal development associated with IPP-201101 treatment.

In rats and rabbits tested with cumulative doses/kg body weight of IPP-201101, there were no signs of toxicity. These cumulative doses were, respectively, 133 and 12 times higher than the highest cumulative dose/kg that is anticipated to be used in a 1-year study in humans (Table 1).

Table 1: Comparative Doses in the Animal Toxicity Studies and the Proposed Human Clinical Study

Toxicity study	Cumulative dose	Body weight	dose/kg	Cumulative Factor
Rat toxicity (group 4)	0.2 mg x 12 inj=2.4 mg	0.24 kg (mean)	10.000 mg/kg	133
Rabbit toxicity (group 3)	0.2 mg x 14 inj=2.8 mg	3.19 kg (mean)	0.875 mg/kg	12
Human (Phase 3) (group 1), 1 year of treatment	0.2 mg x 26 inj=5.2 mg	70 kg (estimated)	0.075 mg/kg	1

inj=injections.

No single-dose toxicity studies have been conducted.

1.3.2 Clinical Studies

The safety and efficacy of IPP-201101 administered sc have been evaluated in 3 completed clinical studies. Treatment with IPP-201101 at doses ranging from 200 to 2000 mcg was generally safe and well tolerated when administered to 18 healthy subjects and 121 patients with SLE in these Phase 1, 2a, and 2b clinical studies. Injection site adverse events were mild in severity and dose related. To date, the reported serious adverse events are due in part to the patients' underlying disease. Data are insufficient to determine the long-term effect of peptide-based therapy on immune competence. More details of the design and results of the completed studies are provided below.

1.3.2.1 Safety and Tolerability Results From a Completed Phase 1 Study in Healthy Men

The Phase 1 study (study IPP-LU.01-05) was a double-blind, placebo-controlled, single-ascending-dose study to investigate the safety, tolerability, and pharmacokinetic profiles of IPP-201101 in 24 healthy men in France. Subjects were treated with an sc injection of either

IPP-201101 or placebo in 3 successive treatment groups (group 1: 500 mcg, group 2: 1000 mcg, and group 3: 2000 mcg), starting with the lowest dose. Each treatment group consisted of 8 subjects and, in each group, 6 subjects received IPP-201101 and 2 subjects received placebo. Subjects were administered the next highest dose only if the preceding dose was safe and well tolerated. During the study, 3 subjects reported a total of 3 adverse events. One adverse event (transient swelling at the injection site appearing 1 hour after injection of the 2000-mcg dose) was considered by the investigator to be possibly related to study drug treatment.

This adverse event was of mild intensity. The other adverse events (ie, headache and bilateral paresthesias of the abdominal wall) were reported after administration of 500 mcg of IPP-201101 and placebo, respectively, and were of moderate intensity. Overall, local tolerability at the injection site was good. No trends or clinically relevant changes from baseline were observed in clinical laboratory test results, vital signs measurements, and 12-lead electrocardiogram (ECG) or physical examination findings.

Although plasma samples were collected for pharmacokinetic analysis, pharmacokinetic parameters could not be calculated because the plasma concentrations were below the lower limit of quantitation of the available assay.

1.3.2.2 Efficacy and Safety Results From a Completed Phase 2a Study in Patients With Systemic Lupus Erythematosus

The Phase 2a study (study IP-002) was an open-label, multiple-dose, 12-week study conducted in Bulgaria to evaluate the efficacy and safety of treatment with IPP-201101 in 20 patients with SLE who had elevated anti-dsDNA Ab titers (more than 70 IU/mL by enzyme-linked immunosorbent assay [ELISA]) at study entry. Two dose levels of IPP-201101 (200 and 1000 mcg) were evaluated in 2 cohorts of 10 patients each. Patients were administered 3 sc injections of IPP-201101 (either 200 or 1000 mcg) on study days 1, 15, and 29, with follow-up visits on study days 8, 43, and 57. For the 200-mcg treatment group, long-term follow-up visits were also conducted at months 4, 5, and 6. Study treatment with 1000 mcg was initiated after the planned interim review of the safety data, up to and including day 15, by the Interim Safety Review Board (ISRB) from all patients receiving 200 mcg.

In this study, there was a clinically meaningful response for patients who received 2 sc injections of 200 mcg of IPP-201101 on study days 1, 15, and 29, as assessed by decrease in anti-dsDNA Ab levels (7 patients had reductions in anti-dsDNA Ab titer of least 20% at study day 43, and 5 patients had a reduction of at least 20% at study day 57; response was sustained in 3 patients at month 6) and reduction from baseline of at least 4 points in the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score (6 patients). In the 1000-mcg treatment group, 1 patient had a reduction of at least 20% in anti-dsDNA Ab titer at study day 43 or study day 57. The average value for anti-dsDNA Ab titer was unchanged over the 6-week follow-up period after completion of study treatment in the 1000-mcg treatment group.

In addition to the 6 patients in the 200-mcg treatment group who were responders by SLEDAI (defined as a reduction from baseline of at least 4 points in the SLEDAI score), 4 patients in the 1000-mcg treatment group were responders by SLEDAI. Five of the 6 responding patients in the 200-mcg treatment group also had at least a 20% reduction in anti-dsDNA Ab titer, whereas 1 of

4 patients in the 1000-mcg treatment group had both a reduction in SLEDAI score and a reduction in anti-dsDNA Ab titer at study day 57.

There were no serious adverse events or withdrawals because of adverse events in the study. Nine (45%) patients experienced a total of 12 adverse events during the course of the study. Adverse events attributed to IPP-201101 treatment were mild dose-related injection site reactions. Injection site reactions were reported more frequently in the high-dose group. In the 200-mcg dose group, 1 patient (10%) experienced mild erythema at the injection site, and 6 patients (60%) in the 1000-mcg dose group experienced injection site reactions. In both treatment groups, reactions at the injection site were mild and resolved within 1 hour. Excluding local injection site reactions, the incidence of adverse events was low, with 2 (10%) patients experiencing an adverse event, including 1 case of muscular pain and 1 case of nausea. Both events occurred in the 1000-mcg dose group. No clinically significant changes in clinical laboratory (hematology, chemistry, or urinalysis) or vital signs results were reported during the study.

1.3.2.3 Efficacy and Safety Results From a Completed Phase 2b Study in Patients With Active Systemic Lupus Erythematosus

The Phase 2b study (study IP-004) was a multicenter, randomized, double-blind, placebo-controlled, dose-ranging study conducted in Bulgaria, Romania, Spain, and Argentina to evaluate the efficacy and safety of treatment with IPP-201101 in patients
with active SLE. Patients were randomly assigned to 1 of 3 treatment groups, as follows:

(1) 200 mcg of IPP-201101 sc every 4 weeks (3 sc injections at baseline and weeks 4 and 8; total dose of 600 mcg) and 3 sc injections of matching placebo at weeks 2, 6, and 10, plus standard of care (SOC)

(2) 200 mcg of IPP-201101 sc every 2 weeks (6 sc injections at baseline and weeks 2, 4, 6, 8, and 10; total dose of 1200 mcg) plus SOC

(3) placebo sc every 2 weeks (6 sc injections at baseline and weeks 2, 4, 6, 8, and 10) plus SOC

A total of 204 patients were planned to be enrolled in this study. The primary efficacy variable for the study was the SLE responder index (SRI) at week 12. The SRI was defined as a reduction from baseline in the SLEDAI 2000 (SLEDAI-2K) total score of at least 4 points, no worsening in Physician's Global Assessment (PhGA) (with worsening defined as an increase in PhGA of more than 0.30 point from baseline), no new British Isles Lupus Assessment Group A (BILAG A) body system score, and no more than 1 new BILAG B body system score from baseline. Statistical significance was assessed at alpha=0.025.Two interim analyses were conducted. The 1st interim analysis was conducted and data reviewed in December 2008 when 125 patients enrolled in the study completed 12 weeks of study drug treatment and had at least 1 efficacy measurement. After data from the 1st interim analysis were reviewed, a decision about the future clinical development of IPP-201101 was made, and enrollment of additional patients into the study was stopped. At this time, 150 patients had been enrolled in the study. The 2nd interim analysis was performed in June 2009 when the 125 patients from the 1st interim analysis completed the study (through week 24). At week 12, there was a statistically significant

difference (p=0.012) in favor of IPP-201101 for the SRI response in patients who received 200 mcg of IPP-201101 every 4 weeks compared with those who received placebo every 2 weeks. At the final analysis, data were analyzed for 150 patients who completed 12 weeks of randomized study treatment and the 24-week follow-up visit or who withdrew from the study. A total of 150 patients (49 patients 200 mcg of IPP-201101 every 4 weeks, 52 patients 200 mcg of IPP-201101 every 2 weeks; and 49 patients placebo every 2 weeks) received study drug. A total of 96.0% of the patients were women; the mean age of the patients was 37.6 years. At week 12, a greater proportion of patients who were receiving 200 mcg of IPP-201101 every 4 weeks (53.1%) achieved an SRI response (p=0.048) compared with those receiving placebo (36.2%). Similarly, 53.1% of patients receiving 200 mcg of IPP-201101 every 4 weeks achieved a clinical response as assessed by SLEDAI-2K at week 12 compared with 38.3% of those who were receiving placebo (p=0.073). Patients receiving 200 mcg of IPP-201101 every 2 weeks showed a response rate of 45.1% each for the SRI response and the clinical response as assessed by SLEDAI-2K, but the differences were not statistically significant when compared with those who were receiving placebo (36.2% for SRI response [p=0.185] and 38.3% for clinical response as assessed by SLEDAI-2K [p=0.248]). In a subgroup analysis of patients with a SLEDAI-2K clinical score of at least 6 at baseline, at week 12, a greater proportion of patients receiving 200 mcg of IPP-201101 every 4 weeks (61.9%) achieved a statistically significant (p=0.016) SRI response compared with those receiving placebo (38.6%). At week 12, the proportion of patients receiving 200 mcg of IPP-201101 every 2 weeks (47.9%) and achieving an SRI response was also higher than that for those receiving placebo (38.6%); however, the difference was not statistically significant (p=0.185). For the subgroup analysis, at week 24, the differences between these groups were not statistically significant ($p \geq 0.113$; 69.0% for patients receiving 200 mcg of IPP-201101 every 4 weeks, 56.5% for those receiving placebo, and 62.5% for those receiving 200 mcg of IPP-201101 every 2 weeks).

At the final analysis, 65 patients (43.3%) reported a total of 202 adverse events. The majority of adverse events were mild or moderate in severity and considered by the investigator to be not related to study drug treatment. The most frequently reported adverse events overall (those occurring in more than 2% of patients) were urinary tract infection, nasopharyngitis, pharyngitis, influenza, bronchitis, nausea, diarrhea, injection site erythema, and headache. The most frequently reported adverse events in the IPP-201101 treatment groups (those occurring in more than 2% of patients) were urinary tract infection, nasopharyngitis, bronchitis, nausea, injection site erythema, and headache. The most frequently reported adverse events in the placebo group (those occurring in more than 2% of patients) were urinary tract infection, pharyngitis, pneumonia, herpes zoster, diarrhea, and conjunctivitis.

Four serious adverse events were reported in 4 patients who have received IPP-201101, including 3 patients who received 200 mcg of IPP-201101 every 4 weeks (gastritis [1 patient], soft tissue infection [1 patient], and pneumonia [1 patient; event led to death of patient]) and 1 patient who received 200 mcg of IPP-201101 every 2 weeks (herpes viral pneumonia). Three serious adverse events were reported in 3 patients who have received placebo (pneumonia in 2 patients and diverticulitis in 1 patient). In the patients who received IPP-201101, of these events, soft tissue infection and herpes viral pneumonia were considered by the investigator to be related to study drug treatment with IPP-201101. Among the placebo patients, both events of pneumonia were considered by the investigator to be related to study drug treatment.

The patient who died because of a serious adverse event of pneumonia was receiving 200 mcg of IPP-201101 every 4 weeks; this event was considered by the investigator to be not related to study drug treatment. The pneumonia occurred 3 days after the patient had received the 4th dose of study drug, which was 19 days after the last dose of IPP-201101. The patient, who was being treated with azathioprine and prednisone at study entry, had pain around the back base of the right lung and hemoptysis. The patient was hospitalized and treated for pneumococcal pneumonia. Treatment in the intensive care unit was required and included mechanical ventilation, antibiotics, steroids, and pressor support. Treatment was complicated by the development of acinetobacter line sepsis. In the investigator's opinion, the pneumonia was not related to treatment with IPP-201101, although the concomitantly administered immunosuppressive medication was considered a contributing factor to the development of pneumonia.

Injection site reactions were more frequently reported in the IPP-201101 treatment groups than in the placebo group. Overall, 17 injection site reactions were reported for 11 patients. Four events were reported in 3 patients who received 200 mcg every 4 weeks, 12 events were reported in 7 patients who received 200 mcg every 2 weeks, and 1 event was reported in 1 patient who received placebo. All events were mild in severity. However, infections such as those listed above did not appear to be more frequently reported in the IPP-201101 treatment groups compared with the placebo group. No clinically significant changes in hematology, chemistry, urinalysis, vital signs results, or ECG findings were reported during the course of the study.

There were 2 additional events of interest reported during the study in 2 patients who each received 200 mcg of IPP-201101 every 4 weeks (1 pregnancy and 1 intraductal breast papilloma). One patient became pregnant and was withdrawn from the study because of this event. The patient delivered a healthy baby at 37 weeks. During the course of the pregnancy, the patient experienced a urinary tract infection, high blood pressure, and proteinuria; the high blood pressure and proteinuria required hospitalization.

Another patient had a nonserious adverse event of an intraductal breast papilloma (a benign tumor of the breast). The event was mild in intensity and considered by the investigator to be unlikely related to study drug treatment. The outcome of this event was resolved. (Zimmer et al. ACR 2012)

1.3.2.4 Efficacy and Safety Results from a Completed Phase 2b Study with trehalose formulation in patients with Active Systemic Lupus Erythematosus

One clinical study have been completed in the CEP 33457 clinical program developed by TEVA former Cephalon.

TEVA, former Cephalon has sponsored an US Phase 2b (Study C33457/2047), randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of a 200 mcg dose of IPP-201101 given every 4 weeks compared with placebo in patients with active SLE. The study consists of a 2-week screening period (visit 1), a 44-week treatment period beginning with a baseline visit in which randomization is completed and study drug treatment starts (visits 2 through 13), and a final assessment 4 weeks after the last dose of study drug (visit 14 [week 48]).

A trehalose formulation of IPP-201101 (P140, foregiremod) has been used. The clinical outcome was negative. IPP-201101 was ineffective with even a trend to be less effective than placebo (D = - 6 %).

1.4 Known and Potential Risks and Benefits to Human Subjects

Treatment with IPP-201101 was generally safe and well tolerated when administered to both healthy subjects and patients with SLE. Injection site reactions were more frequently reported in the IPP-201101 treatment groups than in the placebo group. These injection site adverse events were mild in severity and dose related. The most frequently reported adverse events overall (those occurring in more than 2% of patients) in a Phase 2b study, in addition to injection site reaction, included urinary tract infection, nasopharyngitis, pharyngitis, influenza, bronchitis, nausea, diarrhea, and headache. However, infections such as those listed above did not appear to be more frequently reported in the IPP-201101 treatment groups compared with the placebo group.

To date, the reported serious adverse events are due in part to the patients' underlying disease. No clinically significant changes in hematology, chemistry, urinalysis, vital signs results, or ECG findings have been reported in the clinical program to date.

No serious related unexpected adverse event reports (suspected unexpected serious adverse reactions [SUSAR] or Investigational New Drug [IND] safety reports) had been reported.

Data are insufficient to determine the long-term effect of peptide-based therapy on immune competence.

Additional information regarding risks and benefits to human patients may be found in the current Investigator's Brochure.

1.5 Selection of Drugs and Dosages

The dosage of IPP-201101 to be evaluated in this double-blind study (ie, 200 mcg sc every 4 weeks for 48 weeks) was selected on the basis of results from a Phase 2b study (study IP-004); clinical response was observed with the 200-mcg dose after 12 weeks of study treatment. Review of available adverse event data from the Phase 2b study 2047 performed by TEVA former Cephalon with the trehalose formulation with a 44-week treatment period indicate that the 200-mcg dose is safe and well tolerated. The adverse events reported are similar to those previously reported.

A more detailed description of study drug administration is presented in section 5.1.

1.6 Compliance Statement

This study will be conducted in full accordance with the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonisation (ICH) and any applicable national and local laws and regulations (eg, Title 21 Code of Federal Regulations [21CFR] Parts 50, 54, 56, 312, and 314). Any episode of noncompliance will be documented.

The investigators are responsible for performing the study in accordance with this protocol and

the ICH and Good Clinical Practice (GCP) guidelines and for collecting, recording, and reporting the data accurately and properly. Agreement of each investigator to conduct and administer this study in accordance with the protocol will be documented in separate study agreements with the sponsor and other forms as required by national authorities.

Each investigator is responsible for ensuring the privacy, health, and welfare of the patients during and after the study and must ensure that trained personnel are immediately available in case of a medical emergency. Each investigator must be familiar with the background to, and requirements of, the study and with the properties of the study drug(s) as described in the Investigator's Brochure or package insert.

The principal investigator at each center has the overall responsibility for the conduct and administration of the study at that center and for contacts with study management, with the Independent Ethics Committee/Institutional Review Board (IEC/IRB) and with local authorities.

1.7 Population To Be Studied

It is planned that this study will enroll approximately 200 men and women between 18 and 70 years of age who have serologically active SLE with moderate disease activity on the basis of a standard assessment of disease activity, validated for use as a measure in clinical studies. To be considered for inclusion in this study, patients must have a positive test for antinuclear antibodies (ANA) and/or a positive test for anti-dsDNA Ab and a clinical SLEDAI-2K score of at least 6 points and may not have an "A" score on the BILAG-2004 scale. In addition, patients who are using or were previously using oral corticosteroids or antimalarials, methotrexate, leflunomide, mycophenolate mofetil (MMF), or azathioprine must meet certain dosage requirements regarding these drugs (see section 4.1).

1.8 Relevant Literature and Data

Relevant literature is cited above. Further literature and data may be found in the current Investigator's Brochure.

2 PURPOSE OF THE STUDY AND STUDY OBJECTIVES

2.1 Purpose of the Study

The purpose of this study is to further evaluate the efficacy and safety of IPP-201101 given every 4 weeks for up to 48 weeks, for a maximum of 13 doses. The study will evaluate the clinical response to treatment with IPP-201101 and will also include further assessment of biomarkers and change in steroid use from baseline. Safety assessments will include monitoring of adverse events, clinical laboratory test results, vital signs measurements, 12-lead ECG findings, suicidality assessments, anaphylaxis evaluations, and concomitant medication use.

2.2 Study Objectives

The primary objective of this study is to evaluate the efficacy of a 200-mcg dose every 4 weeks for 48 weeks of IPP-201101 compared with placebo in patients with active systemic lupus erythematosus (SLE) as assessed by the SLE responder index (SRI) at week 52. An SRI response is defined as a reduction from baseline in the Systemic Lupus Erythematosus Disease

Activity Index 2000 (SLEDAI-2K) score of at least 4 points, no worsening in Physician's Global Assessment (PhGA) (with worsening defined as an increase in PhGA of more than 0.30 point from baseline), no new British Isles Lupus Assessment Group A (BILAG A) body system score, and no more than 1 new
BILAG B body system score from baseline.

The secondary efficacy objectives of the study are to evaluate the following:

- the SRI response at each visit during the study
- the reduction of the SLEDAI-2K total score by at least 4 points at each visit during the treatment period
- the effect of IPP-201101 on disease activity, as assessed by the BILAG-2004 disease activity index, at each visit during the treatment period
- the effect of IPP-201101 on the status of disease (PhGA scale) at each visit during the treatment period
- the reduction of the SLEDAI-2K total score by at least 5 points at each visit during the treatment period
- the reduction of the SLEDAI-2K total score by at least 6 points at each visit during the treatment period
- the SRI-5 response at each visit during the treatment period
- the SRI-6 response at each visit during the treatment period
- the effect of IPP-201101 on arthritis, as assessed by the 28-joint count examination for pain and tenderness at each visit during the treatment period
- the effect of IPP-201101 on the incidence of disease flares (ie, Safety of Estrogens in Lupus Erythematosus: National Assessment [SELENA] Flare Index [SFI] and SLEDAI-2K score of greater than 15) at each visit during the treatment period
- the effect of IPP-201101 on the occurrence of SLE–induced organ damage (eg, Systemic Lupus International Collaborative Clinics/American College of Rheumatology [SLICC/ACR] Damage Index [SDI] and adverse event inquiry) at visits at weeks 24 and 52 (or final assessment)
- the effect of IPP-201101 on health-related quality of life, as assessed by completion of the Medical Outcome Survey Short Form 36 (SF-36) at visits at weeks 12, 24, 36, and 52 (or final assessment)
- the effect of IPP-201101 on steroid dose over time throughout the study The exploratory

efficacy objectives of the study are to determine the following:

- the effect of IPP-201101 on the following biologic markers of disease activity at each visit during the treatment period:
  - anti–double-stranded deoxyribonucleic acid antibody (anti-dsDNA Ab)
  - complement components (C3 and C4)
- the effect of IPP-201101 on the following biologic markers of disease activity at visits at weeks 4, 12, 24, 36, and 52 (or final assessment):
  - antinuclear antibody (ANA)

  - anti-uridine rich 70 kilodalton small nuclear ribonucleoprotein particle Ab (anti–U1-70K snRNP Ab)
  - anti-Smith antibody (anti-Sm Ab)
  - C-reactive protein (CRP)
  - immunoglobulin G (IgG), immunoglobulin M (IgM), immunoglobuline A (IgA) and immunoglobulin E (IgE)
- the effect of IPP-201101 on fatigue using the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-Fatigue) scale at visits at weeks 12, 24, 36, and 52 (or final assessment)
- in vitro intracellular and secreted cytokine response

The safety and tolerability of IPP-201101 will be evaluated by the following:

- occurrence of adverse events throughout the study
- clinical laboratory (serum chemistry, hematology, and urinalysis) test results at each visit during the treatment period
- vital signs (systolic and diastolic blood pressures, pulse, temperature, and body weight) measurements at each visit during the treatment period
- 12-lead electrocardiogram (ECG) findings at week 52 (or final assessment)
- physical examination findings, including physical examination symptom directed findings, at specified time points at each visit during the treatment period
- evaluation for suicidality at each visit during the treatment period using the Columbia-Suicide Severity Rating Scale (C-SSRS)
- concomitant medication usage throughout the study
- The immunogenicity of IPP-201101 will be assessed by the following: any presence of anti–IPP-201101 antibodies (anti–IPP-201101 Ab) at visits at weeks 2, 4, 12, 20, 28, 36, 44, and 52 (or final assessment

3 STUDY DESIGN

3.1 General Design and Study Schema

This is a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of a 200-mcg dose of IPP-201101 plus SOC compared with placebo plus SOC in patients with active SLE. The study consists of a 2-week screening period (visit 1), a 48 week treatment period beginning with a baseline visit in which randomization will be completed and study drug treatment will start (visit 2 and visits 4 through 14), and a final assessment 4 weeks after the last dose of study drug (visit 16 [week 52]). NOTE: If needed during the screening period, up to 14 additional days are permitted to confirm eligibility (eg, BILAG-2004, SLEDAI-2K, and PhGA central system assessments, laboratory results ….).

In addition to the typical assessments obtained at the screening visit, such as obtaining medical, psychiatric, and medication history (medication history to be obtained from start of screening) and performing a physical examination and tests to determine the patients' health status and

eligibility for participation in the study, procedures will include assessment of disease activity using the SLEDAI-2K and BILAG-2004 disease activity indices and the SFI, and disease marker testing (ie, at screening, anti-dsDNA Ab, C3, C4, and ANA only]). Eligibility will be confirmed by using a central system to validate the BILAG-2004, SLEDAI-2K, and PhGA assessments . Eligible patients will return to the study center at baseline and will be randomly assigned (stratified by region, SLEDAI-2K screening total score [6 to 9 or ≥10], and racial-ethnic group classification [black/Hispanic or others]) at baseline with an equal probability and in a blinded fashion to receive either IPP-201101 or placebo sc every 4 weeks for 48 weeks. Pretreatment assessments will be performed and the 1st dose of 200 mcg sc of IPP-201101 or placebo (sc) will be administered after all assessments have been completed. Patients will be monitored for systemic symptoms for at least 1 hour after the first 2 doses of study drug have been administered. For subsequent doses, patients will be monitored, at the discretion of the investigator, in the study center after study drug treatment.

Patients will return to the study center 2 weeks after administration of the 1st dose of study drug for immunogenicity testing, and every 4 weeks for 48 weeks (weeks 4, 8, 12,16, 20, 24, 28, 32, 36, 40, 44, and 48) to receive study drug. Patients may continue on their usual treatment for SLE (ie, SOC) as long as the inclusion and exclusion criteria regarding these treatments are met and the total weekly steroid dose does not exceed 80 mg of prednisone equivalent/week; the dosages for immunosuppressive medications may change, if needed, only as directed in the protocol. Efficacy assessments include SLEDAI-2K, BILAG-2004, PhGA scale, SF-36 questionnaire, biologic markers of disease, SFI, SDI, FACIT-Fatigue scale, and change in steroid dose over time. Adverse events will be recorded throughout the study. Safety will also be assessed by evaluating clinical laboratory test results, vital signs measurements, 12-lead ECG findings, physical examination findings, assessment of suicidality using the C-SSRS, assessment for anaphylaxis using the Clinical Criteria for Diagnosing Anaphylaxis, and concomitant medication usage throughout the study. Immunogenicity will also be assessed at weeks 4, 12, 20, 28, 36, 44, and 52 by detection of any presence of anti–IPP-201101 Ab. In addition to standard safety monitoring, an independent, external Data and Safety Monitoring Board (DSMB) will oversee the safety of the patients and monitor the occurrence of flare throughout the study. The DSMB will meet as specified in its charter.

Blood samples for measurement of IPP-201101 plasma concentrations will be collected prior to and after study drug administration at weeks 0, 16, and 32 from patients at selected North American and Western European study centers. A blood sample for measurement of the concentration of IPP-201101 will also be obtained from all patients who have a serious adverse event and/or have an adverse event leading to withdrawal from the study.

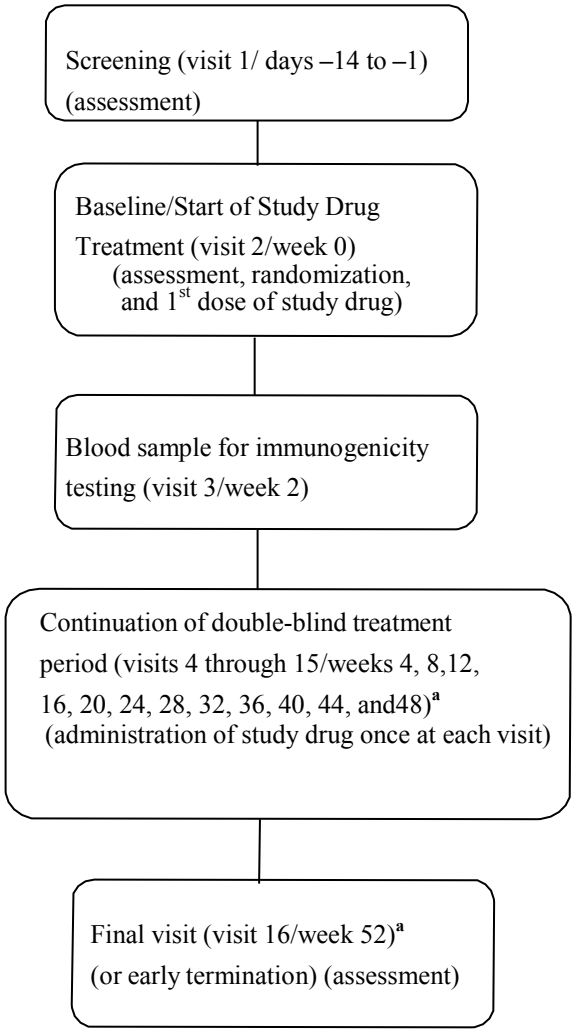
Blood samples for measurement of in vitro intracellular and secreted cytokine response will be collected prior to study drug administration at weeks 0, 4, 12, 24 and 48 from patients at selected study centers.

Patients who complete the 48-week treatment period will return to the study center at week 52 for final procedures and assessments. Patients who withdraw from the study before completion of the 48-week treatment period will have their final procedures and assessments performed at their last visit. Any patient with a positive test result for anti–IPP-201101 Ab at the final study

visit will be followed with additional immunogenicity testing at 8-week intervals until the level returns to baseline value or the levels are judged by the investigator to be chronic, or the patient is lost to follow-up. Study procedures and assessments with their timing are summarized in Table 2. Patients who complete all study visits will be eligible for participation in an open-label extension study to assess the continued effectiveness and safety of IPP-201101 treatment. .

The study schema is presented in Figure 1.

Figure 1: Overall Study Schema



[a] If patient is withdrawn from the study before completion of 48 weeks of treatment (13 doses of study drug), final procedures and assessments will be performed at early termination visit.

3.2 Primary and Secondary Measures/Variables and Endpoints

3.2.1 Primary Efficacy Measure/Variable and Endpoint

The primary efficacy variable for this study is the proportion of patients achieving a combined clinical response using the SRI at week 52. An SRI response is defined as a reduction from baseline in the SLEDAI-2K score of at least 4 points, no worsening in PhGA (with worsening defined as an increase in PhGA of more than 0.30 point from baseline), no new BILAG A body system score, and no more than 1 new BILAG B body system score from baseline.

3.2.2 Secondary Efficacy Measures/Variables and Endpoints

The secondary efficacy variables and endpoints for this study are as follows:

- proportion of patients achieving an SRI response at each visit during the treatment period
- proportion of patients achieving a reduction of at least 4 points in the SLEDAI-2K total score at each visit during the treatment period
- proportion of patients achieving a clinical SLEDAI-2K response at each visit during the treatment period, where the clinical response is defined as a reduction of at least 4 points in the SLEDAI-2K clinical score
- proportion of patients achieving a BILAG-2004 response at each visit during the treatment period (no new BILAG A body system score and no more than 1 new BILAG B body system score from baseline)

  • proportion of patients achieving a BILAG-2004 clinical response at each visit during the treatment period (an improvement in at least 1 category from a B score to a C or D score, with no worsening in any other category)
- proportion of patients showing no worsening on a PhGA scale at each visit during the treatment period
- proportion of patients achieving a reduction of 5 points in the SLEDAI-2K total score at each visit during the treatment period
- proportion of patients achieving a reduction of 6 points in the SLEDAI-2K total score at each visit during the treatment period
- proportion of patients achieving an SRI-5 response at each visit during the treatment period
- proportion of patients achieving an SRI-6 response at each visit during the treatment period
- proportion of patients showing an improvement in tender and swollen joint counts using the 28-joint count examination for pain and tenderness at each visit during the treatment period
- SFI at each visit during the treatment period
  - — time to first mild to moderate flare
  - — incidence of mild to moderate flare
  - — time to severe flare (NOTE: A severe flare leads to early withdrawal)
- changes in the SDI over time (assessed at screening and weeks 24 and 52 [or final assessment])
- absolute and relative changes in the SF-36 at weeks 12, 24, 36, and 52 (or final assessment)

proportion of patients with changes in steroid dose over time throughout the study

The exploratory efficacy variables and endpoints for this study are as follows:

- changes in the biomarkers anti-dsDNA Ab, C3, and C4 at each visit during the treatment period
- changes in the following biomarkers at weeks 4, 12, 24, 36, and 52 (or final assessment):
  - — ANA
  - — anti–U1-70K snRNP Ab

  - anti-Sm Ab
  - CRP
  - IgG, IgM, IgA and IgE
- absolute and relative changes in the FACIT-Fatigue at weeks 12, 24, 36, and 52 (or final assessment)
- in vitro intracellular and secreted cytokine response

3.2.3 Safety Measures and Endpoints

The safety and tolerability of IPP-201101 will be assessed throughout the study by evaluating adverse events; clinical laboratory results; vital signs measurements; 12-lead ECG findings; physical examination findings, including physical examination symptom directed findings; and concomitant medication usage. Suicidality will be assessed using the C-SSRS. Adverse events that are suggestive of anaphylaxis or a drug hypersensitivity reaction will be evaluated as per the Clinical Criteria for Diagnosing Anaphylaxis (Appendix I).

3.2.4 Pharmacokinetic Measure/Variable and Endpoint

A blood sample for measurement of IPP-201101 concentrations will be obtained prior to and 5 minutes and 1, 2, and 24 hours after study drug administration at weeks 0,16, and 32 (visits 2, 7, and 11, respectively) from patients at selected North American and Western European study centers.

A blood sample for measurement of the concentration of IPP-201101 will be obtained from all patients who have a serious adverse event and/or have an adverse event leading to withdrawal from the study.

3.2.5 Immunogenicity Measure/Variable and Endpoint

The immunogenicity variable/endpoint for this study is as follows:

- any presence of anti–IPP-201101 Ab at visits at weeks 2, 4, 12, 20, 28, 36, 44, and 52 (or final assessment)

Any patient with a positive test result for anti–IPP-201101 Ab at the final study visit will be followed with additional immunogenicity testing at 8-week intervals until the level returns to baseline value or the levels are judged by the investigator to be chronic, or the patient is lost to follow-up.

3.3 Randomization and Blinding

This is a randomized, double-blind, placebo-controlled study. To balance the distribution of the standard of care at baseline among the patients, the randomization will be stratified for 3 baseline characteristics, as follows: by region, SLEDAI-2K screening total score (6 to 9 or ≥10), and racial-ethnic group classification (black/Hispanic or others). Within each stratum, eligible patients will be randomly assigned with a 1:1 ratio to receive either 200 mcg of IPP-201101 or placebo sc every 4 weeks for 48 weeks.

The randomization code will be generated by ImmuPharma or its designee following specifications from the Biometrics Department. A statistician not assigned to the study will be responsible for review and approval of the randomization code, and the final randomization code will be maintained by ImmuPharma or its designee t. ImmuPharma clinical personnel involved in the study will also be blinded to the study drug identity until the database is locked for analysis and the treatment assignment revealed.

Patients will be randomly assigned to treatment through a qualified randomization service provider (eg, interactive response technology [IRT]). Upon receiving the required patient identification, region, SLEDAI-2K screening total score, and racial-ethnic group classification, the IRT will assign the new patient to the next available randomization code within the randomization stratum for the appropriate region, SLEDAI-2K screening total score, and racial-ethnic group classification categories according to the sequence that is specified by ImmuPharma.

Patients and investigators will remain blinded to treatment assignment during the study.

3.4 Study Drugs and Dosage

3.4.1 Investigational Product and Dosage

IPP-201101 is a white to off-white, amorphous powder and is supplied in single-dose glass vials as lyophilized product for reconstitution. Before reconstitution, vials of study drug must be stored under refrigerated conditions (2° to 8° C [36° to 46° F]) in a secure place and protected from light. Each vial contains a sterile formulation of 220 mcg of IPP-201101, 59 mg of mannitol (and acetic acid used for pH adjustment, if necessary). This product does not contain preservatives. The study center will receive box(es) with up to 13 vials per box. Each vial will be labeled with a 4-digit treatment number and each box will contain IPP-201101. Prior to administration, IPP-201101 should be reconstituted with 1.1 mL sterile water for injection (volume of injection of 1.0 mL). After reconstitution, the vial can be stored at controlled room temperature (20° to 25° C [68° to 77° F]) for up to 2 hours prior to administration and does not need to be protected from light. Patients randomly assigned to IPP-201101 will be administered a dosage of 200 mcg sc every 4 weeks for 48 weeks (a total of 13 doses will be administered).The pharmacy manual provided by ImmuPharma or its designee includes details on storage, administration, reconstitution, syringe information, and preparation of the Investigational Product. A more detailed description of the administration procedures is given in section 5.1.

3.4.2 Other Study Drugs and Dosage

Placebo vials matching the single-dose vials of IPP-201101 will be supplied by ImmuPharma or its designee. Each vial contains a white to off-white, amorphous powder as a lyophilized sterile formulation of mannitol dehydrate (and acetic acid used for pH adjustment, if necessary). Before reconstitution, vials of placebo must be stored under refrigerated conditions (2° to 8° C [36° to 46° F]) in a secure place and protected from light. The study center will receive box(es) with up to 13 vials per box. Each vial will be labeled with a 4-digit treatment number and each box will contain placebo vials. Prior to administration, placebo should be reconstituted with 1.1

mL sterile water for injection (volume of injection of 1.0 mL). After reconstitution, the vial can be stored at controlled room temperature (20° to 25° C [68° to 77° F]) for up to 2 hours prior to administration and does not need to be protected from light. Patients randomly assigned to placebo will be administered placebo sc every 4 weeks for 48 weeks (a total of 13 doses will be administered).

The pharmacy manual provided by ImmuPharma includes details on storage, administration, reconstitution, syringe information, and preparation of placebo. A more detailed description of the administration procedures is given in section 5.1.

3.5 Duration of Patient Participation

This study will consist of a screening period up to 2 weeks and a 48-week treatment period. Patients will return to the study center approximately 4 weeks after administration of the last dose of study drug (at 48 weeks) for the final assessment (week 52). Patients are expected to participate in the study for up to approximately 54 weeks.

3.6 Stopping Rules and Discontinuation Criteria

A patient may discontinue participation in the study at any time for any reason (eg, lack of efficacy, consent withdrawn, or adverse event). The investigator and/or sponsor can withdraw a patient from the study at any time for any reason (eg, protocol violation or deviation as defined in section 11.1.2, noncompliance, or adverse event).

An independent, external DSMB will oversee the safety of the patients enrolled in the study and monitor the occurrence of flare throughout the study. The DSMB will meet as specified in its charter. The DSMB may recommend stopping the study for safety concerns. Toxicity will be monitored using the Modified World Health Organization (WHO) Toxicity Criteria, which includes graded adverse events on a scale from 0 to 4 (see Appendix A).Individual patients will be withdrawn from the study if any of the following occur:

Event	Rule for withdrawing patient
Grade 2 event	The patient will be treated according to the investigator's usual standard of care (SOC). If the event does not improve to grade 1 or less within 4 weeks from the onset of grade 2 severity, the medical monitor should be contacted to determine if the patient should be withdrawn from the study.

Grade 3 event (one grade 3 event not related to treatment)	The patient will be treated according to the investigator's usual SOC. If the event does not improve to grade 1 or less within 4 weeks from the onset of grade 3 severity, the medical monitor should be contacted to determine if the patient should be withdrawn from the study.
Grade 3 event (one grade 3 event related to treatment or two grade 3 events not related to treatment)	The patient will be withdrawn from the study.
Grade 4 event (any grade 4 event, related or not related to treatment)	The patient will be withdrawn from the study.
Pregnancy	The patient will be withdrawn from the study.
Serious intercurrent illness or significant worsening of intercurrent illness (eg, diagnosis of any cancer, lymphoma or leukemia, anaphylaxis, severe infections)	The patient will be withdrawn from the study.
Severe flare	The patient will be withdrawn from the study.

This study may be prematurely terminated if, in the opinion of the DSMB or the sponsor, there is sufficient and reasonable cause. Written notification documenting the reason for study termination will be provided by the terminating party to all involved.

In order to ensure patient safety, patients who are determined to be treatment failures will be withdrawn from the study. Patients may be treated for treatment failure at the discretion of the investigator. Treatment failure is defined as any of the following:

- occurrence of a severe flare according to the SFI (also results in withdrawal from the study)
- increase in use of background oral corticosteroids beyond 80 mg of prednisone equivalent/week. (NOTE: Treatment of mild/moderate flare is permitted as detailed in section 5.2. The use of steroids for the treatment of a mild or moderate flare or for the treatment of conditions other than SLE will not be permitted beginning at week 44 [visit 14] through week 52 [visit 16].)
- initiation of pulse iv steroid therapy (ie, 250 to 1000 mg iv total daily dose of methylprednisolone)
- increase in the dose of immunosuppressive agents (methotrexate, azathioprine, MMF, leflunomide) above the baseline level
- initiation of new immunosuppressive therapy (cyclophosphamide, methotrexate, azathioprine, cyclosporin, tacrolimus, leflunomide, MMF)

- initiation of therapy with biologics for the treatment of SLEte, azathioprine, cyclosporin, tacrolimus, leflunomide, MMF)

3.7 Study Drug Supply and Accountability

3.7.1 Study Drug Storage and Security

Before reconstitution, vials of the study drug must be stored under refrigerated conditions (2° to 8°C [36° to 46° F]) in a secure place and protected from light.

3.7.2 Study Drug Accountability

Each study drug shipment will include a packing slip, explaining the contents of the shipment, and drug return instructions and forms.

The investigator is responsible for ensuring that deliveries of study drug and other study materials from the sponsor are correctly received and recorded, handled and stored safely and properly in accordance with the CFR or local regulations, and used in accordance with this protocol.

A record of study drug accountability (ie, study drug and other materials received, used, returned, or destroyed) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies. Empty, partially used, and unused vials of study drug will be destroyed at the study center or returned to ImmuPharma or its designee.

3.8 Maintenance of Randomization and Blinding

The final randomization code will be maintained by the Development Manufacturing group. At the time of analyses, when treatment codes are to be revealed, ImmuPharma or its designee will provide the randomization code to the statistician assigned to this study.

Individuals responsible for sample bioanalysis will know which patients received IPP-201101 and which received placebo during the study for all patients for whom sample bioanalysis and pharmacokinetic data analysis is conducted. Bioanalytical staff will not have access to any clinical data and will provide concentration data to other staff members during the study in a manner that will not identify individual patients (ie, a dummy patient identifier will be linked with an individual patient's concentration data).

In the case of an emergency, if it is necessary to know what treatment a specific patient has received, the investigator may determine the patient's treatment using IRT after consultation with ImmuPharma or its designee. In an extreme emergency, if the investigator is unable to contact ImmuPharma or its designee, the investigator may determine the patient's treatment using IRT without prior authorization. When this occurs, the investigator must contact the individual identified in the clinical study personnel contact information section of this protocol immediately; the patient will be withdrawn from the study, and the event will be recorded on the study completion record of the case report form (CRF). Proper documentation must be maintained when a treatment code is revealed. For a serious and unexpected adverse event

considered related to the study drug or study procedure, ImmuPharma or its designee may independently request that the treatment code be revealed (on a case-by-case basis). If this occurs, Biometrics Department personnel involved in analysis of the data will remain blinded to treatment.

3.9 Source Data Recorded on the Case Report Form

All patient data must have supportive source documentation in the medical records, or equivalent, before they are transcribed onto the CRF. Data may not be recorded directly onto the CRF and considered as source data unless the study center obtains written documentation from ImmuPharma or its designee or its designee, prior to the beginning of the study, indicating which data are permitted to be recorded directly on to the CRF. Source documents, including test results and/or assessments (eg, clinical laboratory test results, ECG data and assessments, efficacy measurements) collected or performed by institutions outside of the study center, are retained by the study center (see section 13.2.1). The CRFs are filed in the ImmuPharma central file.

3.10 Time Schedule

The study started in the 1st quarter of 2016 and expected be completed in the 1st quarter of 2018, with a study duration of approximately 36 months. It is anticipated that approximately 270 patients may be screened for participation in the study prior to completion of enrollment. Approximately 200 patients from approximately 50 centers globally are planned to be enrolled in the study. Patient enrollment accrual is expected to occur at an average rate of 0.60 patient/month/center. Patient enrollment will end when the planned number of enrolled patients is reached, unless the study is terminated early.

These accrual rates are based on available retrospective data from similar studies in this patient population. Each investigator should make every effort to ensure that the planned accrual rate is maintained, that CRFs are completed promptly and completely, and that data quality is maintained at all times. Each investigator should discuss with the study monitor any anticipated problems with recruitment or delays in study completion.

3.11 Study Procedures

Study procedures and assessments with their timing are summarized in Table 2.

Table 2: Study Procedures and Assessments

	Pretreatment	Treatment										FV/ET
	V1	V2	V3	V4	V5	V6	V7/V8	V9	V10/V11	V12	V13/V14/V15	V16
Procedures and assessments	**Screening D –14 to –1**	**BL/Start study treatment W0**	**W2**	**W4**	**W8**	**W12**	**W16/W20**	**W24**	**W28/W32**	**W36**	**W40/W44/W48[a]**	**W52[a]**
Informed consent	X											
I/E criteria review[b]	X	X										
Medical/psychiatric history	X											
PE	X[c]											X[d]
PE symptom directed[d]		X		X	X	X	X	X	X	X	X	
Clinical laboratory tests (serum chemistry,[e] hematology,[f] urinalysis[g])	X	X		X	X	X	X	X	X	X	X	X
HBsAg, HCV Ab	X											
ANA	X	X		X		X		X		X		X
Anti-dsDNA Ab, C3, C4	X	X		X	X	X	X	X	X	X	X	X
Anti–U1-70K snRNP Ab, anti-Sm Ab, CRP, IgG, IgM, IgE, IgA		X		X		X		X		X		X
Hemolysis tests[h]	X											
Pharmacokinetic samples[i]		X					X[i]		X[i]			
Immunogenicity samples[j]		X	X	X		X	X[j]		X[j]	X	X[j]	X
In vitro intracellular and secreted cytokine response		X		X				X			X	
Vital signs[k]	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[l]	X	X		X	X	X	X	X	X	X	X	X
12-lead ECG	X											X
Concomitant medication review	X[m]	X	X	X	X	X	X	X	X	X	X[m]	X[m]
Adverse event inquiry[n]	X	X	X	X	X	X	X	X	X	X	X	X
SLEDAI-2K[o]	X	X		X	X	X	X	X	X	X	X	X
BILAG-2004[o]	X	X		X	X	X	X	X	X	X	X	X
28-joint count exam for pain and tenderness		X		X	X	X	X	X	X	X	X	X
SFI[v] (,Safety of Estrogens in Lupus Erythematosus: National Assessment [SELENA] Flare Index)	X	X		X	X	X	X	X	X	X	X	X
SDI[o](Systemic Lupus International Collaborative Clinics/American College of Rheumatology [SLICC/ACR] Damage Index)	X							X				X
SF-36		X				X		X		X		X
PhGA[v]		X		X	X	X	X	X	X	X	X	X
FACIT-Fatigue		X				X		X		X		X
C-SSRS[p]		X		X	X	X	X	X	X	X	X	X
Access IRT	X[q]	X[r]		(X)[r]	(X)[r]	(X)[r]	(X)[r]	(X)[r]	(X)[r]	(X)[r]	(X)[r]	X[s]
Study drug administration[t,u]		X		X	X	X	X	X	X	X	X	

Footnotes and abbreviations appear on the next page.(continued)

Footnotes to Table 2

[a] If a patient is withdrawn from the study before completion of 48 weeks of treatment, final procedures and assessments will be performed at the last visit.
[b] The clinical SLEDAI-2K score during screening must be at least 6 for the patient to be enrolled.
[c] Physical examination will include measurement of height at screening only and measurement of body weight at week 52 (or final assessment).
[d] Physical examination symptom directed will include measurement of body weight.
[e] Serum chemistry laboratory parameters will include a comprehensive metabolic panel and creatine phosphokinase.
[f] Hematology laboratory parameters will include complete blood count with differential.
[g] Urinalysis parameters will include urine dipstick, microscopic urinalysis, and spot protein-creatinine ratio.
[h] Coombs' test will be obtained at screening. At subsequent visits, Coombs' test, haptoglobin, and peripheral smear will be obtained if hemolysis is suspected or confirmed.
[i] A blood sample (5 mL) for measurement of IPP-201101 concentrations will be obtained prior to and 5 minutes and 1, 2, and 24 hours after study drug administration at weeks 0, 16, and 32 from patients at selected North American and Western European study centers. A blood sample for measurement of the concentration of IPP-201101 will be obtained from all patients who have a serious adverse event and/or have an adverse event leading to withdrawal from the study.
[j] Anti–IPP-201101 Ab testing will be performed at visit 2 (week 0; baseline/start of study drug treatment), visit 3 (week 2), visit 4 (week 4), visit 6 (week 12), visit 8 (week 20), visit 10 (week 28), visit 12 (week 36), visit 14 (week 44), and the final assessment (or early termination) (visit 16 [week 52]). All samples will be collected prior to administration of study drug at that particular visit. Any patient with a positive test result for anti–IPP-201101 Ab at the final study visit will be followed with additional immunogenicity testing at 8-week intervals until the level returns to baseline value or the levels are judged by the investigator to be chronic, or the patient is lost to follow-up.
[k] Vital signs measurements will include systolic and diastolic blood pressures, pulse, and temperature. The same position and arm should be used each time vital signs are measured for a given patient.
[l] At screening, baseline, weeks 4 through 48, and week 52 (or final assessment), urine pregnancy tests will be performed on all women prior to study drug administration regardless of childbearing potential.
[m] Concomitant medication usage will be obtained from the start of screening. Background therapies for SLE may not change from week 44 to week 52.
[n] Adverse events that are suggestive of anaphylaxis or a drug hypersensitivity reaction will be evaluated as per the Clinical Criteria For Diagnosing Anaphylaxis.
[o] Eligibility will be validated by a central system .
[p] C-SSRS will be administered directly to the patient using IRT and assessed using C-SSRS Baseline version at baseline (visit 2) and C-SSRS Since Last Visit version at visits 4 through 16.
[q] At screening, using IRT each patient will be assigned with a 6-digit personal identification screening number.
[r] The IRT will be accessed at baseline/start of study drug treatment for drug kit assignment. The IRT will also assign a 5-digit treatment number. In addition, the IRT will be accessed during the study for drug resupply.
[s] The IRT will be accessed at final visit for study disposition.
[t] Patients will be randomly assigned to receive a 200-mcg dose of IPP-201101 or placebo. IPP-201101 or placebo will be administered subcutaneously every 4 weeks from weeks 0 to 48. Patients who continue to meet the inclusion/exclusion criteria will be assigned a permanent 4-digit unique randomization number using the IRT. The IRT will assign a 5-digit treatment number. The 1st dose of study drug will be administered at baseline (visit 2) after all assessments have been completed. Patients should be monitored for at least 1 hour after study drug administration at visits 2 and 4 and then at the discretion of the investigator.
[u] Study drug may not be administered by the same individual performing the SLEDAI-2K, BILAG-2004, PhGA, SFI, and SDI. These disease activity indices must be completed before study drug is administered (at visits at which study drug is administered).
[v] PhGA, SLEDAI 2K and SFI are captured on the same form and then assessed in BLIPS software.

V=visit; D=day; W=week; BL=baseline; FV=final visit; ET=early termination; I/E=inclusion/exclusion; PE=physical examination; HBsAg=hepatitis B surface antigen; HCV Ab=hepatitis C virus antibody; ANA=antinuclear antibody; anti-dsDNA Ab=anti–double-stranded deoxyribonucleic acid antibody; C3=complement component 3; C4=complement component 4; anti–U1-70K snRNP Ab=anti-uridine rich 70 kilodalton small nuclear ribonucleoprotein particle antibody; anti-Sm Ab=anti–Smith antibody; CRP=C-reactive protein; IgG=immunoglobulin G; IgM=immunoglobulin M; IgE=immunoglobulin E, IgA=immunoglobulin A; Ab=antibody; ECG=electrocardiogram; IRT=Interactive Response Technology; SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000; BILAG-2004=British Isles Lupus Assessment Group 2004; exam=examination; SELENA=Safety of Estrogens in Lupus Erythematosus: National Assessment; SLICC/ACR=Systemic Lupus International Collaborative Clinics/American College of Rheumatology; SF-36=Medical Outcome Survey Short Form 36; SFI=Safety of Estrogens in Lupus Erythematosus: National Assessment Flare Index; SDI=SLICC/ACR Damage Index; PhGA=Physician's Global Assessment; FACIT-Fatigue=Functional Assessment of Chronic Illness Therapy–Fatigue Scale; C-SSRS=Columbia-Suicide Severity Rating Scale.

3.11.1 Procedures for Screening and Enrollment (Visit 1)

A signed and dated informed consent form will be obtained before screening procedures. Evaluations obtained as part of routine medical care and performed during the screening period may be used in place of the study-specific evaluations. Patients will acknowledge and agree to the possible use of this information for the study by giving informed consent.

After informed consent is obtained, patients who are screened will be assigned a 6-digit patient identification number via IRT such that all patients from each center are given consecutive identification numbers in successive order of inclusion. The two first digits of the screening number will be the designated investigator country, the two following digits will be designated the center number, and the last 2 digits will be assigned at the investigator center (eg, the 3rd patient screened at center 5 in USA would be given the number of 010503).

The screening visit (visit 1) will take place not more than 2 weeks before the baseline visit. An additional 14 days will be allowed for the receipt of data needed to confirm eligibility (eg, BILAG-2004, SLEDAI-2K, and PhGA central system assessment, laboratory results ….). The following procedures will be performed at visit 1:

- obtain written informed consent
- inclusion/exclusion criteria review; confirm that clinical SLEDAI-2K score is at least 6
- medical and psychiatric history review
- physical examination (including measurement of height at screening only)
- clinical laboratory tests
- hepatitis B surface antigen [HBsAg], hepatitis C virus antibody [HCV Ab], ANA
- anti-dsDNA Ab, C3, and C4
- hemolysis testing (Coombs' test only)
- vital signs measurements (includes systolic and diastolic blood pressures, pulse, and temperature)
- urine pregnancy test on all women regardless of childbearing potential
- 12-lead ECG
- concomitant medication review (at the start of screening)
- adverse event inquiry
- SLEDAI-2K
- BILAG-2004
- SFI
- SDI

3.11.2 Procedures Before Study Drug Treatment (Baseline/Start Study Drug Treatment [Visit 2/Week 0])

Patients who meet the inclusion/exclusion criteria at visit 1 will continue to visit 2 (week 0); if they continue to meet all criteria, baseline evaluations will be conducted, randomization/stratification will occur via IRT, and study drug will be administered. NOTE: Week 0 refers to the start of the 1st week of study drug treatment, which will begin with the baseline visit.

In addition, a blood sample (5 mL) will be obtained for measurement of IPP-201101 plasma concentrations prior to and 5 minutes and 1, 2, and 24 hours after study drug administration from patients at selected North American and Western European study centers. The actual dates and times of study drug administration and the date and time of sampling will be recorded on the CRF.

The following procedures will be performed at visit 2:

- inclusion/exclusion criteria review
- physical examination symptom directed
- clinical laboratory tests
- ANA
- anti-dsDNA Ab, C3, and C4
- anti–U1-70K snRNP Ab, anti-Sm Ab, CRP, IgG, IgM, , IgA
- anti–IPP-201101 Ab
- vital signs measurements (includes systolic and diastolic blood pressures, pulse, and temperature)
- urine pregnancy test on all women regardless of childbearing potential
- concomitant medication review
- adverse event inquiry
- SLEDAI-2K
- BILAG-2004
- 28-joint count examination for pain and tenderness
- SFI
- SF-36
- PhGA
- FACIT-Fatigue
- C-SSRS Baseline version
- In vitro intracellular and secreted cytokine response
- access eCRF for randomization number and study drug administration. Randomization number and treatment number will be allocated automatically by the system.

A patient who is not enrolled in the study at the end of the baseline visit, eg, because entry

criteria were not met or enrollment did not occur within the specified time, may be considered for screening again if, eg, there was a change in the patient's medical background or a modification of study entry criteria. (NOTE: Details of rescreening criteria and procedures are included in the Monitoring Plan for this study.)

Patients who continue to meet the inclusion/exclusion criteria and are approved for randomization will be assigned a permanent 4-digit unique randomization number preceded by 'R' using the IRT (integrated with the eCRF). The IRT will also assign a 5-digit treatment number at each visit at which study drug is administered (ie, baseline [visit 2] and visits 4 through 15). The 5-digit treatment number will correspond to the number on the individual vial of study drug that is to be administered. The 1st dose of study drug will be administered at this visit after all assessments have been completed. Patients should be monitored for at least 1 hour after study drug administration at visits 2 and 4 and then at the discretion of the investigator.

Throughout the study, a blood sample for measurement of the concentration of IPP-201101 will be obtained from all patients who have a serious adverse event and/or have an adverse event leading to withdrawal from the study.

3.11.3 Procedures During Study Drug Treatment

3.11.3.1 Visit 3 (Week 2)

The following procedures/assessments will be performed at visit 3 (week 2):

- anti–IPP-201101 Ab
- vital signs measurements (includes systolic and diastolic blood pressures, pulse, and temperature)
- concomitant medication review
- adverse event inquiry

3.11.3.2 Visit 4 (Week 4)

The following procedures/assessments will be performed at visit 4 (week 4):

- physical examination symptom directed
- clinical laboratory tests
- ANA
- anti-dsDNA Ab, C3, and C4
- anti–U1-70K snRNP Abanti-Sm Ab, CRP, IgG, IgM, IgE, IgA
- anti–IPP-201101 Ab
- vital signs measurements (includes systolic and diastolic blood pressures, pulse, and temperature)
- urine pregnancy test on all women regardless of childbearing potential
- concomitant medication review
- adverse event inquiry
- SLEDAI-2K

- BILAG-2004
- 28-joint count examination for pain and tenderness
- SFI
- PhGA
- C-SSRS Since Last Visit version
- In vitro intracellular and secreted cytokine response
- Access eCRF page for treatment allocation..
- study drug administration after all assessments have been completed. (Patients should be monitored for at least 1 hour after study drug administration.)

3.11.3.3 Visit 5 (Week 8)

The following procedures/assessments will be performed at visit 5 (week 8):

- physical examination symptom directed
- clinical laboratory tests
- anti-dsDNA Ab, C3, and C4 only
- vital signs measurements (includes systolic and diastolic blood pressures, pulse, and temperature)
- urine pregnancy test on all women regardless of childbearing potential
- concomitant medication review
- adverse event inquiry
- SLEDAI-2K
- BILAG-2004
- 28-joint count examination for pain and tenderness
- SFI
- PhGA
- C-SSRS Since Last Visit version
- access eCRF page for treatment allocation.
- study drug administration after all assessments have been completed. (Patients should be monitored, at the discretion of the investigator, for at least 1 hour after study drug administration.)

3.11.3.4 Visit 6 (Week 12)

The following procedures/assessments will be performed at visit 6 (week 12):

- physical examination symptom directed
- clinical laboratory tests
- ANA
- anti-dsDNA Ab, C3, and C4
- anti–U1-70K snRNP Ab, anti-Sm Ab, CRP, IgG, IgM, IgE, IgA

- anti–IPP-201101 Ab
- vital signs measurements (includes systolic and diastolic blood pressures, pulse, and temperature)
- urine pregnancy test on all women regardless of childbearing potential
- concomitant medication review
- adverse event inquiry
- SLEDAI-2K
- BILAG-2004
- 28-joint count examination for pain and tenderness
- SFI
- SF-36
- PhGA
- FACIT-Fatigue
- C-SSRS Since Last Visit version
- access eCRF page for treatment allocation.
- study drug administration after all assessments have been completed. (Patients should be monitored, at the discretion of the investigator, for at least 1 hour after study drug administration.)

3.11.3.5 Visits 7 and 8 (Weeks 16 and 20)

The following procedures/assessments will be performed at visits 7 and 8 (weeks 16 and 20, respectively):

- physical examination symptom directed
- clinical laboratory tests
- anti-dsDNA Ab, C3, and C4 only
- anti–IPP-201101 Ab (visit 8, week 20)
- vital signs measurements (includes systolic and diastolic blood pressures, pulse, and temperature)
- urine pregnancy test on all women regardless of childbearing potential
- concomitant medication review
- adverse event inquiry
- SLEDAI-2K
- BILAG-2004
- 28-joint count examination for pain and tenderness
- SFI
- PhGA
- C-SSRS Since Last Visit version
- access eCRF page for treatment allocation.

- study drug administration after all assessments have been completed. (Patients should be monitored, at the discretion of the investigator, for at least 1 hour after study drug administration.)

In addition, a blood sample (5 mL) will be obtained for measurement of IPP-201101 plasma concentration prior to and 5 minutes and 1, 2, and 24 hours after study drug administration at visit 7 (week 16) from patients at selected North American and Western European study centers. The actual dates and times of study drug administration and the date and time of sampling will be recorded on the CRF.

3.11.3.6 Visit 9 (Week 24)

The following procedures/assessments will be performed at visit 9 (week 24):

- physical examination symptom directed
- clinical laboratory tests
- ANA
- anti-dsDNA Ab, C3, and C4
- anti–U1-70K snRNP Ab, anti-Sm Ab, CRP, IgG, IgM, IgE, IgA
- vital signs measurements (includes systolic and diastolic blood pressures, pulse, and temperature)
- urine pregnancy test on all women regardless of childbearing potential
- concomitant medication review
- adverse event inquiry
- SLEDAI-2K
- BILAG-2004
- 28-joint count examination for pain and tenderness
- SFI
- SDI
- SF-36
- PhGA
- FACIT-Fatigue
- C-SSRS Since Last Visit version
- In vitro intracellular and secreted cytokine response
- Access eCRF page for treatment allocation.
- study drug administration after all assessments have been completed. (Patients should be monitored, at the discretion of the investigator, for at least 1 hour after study drug administration.)

3.11.3.7 Visits 10 and 11 (Weeks 28 and 32)

The following procedures/assessments will be performed at visits 10 and 11 (weeks 28 and 32, respectively):

- physical examination symptom directed
- clinical laboratory tests
- anti-dsDNA Ab, C3, and C4 only
- anti–IPP-201101 Ab (visit 10 [week 28])
- vital signs measurements (includes systolic and diastolic blood pressures, pulse, and temperature)
- urine pregnancy test on all women regardless of childbearing potential
- concomitant medication review
- adverse event inquiry
- SLEDAI-2K
- BILAG-2004
- 28-joint count examination for pain and tenderness
- SFI
- PhGA
- C-SSRS Since Last Visit version
- access eCRF page for treatment allocation.
- study drug administration after all assessments have been completed. (Patients should be monitored, at the discretion of the investigator, for at least 1 hour after study drug administration.)

In addition, a blood sample (5 mL) will be obtained for measurement of IPP-201101 plasma concentration prior to and 5 minutes and 1, 2, and 24 hours after study drug administration at visit 11 (week 32) from patients at selected North American and Western European study centers. The actual dates and times of study drug administration and the date and time of sampling will be recorded on the CRF.

3.11.3.8 Visit 12 (Week 36)

The following procedures/assessments will be performed at visit 12 (week 36):

- physical examination symptom directed
- clinical laboratory tests
- ANA
- anti-dsDNA Ab, C3, and C4
- anti–U1-70K snRNP Ab, anti-Sm Ab, CRP, IgG, IgM, IgE, IgA
- anti–IPP-201101 Ab
- vital signs measurements (includes systolic and diastolic blood pressures, pulse, and

temperature)
- urine pregnancy test on all women regardless of childbearing potential
- concomitant medication review
- adverse event inquiry
- SLEDAI-2K
- BILAG-2004
- 28-joint count examination for pain and tenderness
- SFI
- SF-36
- PhGA
- FACIT-Fatigue
- C-SSRS Since Last Visit version
- Access eCRF page for treatment allocation.
- study drug administration after all assessments have been completed. (Patients should be monitored, at the discretion of the investigator, for at least 1 hour after study drug administration.)

3.11.3.9 Visits 13, 14, and 15 (Weeks 40, 44, and 48)

The following procedures/assessments will be performed at visits 13, 14, and 15 (weeks 40, 44, and 48 respectively):

- physical examination symptom directed
- clinical laboratory tests
- anti-dsDNA Ab, C3, and C4 only
- anti–IPP-201101 Ab (visit 14 [week 44])
- vital signs measurements (includes systolic and diastolic blood pressures, pulse, and temperature)
- urine pregnancy test on all women regardless of childbearing potential
- concomitant medication review (NOTE: Background therapies for SLE may not change from week 44 to week 52.)
- adverse event inquiry
- SLEDAI-2K
- BILAG-2004
- 28-joint count examination for pain and tenderness
- SFI
- PhGA
- C-SSRS Since Last Visit version
- In vitro intracellular and secreted cytokine at Visit 48
- access eCRF page for treatment allocation.

Study drug administration after all assessments have been completed. (Patients should be monitored, at the discretion of the investigator, for at least 1 hour after study drug administration.)

3.11.4 Procedures After Study Drug Treatment (Visit 16/Week 52)

Patients who participate in the study in compliance with the protocol for at least 48 weeks of treatment will be considered to have completed the study. Patients who complete all study visits will be eligible for participation in a open-label study to assess the continued effectiveness and safety of IPP-201101 treatment.

If a patient is withdrawn from the study before completion of 48 weeks of study drug treatment, final evaluations will be performed at the last visit. To be evaluable for efficacy, a patient must be treated with at least 1 dose of study drug and must have all components of the SRI (baseline SLEDAI-2K total score, BILAG-2004 body system scores, and PhGA score) available. Patients with ongoing adverse events or clinically significant abnormal laboratory test results (as interpreted by the investigator) will be monitored as described in section 7.1.2 and section 7.2, respectively.

If a patient withdraws from the study during the treatment period, the reason must be determined and recorded on the patient's CRF (see section 4.3). For patients who withdraw consent, every attempt will be made to determine the reason. A blood sample for measurement of the concentration of IPP-201101 will be obtained from all patients who have an adverse event leading to withdrawal from the study and/or all patients who have a serious adverse event.

For patients who complete the study, final evaluations will be performed at visit 16 (week 52). For patients who withdraw prematurely from the study before completion of 48 weeks of study drug treatment, final evaluations will be performed at the last visit. The following procedures will be performed at visit 16 (week 52) or at early termination (before completion of the 48 weeks of study drug treatment), if applicable:

- physical examination
- clinical laboratory tests
- ANA
- anti-dsDNA Ab, C3, and C4
- anti–U1-70K snRNP Ab, anti-Sm Ab, CRP, IgG, IgM, IgE, IgA
- anti–IPP-201101 Ab (NOTE: Any patient with a positive test result for anti–IPP-201101 Ab at the final study visit will be followed with additional immunogenicity testing at 8-week intervals until the level returns to baseline value or the levels are judged by the investigator to be chronic, or the patient is lost to follow-up)
- vital signs measurements (includes systolic and diastolic blood pressures, pulse, and temperature)
- urine pregnancy test on all women regardless of childbearing potential
- 12-lead ECG
- concomitant medication review
- adverse event inquiry

- SLEDAI-2K
- BILAG-2004
- 28-joint count examination for pain and tenderness
- SFI
- SDI
- SF-36
- PhGA
- FACIT-Fatigue
- C-SSRS Since Last Visit version
- access IRT to record final patient disposition

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Patient Inclusion Criteria

Patients are included in the study if all of the following criteria are met:

(a) The patient is a man or woman between 18 and 70 years of age with an established diagnosis of SLE as defined by ACR Classification Revised Criteria. The diagnosis is fulfilled provided that at least 4 criteria are met.

(b) The patient has a positive test result for ANA at screening (titer must be at least 1:80 [by human epithelial cell tumor line (HEp-2) ANA assay]) **and/or** a positive test result for anti-dsDNA Ab at screening (value must be 30 IU/mL or more by enzyme-linked immunosorbent assay [ELISA]).

(c) Written informed consent is obtained.

(d) Women must be surgically sterile, 2 years postmenopausal, or, if of childbearing potential, using a medically accepted method of contraception, and must agree to continued use of this method for the duration of the study and for 30 days after discontinuation of study drug treatment. Acceptable methods of contraception include barrier method with spermicide, abstinence (when this is in line with the preferred and usual lifestyle of the subject), intrauterine device (IUD), or steroidal contraceptive (oral, transdermal, implanted, and injected) in conjunction with a barrier method.

(e) The patient has a SLEDAI-2K clinical score of at least 6 points **during screening**. A SLEDAI-2K clinical score is the calculated score without inclusion of the points that may be contributed by having a positive titer for anti-dsDNA Ab or decreased serum complement levels.

(f) The patient does not have an "A" score on the BILAG-2004 scale.

(g) If the patient is using oral corticosteroids, the weekly cumulative dose must not exceed 80 mg of prednisone equivalent; the weekly dose must be stable over the 4 weeks preceding the 1st dose of study drug.

(h) If the patient is using antimalarials, methotrexate, leflunomide, MMF, or azathioprine, the start date must be at least 3 months prior to the 1st dose of study drug, and the daily dose

must be stable over the 4 weeks preceding the 1st dose of study drug.

(i) If the patient is not currently using corticosteroids, antimalarials, methotrexate, MMF, or azathioprine, the last dose (in case of previous use) must be at least 4 weeks prior to the 1st dose of study drug. For leflunomide, the stop date must be at least 8 weeks before the 1st dose of study drug, unless an adequate cholestryamine washout has been performed. If cholestyramine washout is performed, the last use of leflunomide must be at least 4 weeks before the 1st dose of study drug.

The patient must be willing and able to comply with study restrictions, to remain at the study center for the required duration during each study visit, and to return to the study center for the final assessment as specified in this protocol.

4.2 Patient Exclusion Criteria

Patients are excluded from participating in this study if 1 or more of the following criteria are met:

(a) The patient has been treated with intramuscular or intravenous (iv) pulse steroids (ie, 250 to 1000 mg iv total daily dose of methylprednisolone) within 4 weeks of the 1st dose of study drug. The use of intra-articular steroids may be allowed after consultation with the medical expert.

(b) The patient has received tacrolimus, cyclosporin A, or iv immunoglobulins (IVIG) within 3 months of the 1st dose of study drug.

(c) The patient has received cyclophosphamide within 6 months prior to the 1st dose of study drug.

(d) The patient has been treated for SLE with agents such as fusion proteins, therapeutic proteins, or monoclonal antibodies or antibody fragments, within 6 months of the 1st dose of study drug.

(e) The patient has received B-cell depleting agents such as rituximab, belimumab or epratuzumab within one year of the 1st dose of study drug and has not yet normalized the B-cell count (ie, $CD20^+$ B-cell count is less than normal range and the absolute lymphocyte count [ALC] is less than normal range).

(f) The patient has New York Heart Association (NYHA) Class III or IV congestive heart failure.

(g) The patient has an estimated glomerular filtration rate (eGFR) of less than 30 mL/min/1.73 m^2 (via Modification of Diet in Renal Disease [MDRD] equation).

(h) The patient has an aspartate aminotransferase (AST) or alanine aminotransferase (ALT) value greater than 2 times the upper limit of the normal range (ULN) or a total bilirubin level greater than 1.5 times ULN.

(i) The patient has a planned immunization with a live or live attenuated vaccine within 3 months prior to administration of the 1st dose of study drug and for 3 months after administration of the last dose of study drug.

(j) The patient has any clinically significant abnormalities on ECG that are not related to SLE, as determined by the investigator. Patients with stable ECG changes without evidence of active cardiovascular disease may participate at the discretion of the investigator and

medical monitor.

(k) The patient has an ongoing active systemic infection requiring treatment or a history of severe infection, such as hepatitis or pneumonia, in the 3 months prior to administration of the 1st dose of study drug. Less severe infections in the 3 months prior to administration of the 1st dose of study drug are permitted at the discretion of the investigator and medical monitor.

(l) The patient has any concomitant medical condition unrelated to SLE that may interfere with his or her safety or with evaluation of the study drug, as determined by the investigator.

(m) The patient has a history of a medical condition other than SLE that has required treatment with oral corticosteroids in excess of 80 mg of prednisone equivalent/week within 3 months of the 1st dose of study drug.

(n) The patient has a positive test result for HBsAg or HCV Ab.

(o) The patient has a known positive history of antibodies to human immunodeficiency virus (HIV) or HIV disease or other immunosuppressive state (eg, agammaglobulinemia, etc).

(p) The patient has a history of alcohol or substance dependence or abuse (with the exception of nicotine), according to the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association, Fourth Edition, Text Revision (DSM-IV-TR), within 3 months of the screening visit or has current substance abuse.

(q) The patient has a history of severe allergic reactions to or hypersensitivity to any component of the study drug or placebo.

(r) The patient has undergone or is undergoing treatment with another investigational drug for the treatment of lupus within 6 months prior to the 1st dose of study drug or has received any other investigational drug for any other condition within 4 weeks prior to the 1st dose of study drug.

(s) The patient has previously participated in a clinical study with IPP-201101.

(t) The patient is a pregnant or lactating woman. (Any women becoming pregnant during the study will be withdrawn from the study.)

(u) The patient is unlikely to comply with the study protocol or is unsuitable for any other reason, as judged by the investigator or medical monitor.

4.3 Withdrawal Criteria and Procedures

In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), each patient is free to withdraw from the study at any time. Each investigator also has the right to withdraw a patient from the study in the event of intercurrent illness, adverse events, pregnancy (see section 7.2.4), or other reasons concerning the health or well-being of the patient, or in the case of lack of cooperation. In addition, a patient may be withdrawn from the study as described in sections 3.6, 3.8, 5.2, 5.3, and 7.1.6.

Should a patient decide to withdraw after administration of study drug, or should the investigator decide to withdraw the patient, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the patient's withdrawal should be made and an explanation given of why the patient is withdrawing or being withdrawn from the study.

The reason for and date of withdrawal from study drug treatment and the reason for and date of withdrawal from the study must be recorded on the CRF. If a patient withdraws consent, every attempt will be made to determine the reason. If the reason for withdrawal is an adverse event or a clinically significant abnormal laboratory test result, monitoring will continue until the event has resolved or stabilized, until the patient is referred to the care of a local health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made. The specific event or test results must be recorded on the CRF. In addition, a blood sample will be obtained for measurement of the concentration of IPP-201101 from all patients who have a serious adverse event and/or have an adverse event leading to withdrawal from the study. All evaluations should be performed, according to the protocol, on the last day the patient receives study drug, or as soon as possible thereafter.

5 TREATMENT OF PATIENTS

5.1 Study Drugs Administered

After successfully meeting entry criteria, during the screening and baseline visits, eligible patients will be randomly assigned to the IPP-201101 treatment group or to the placebo treatment group (see section 3.3). Study drug will be packaged in single-dose vials; the study center with receive box(es) with up to 13 vials per box. Each vial will be labeled with a 4-digit treatment number and each box will contain a mix of IPP-201101 or placebo vials (see section 3.4). Study drug exposure will be measured, and study drug will be administered sc by qualified study personnel at visit 2 and visits 4 through 15. Study drug may not be administered by the same individual performing the SLEDAI-2K, BILAG-2004, or PhGA. Study drug should be administered at each study visit after all study visit procedures and assessments have been completed.

The pharmacy manual provided by ImmuPharma includes details on storage, administration, reconstitution, syringe information, and preparation of the study drug.

5.1.1 Investigational Product and Dosage

Prior to administration, IPP-201101 should be reconstituted with 1.1 mL sterile water for injection (volume of injection of 1.0 mL). Patients randomly assigned to IPP-201101 will be administered a dosage of 200 mcg sc every 4 weeks for 48 weeks.

A more detailed description of the product is provided in section 3.4.

5.1.2 Other Study Drugs and Dosage

Patients randomly assigned to placebo will be administered placebo sc every 4 weeks for 48 weeks. Prior to administration, placebo should be reconstituted with 1.1 mL sterile water for injection (volume of injection of 1.0 mL).

A more detailed description of the product is provided in section 3.4.

5.2 Prior and Concomitant Therapy or Medication

Any prior or concomitant therapy or medication given to a patient from the start of screening or during study drug administration will be indicated on the CRF. Other medications used for SLE or other disorders will also be captured on the CRF, as detailed below. Dosage and generic name or trade name will be indicated. The sponsor will encode all therapy and medication according to the WHO drug dictionary (WHO Drug).

As described in section 4.1, if the patient is using oral corticosteroids, the weekly cumulative dose must not exceed 80 mg of prednisone equivalent; the weekly dose must be stable over the 4 weeks preceding the 1st dose of study drug. If a patient is taking oral corticosteroids at study entry, the dose may be decreased during the study at the investigator's discretion. The dose of background corticosteroid medication may be increased to treat the patient for minor fluctuations in lupus disease activity (ie, a mild or moderate flare). However, the dose of oral corticosteroid may not exceed 30 mg of prednisone or equivalent per day for more than 2 weeks. If a patient not previously treated with corticosteroids requires initiation of treatment with corticosteroids during the study to treat minor fluctuations in lupus disease activity (ie, a mild or moderate flare), the dose of oral corticosteroid may not exceed 30 mg of prednisone or equivalent per day for more than 2 weeks. If a patient requires a temporary increase in corticosteroid dose or a short course of corticosteroid treatment (ie, 2 weeks) and the medication is unable to be tapered to the baseline dose or be withdrawn, respectively, the patient is to be withdrawn from the study. If a patient requires treatment with corticosteroids for a condition other than SLE, these same restrictions on corticosteroid use, and those detailed in section 4.2, will apply. The use of intra-articular steroids may be allowed after consultation with the medical expert.

Also, if the patient is using antimalarials, methotrexate, leflunomide, MMF, or azathioprine, the start date must be at least 3 months prior to the 1st dose of study drug, and the daily dose must be stable over the 4 weeks preceding the 1st dose of study drug. Dosages of these medications should remain stable during the study. In addition, if the patient is not currently using corticosteroids, antimalarials, methotrexate, MMF, or azathioprine, the last dose (in case of previous use) must be at least 4 weeks prior to the 1st dose of study drug. For leflunomide, the stop date must be at least 8 weeks before the 1st dose of study drug, unless an adequate cholestyramine washout has been completed. (NOTE: If cholestyramine washout is performed, the last use of leflunomide must be at least 4 weeks before the 1st dose of study drug.) If used, these medications should also be indicated on the CRF. If a patient requires treatment with any of these medications for a condition other than SLE, these same restrictions, and those detailed in section 4.2, will apply.

Changes in background therapies, including use of corticosteroids as a background therapy or for treatment of a mild or moderate flare or of a condition other than SLE, should not occur beginning with week 44 (visit 14). Any tapering of medication (ie, for clinically meaningful improvement in disease activity, dose reduction, or medication discontinuation because of toxicity) should be discussed with the medical monitor. Medication holidays (eg, less than or equal to 2 weeks) for short periods because of intercurrent illness or surgical procedures may be permitted and should be discussed with the medical monitor. However, background therapies must be stable for at least 4 weeks prior to the 1st dose of study drug.
Patients will be withdrawn from the study if any of the following occur:

- an increase in use of background oral corticosteroids beyond 80 mg of prednisone equivalent/week (NOTE: Treatment of mild/moderate flare is permitted as detailed in section 5.2. The use of corticosteroids for the treatment of a mild or moderate flare or for the treatment of conditions other than SLE will not be permitted beginning at week 44 [visit 14] through week 52 [visit 16])
- an inability to reduce corticosteroid dose to the baseline dose or to withdraw therapy if the patient required a temporary increase in corticosteroid dose or a short course of corticosteroid treatment (ie, 2 weeks) and the medication is unable to be tapered to the baseline dose or be withdrawn, respectively
- therapy is initiated with pulse iv steroids
- an increase in the baseline dose of immunosuppressive agents (methotrexate, azathioprine, MMF)
- initiation of new immunosuppressive therapy (cyclophosphamide, methotrexate, azathioprine, cyclosporin, tacrolimus, leflunomide, MMF)
- initiation of therapy with biologics for the treatment of SLE
- any change in the doses of background therapies beginning with week 44 (visit 14) More information is provided in section 3.6 and Appendix B.

Patients will be excluded from participation in the study for any of the following reasons:

- they have been treated with iv pulse steroids within 4 weeks of the 1st dose of study drug
- they have received tacrolimus, cyclosporin A, or IVIG within 3 months of the 1st dose of study drug
- they have received cyclophosphamide or have been treated with biologic agents for SLE, such as fusion proteins, therapeutic proteins, or monoclonal antibodies or antibody fragments, within 6 months of the 1st dose of study drug
- they have received B-cell depleting agents such as rituximab or belimumab within one year of 1st dose of study drug and have not yet normalized the B-cell count
- they have a planned immunization with a live or live attenuated vaccine within 3 months prior to administration of the 1st dose of study drug and for 3 months after the last dose of study drug is administered

More information is provided in section 4.2 and Appendix B.

At each study center visit after the screening visit, the investigator will ask the patient whether any medications (other than study drug), including over-the-counter (OTC) medications, were taken since the previous visit (see Appendix B).

5.3 Procedures for Monitoring Patient Compliance

Each investigator will be responsible for monitoring patient compliance. Patients can be withdrawn from the study at any time if the investigator or the sponsor determines that the patient is not in compliance with the study protocol.

6 ASSESSMENT OF EFFICACY

6.1 Primary Efficacy Variable

The primary efficacy variable for this study is the proportion of patients achieving a combined clinical response using the SRI at week 52. An SRI response is defined as a reduction from baseline in the SLEDAI-2K score of at least 4 points, no worsening in PhGA (with worsening defined as an increase in PhGA of more than 0.30 point from baseline), no new BILAG A body system score, and no more than 1 new BILAG B body system score from baseline. The combined clinical response is intended to demonstrate an improvement in overall disease activity without worsening of disease in any organ system as determined by the investigator's quantitative and qualitative assessments.

The SLEDAI-2K is a validated objective measure that assesses disease activity within the last 28 days before completion of the index. It is a global index and includes 24 weighted clinical and laboratory variables. The total score (sum of all 24 scores) ranges from 0 to 105. A SLEDAI-2K score of 6 to 10 is indicative of moderate disease activity, and improvement is defined as a reduction of greater than 3 points (Appendix C). The SLEDAI-2K was chosen because it is an accepted scale for assessing disease activity, has been shown to be reliable and sensitive to change, and is easy for clinicians to use. The SLEDAI-2K should be administered at each visit throughout the study by the same physician assessor trained and qualified to use this scale.

The PhGA will be completed by the physician using a 3-inch visual analog scale (VAS) labeled from 0=none to 3=severe (Appendix C). This scale was chosen because it measures a domain of disease activity that may not be fully assessed in the other measures of disease activity. A change of greater than 0.3 point on the VAS indicates worsening. The PhGA should be administered at each visit throughout the study by the same physician assessor trained and qualified to use this scale.

The BILAG-2004 is a validated objective and subjective global measure of the disease activity of SLE based upon the physician intention to treat and refers to disease activity within the last month prior to completion of the index. It includes 97 clinical and laboratory items to evaluate SLE disease activity in 9 organ systems; each organ system is assigned a score displayed as a grade from A to E, as follows: A=very active disease; B=patient needs increase in treatment for moderately active disease; C=stable or mild disease; D=previous organ involvement but no current disease activity; and E=no current disease activity and the organ system has never been involved (Appendix D). The BILAG-2004 was chosen because it is a reliable scale for evaluating SLE disease activity on the basis of the physician's intent to treat. The individual body system scores are evaluations of disease activity in individual organ systems that may be improving, worsening, or stable, and they provide information that is comparable and complementary to the SLEDAI-2K score. The BILAG-2004 should be administered at each visit throughout the study by the same physician assessor trained and qualified to use this scale.

6.2 Secondary Efficacy Variables

The secondary efficacy variables and endpoints for this study are as follows:

- proportion of patients achieving an SRI response at each visit during the treatment period
- proportion of patients achieving a reduction of at least 4 points in the SLEDAI-2K total

score at each visit during the treatment period

- proportion of patients achieving a clinical SLEDAI-2K response at each visit during the treatment period, where the clinical response is defined as a reduction of at least 4 points in the SLEDAI-2K clinical score
- proportion of patients achieving a BILAG-2004 response at each visit during the treatment period (no new BILAG A body system score and no more than 1 new BILAG B body system score from baseline)
- proportion of patients achieving a BILAG-2004 clinical response at each visit during the treatment period (an improvement in at least 1 category from a B score to a C or D score, with no worsening in any other category)
- proportion of patients showing no worsening on a PhGA scale at each visit during the treatment period
- proportion of patients achieving a reduction of 5 points in the SLEDAI-2K at each visit during the treatment period
- proportion of patients achieving a reduction of 6 points in the SLEDAI-2K at each visit during the treatment period
- proportion of patients achieving an SRI-5 response at each visit during the treatment period
- proportion of patients achieving an SRI-6 response at each visit during the treatment period
- proportion of patients showing an improvement in tender and swollen joint counts using the 28-joint count examination for pain and tenderness at each visit during the treatment period
- SFI at each visit during the treatment period
  - time to first mild to moderate flare
  - incidence of mild to moderate flare
  - time to severe flare (NOTE: A severe flare leads to early withdrawal)
- changes in the SDI over time (assessed at screening and weeks 24 and 52 (or final assessment)
- absolute and relative changes in the SF-36 at weeks 12, 24, 36, and 52 (or final assessment)
- proportion of patients with changes in steroid dose over time throughout the study

The exploratory efficacy variables and endpoints for this study are as follows:

- changes in the biomarkers anti-dsDNA Ab, C3, and C4 at each visit during the treatment period
- changes in the following biomarkers at weeks 4, 12, 24, 36, and 52 (or final assessment):
  - ANA
  - anti–U1-70K snRNP Ab
  - anti-Sm Ab
  - CRP
  - IgG, IgM, IgA and IgE
- absolute and relative changes in the FACIT-Fatigue at weeks 12, 24, 36, and 52 (or final assessment)

- in vitro intracellular and secreted cytokine response

These secondary and exploratory measures are generally accepted by the clinical and regulatory communities to assess the physical, serologic, and psychosocial aspects of SLE. The SLEDAI-2K, BILAG-2004 (including body system scores), and PhGA are described in section 6.1. More information on the remaining measures is provided below (sections 6.2.1 through 6.2.7).

6.2.1 Medical Outcome Survey Short Form 36

The SF-36 is a survey of patient health and evaluates vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health (Appendix G). This survey was chosen because it monitors and compares the psychosocial aspects of disease burden that are not fully assessed by the global scores of SLE disease activity.

6.2.2 28-Joint Count Examination for Pain and Tenderness

The 28-joint count examination for pain and tenderness was developed for use in the assessment of rheumatoid arthritis and has become a standard for use in both clinical practice and clinical studies. It has been thoroughly validated and employed reliably in clinical studies and other analyses (Appendix F). The 28-joint count examination for pain and tenderness was chosen because tender and swollen joints are a significant cause of morbidity in patients with SLE, and lupus arthritis will be quantitated and formally evaluated using this instrument as an exploratory endpoint.

6.2.3 Biomarkers

Biomarkers in SLE are often used for diagnosis but do not always correlate with changes in disease activity. The following biomarkers will be evaluated to determine if a change in level correlates with a change in disease activity: anti-dsDNA Ab, anti–U1-70K snRNP Ab, ANA, anti-Sm Ab, and C3, C4, CRP, IgG, IgM, IgA and IgE.

6.2.4 Functional Assessment of Chronic Illness Therapy–Fatigue

The FACIT-Fatigue scale is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function. The FACIT-Fatigue scale was chosen because it measures the fatigue component of health-related quality of life and is self-administered (Appendix G).

6.2.5 Safety of Estrogens in Lupus Erythematosus: National Assessment Flare Index

The SFI divides flares into 2 categories: mild/moderate and severe (Appendix C). This index was chosen because it is a measure of the difference in disease activity over time.

6.2.6 Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index

The SDI assesses specific comorbidities associated with SLE. It consists of 39 items and covers 12 organ systems (Appendix H). This index was chosen because it has been shown to be valid and reliable and is a measure that is distinct from disease activity.

6.2.7 Steroid Dose

Because chronic treatment with glucocorticoids is associated with significant morbidity, such as bone loss, cataract formation, weight gain, and susceptibility to infection, the change in oral corticosteroid dose over the course of the study will be evaluated. The change in steroid dose will be evaluated to determine the proportion of patients taking a dose less than 7.5 mg of prednisone equivalent/day, a dose of 7.5 mg prednisone equivalent/day or more, and none per day.

6.3 Methods and Timing of Assessing, Recording, and Analyzing Efficacy Data

Methods and timing of assessing efficacy data are discussed in section 3.11. Procedures for recording efficacy data are discussed in section 14.1, and methods of analyses are discussed in section 10.

7 ASSESSMENT OF SAFETY

In this study, safety will be assessed by evaluating the following: reported adverse events clinical laboratory test results, vital signs measurements, 12-lead ECG findings, physical examination results (including physical examination symptom directed findings), concomitant medication usage, suicidality, and anaphylaxis.

During the conduct of the study, an independent, external DSMB will oversee the safety of the patients enrolled in the study and monitor the occurrence of flare throughout the study to ensure the continuing safety of the study patients and study conduct issues.

7.1 Adverse Events

7.1.1 Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a patient that develops or worsens in severity during the conduct of a clinical study of a pharmaceutical product and does not necessarily have a causal relationship to the study drug. An adverse event can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of the study, or significant worsening of the disease under study (or any concurrent disease), whether or not considered related to the study drug.

Accordingly, an adverse event could include any of the following:

- intercurrent illnesses
- physical injuries
- events possibly related to concomitant medication
- significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions. (NOTE: A condition, recorded as pre-existing, that is intermittently symptomatic [eg, headache] and which occurs during the study should be

recorded as an adverse event.)

- drug interactions
- events occurring during diagnostic procedures or any washout phase of the study
- laboratory or diagnostic test abnormalities occurring after the start of the study (ie, after screening and once confirmed by repeat testing) that results in the withdrawal of the patient from the study, requires medical treatment or further diagnostic work-up, or is considered by the study investigator to be clinically significant.
  NOTE: Abnormal laboratory test results at the screening visit that preclude a patient from entering the study or receiving study treatment are not considered adverse events, but will be recorded to monitor data from patients who do not meet screening criteria.

7.1.2 Recording and Reporting Adverse Events

For the purpose of adverse event recording, the study period is defined as that time period from signature of the informed consent form through the end of the final assessment. All adverse events that occur during the study period must be recorded on the CRF, regardless of the severity of the event or judged relationship to the study drug. For serious adverse events, the Serious Adverse Event Transmittal Form must also be completed and the serious adverse event reported immediately (see section 7.1.5). Any reported serious adverse event that occurs after the study follow-up period (regardless of time after study participation) will be assessed for its relationship to the study drug or to the patient's participation in the study. If a serious adverse event occurs after the study follow-up period and is considered related to the study drug or a study procedure by the investigator, it must be recorded on the Serious Adverse Event Transmittal Form and reported immediately.

At each contact with the patient, the investigator must query the patient for adverse events by asking an open-ended question such as, "Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe." All reported or observed signs and symptoms will be recorded individually, except when considered manifestations of a medical condition or disease state. A precise diagnosis will be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings will be recorded collectively as a single diagnosis on the Serious Adverse Event Transmittal Form and on the CRF.

The clinical course of each adverse event will be monitored at suitable intervals until resolved or stabilized, until the patient is referred to the care of a local health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made.

The onset and end dates, duration, action taken regarding study drug, treatment administered, and outcome for each adverse event must be recorded on the CRF. The relationship of each adverse event to study drug treatment and study procedures, and the severity and seriousness of each adverse event, as judged by the investigator, must be recorded as described below.

7.1.3 Severity of an Adverse Event

The severity of each adverse event will be graded according to the Modified WHO Toxicity Criteria, which is a toxicity scale with events from grades 0 to 4 (Appendix A).

Adverse events that are not included in the modified WHO Toxicity Scale will be graded according to a similar 4-point scale (grade 1=mild, 2=moderate, 3=severe, and 4=life-threatening) using the following definitions:

Mild	The patient is aware of the event or symptom, but the event or symptom is easily tolerated.
Moderate	The patient experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.
Severe	Significant impairment of functioning: the patient is unable to carry out usual activities.
Life-threatening	The patient's life is at risk from the event.

7.1.4 Relationship of an Adverse Event to the Study Drug

For each adverse event, the relationship to the study drug must be recorded as either related (there is a reasonable possibility of a causal relationship between the event and the study drug) or not related (there is not a reasonable causal relationship between the event and the study drug). In general, a causal relationship will be assigned when facts, evidence, or arguments exist to support the causal relationship.

When assessing a relationship between study drug and an adverse event, the following parameters are to be considered:

- The causal relationship is reasonable on the basis of clinical judgment and given the currently available data.
- A temporal relationship exists between treatment with the study drug or protocol-specified procedures and the adverse event.
- A biologic plausibility of relationship is present.
- Any underlying concurrent illness and/or therapies the patient has received are considered.
- The event abates on discontinuation of treatment with the study drug (dechallenge), if applicable.
- The event reappears on repeat exposure to treatment with the study drug (rechallenge), if applicable.

7.1.5 Serious Adverse Events

7.1.5.1 Definition of a Serious Adverse Event

A serious adverse event is an adverse event occurring at any dose that results in any of the following outcomes or actions:

- death
- a life-threatening adverse event (ie, the patient was at immediate risk of death from the event as it occurred); does not include an event that, had it occurred in a more severe form, might have caused death
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity (refers to a substantial disruption of one's

ability to conduct normal life functions)

- a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent 1 of the outcomes listed in this definition
  NOTE: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

Hospitalizations scheduled for an elective procedure or for treatment of a pre-existing condition that has not worsened during participation in the study will not be considered serious adverse events.

An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a nonserious adverse event.

7.1.5.2 Reporting a Serious Adverse Event

All serious adverse events (as described in section 7.1.5.1) that occur either during the study period (including the protocol-defined follow-up period), regardless of judged relationship to the study drug, or after the study period, if considered related to study drug or to the patient's participation in the study, must be immediately reported to ORION Pharmacovigilance . The report must be made within 24 hours of the investigator's knowledge of the event. In addition, a blood sample will be obtained for measurement of the concentration of IPP-201101 from all patients who have a serious adverse event recorded as related to study drug (see also section 7.1.6).

Within 24 hours of the investigator's awareness of the serious adverse event, the investigator must provide ORION Pharmacovigilance, by facsimile, with a signed Serious Adverse Event Transmittal Form completed to the greatest extent possible and a copy of all relevant source documents, including the corresponding completed adverse event, medical history, and concomitant medications pages of the CRF as appropriate. (For adverse event reporting instructions see section 7.1.2.).

If it is not possible to complete all sections of the SAE form within 24 hours, transmission of the form must not be delayed and the outstanding information should be sent on a follow-up SAE form.

If the SAE is reported by telephone, all points on the SAE form should be covered in the initial telephone report and followed by a completed and signed SAE form to confirm the verbal information previously reported.

Information on SAEs will be recorded on a specific Non Carbon Repeat (NCR) SAE form. Blank copies are included in the study Investigator's File.

The SAE form must be completed as fully as possible with information relevant to the SAE(s) being reported. All fields should be populated or marked accordingly if no information is available.

In cases of death reported as an SAE, the report should detail the main and contributory causes of death. This information should also be accompanied by a death certificate or autopsy report, if

available.

For all SAEs where important or relevant information is missing, active follow-up should be undertaken. Investigators or other site personnel should inform the ORION Clinical Services' Pharmacovigilance Department of any follow-up information on a previously reported SAE. The follow-up information must be presented on an SAE form marked as follow-up. It is necessary only to provide the new information, with the SAE form signed by an Investigator.

Investigators or other site personnel should send relevant or requested supporting documentation (e.g., ECG, laboratory results, autopsy report) to the Pharmacovigilance Department of ORION Clinical Services.

The Investigator will ensure that all the necessary information is provided within the timelines stipulated by the ORION Clinical Services' Pharmacovigilance Department when the request for information is made.

Follow-up reports should be completed and faxed following the same procedure as for the initial report.

In the US and European Union (EU), the facsimile to the sponsor is to be addressed as follows:

Study Contact for Reporting Serious Adverse Events.
ORION Clinical Services Ltd
pharmacovigilance@orioncro.com
EU SAE Fax: +44 (0)1753 695 101
Back-up EU SAE Fax: +44 (0)1753 695 124
US SAE Fax: +00 1 609 514 1000
Back-up US SAE Fax: +00 1 609 452 7888

In the US, the investigator must ensure that the IRB is also informed of the event in accordance with local regulations.

In the EU, ImmuPharma or its designee must ensure that the IEC is also informed of the event in accordance with local regulations.

Each report of a serious adverse event will be reviewed and evaluated to assess the nature of the event and the relationship of the event to the study drug, study procedures, and to underlying disease. This will be done by the investigator and ImmuPharma or its designee. On the basis of this assessment, a decision will be made concerning the need for further medical intervention. If a serious, unexpected adverse event is believed to be related to the study drug or study procedures, ImmuPharma or its designee will take appropriate steps to notify all investigators participating in clinical studies of IPP-201101 conducted under ImmuPharma IND applications and the appropriate regulatory authorities.

In addition to notifying the investigators and regulatory authorities, other measures may be required, including the following:

- alteration of existing research by modification of the protocol

- discontinuation or suspension of the study
- alteration of the process of informed consent by modification of the existing consent form and informing current study participants of new findings
- modification of listings of expected toxicities to include adverse events newly identified as related to IPP-201101

7.1.6 Withdrawal Due to an Adverse Event

Any patient who experiences an adverse event may be withdrawn from the study at any time at the discretion of the investigator. If a patient is withdrawn wholly or in part because of an adverse event, both the adverse events page and termination page of the CRF will be completed at that time. In addition, a blood sample will be obtained for measurement of the concentration of IPP-201101 from all patients who have an adverse event assessed as related to study drug leading to withdrawal from the study (see also section 7.1.5.2). The patient will be monitored until the event has resolved or stabilized, until a determination of a cause unrelated to the study drug or study procedure is made, or until the patient is referred to the care of a local health care professional. The investigator must inform the medical monitor as soon as possible of all patients who are being considered for withdrawal due to adverse events. Additional reports must be provided when requested.

If a patient is withdrawn from the study for multiple reasons that include adverse events, the termination page of the CRF should indicate that the withdrawal was related to an adverse event.

Stopping rules and discontinuation criteria for any toxicity are described in section 3.6.

7.1.7 Withdrawal From the Study Due to Severe Flares

A patient will be withdrawn from the study for a severe lupus flare as per the SFI as described in section 3.6.

7.1.8 Medical Emergencies

Medical emergencies must be reported to the individual identified in the clinical study personnel contact information section of this protocol.

Equipment, supplies, and properly skilled medical personnel must be accessible for an adverse event requiring immediate treatment. Any dose of study drug (whether the investigational product, reference therapy, or a placebo), whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to ImmuPharma or its designee . When the identification of the study drug must be known, the investigator must follow the procedures outlined in section 3.8.

7.1.9 Protocol Deviations Because of an Adverse Event

If a patient experiences an adverse event or medical emergency, departures from the protocol may be allowed on a case-by-case basis. After stabilization and/or treatment for the emergency to protect patient safety has been administered, the investigator or other physician in attendance in such an emergency must contact the individual identified in the clinical study personnel

contact information section of this protocol, as soon as possible to discuss the circumstances of the emergency. The investigator, in consultation with ImmuPharma or its designee, will decide whether the patient should continue to participate in the study. Any protocol deviation related to adverse events must be noted on the CRF and in source documents along with the reason for such deviations.

7.2 Clinical Laboratory Tests

All clinical laboratory test results outside of the reference range will be interpreted by the investigator using the following categories:

- abnormal but not a clinically significant worsening
- abnormal and a clinically significant worsening

A laboratory test result that has significantly worsened (according to medical judgment) compared with the baseline result will be recorded on the CRF as an adverse event and monitored as described in section 7.1.2. An adverse event includes a laboratory or diagnostic test abnormality (once confirmed by repeat testing) that results in the withdrawal of the patient from the study, the temporary or permanent cessation of treatment with study drug, or requires medical treatment or further diagnostic work-up.

Clinical laboratory tests (serum chemistry, hematology, and urinalysis) will be performed at screening (visit 1), baseline/start of study drug treatment (visit 2), visits 4 through 15, and at the final assessment (or early termination). Clinical laboratory tests will be performed using the central laboratory identified in the front matter of this protocol (and in the Laboratory Procedures Manual provided in the study file documents). Specific laboratory tests to be performed are listed below.

7.2.1 Serum Chemistry

The following serum chemistry tests will be performed:

- calcium
- phosphate
- sodium
- potassium
- chloride
- bicarbonate or carbon dioxide
- glucose
- blood urea nitrogen (BUN)
- creatinine
- cholesterol
- uric acid
- ALT
- AST
- lactate dehydrogenase (LDH)

- gamma-glutamyl transpeptidase (GGT)
- alkaline phosphatase
- creatine phosphokinase
- total protein
- albumin
- total bilirubin
- direct bilirubin

7.2.2 Hematology

The following hematology tests will be performed:

- hemoglobin
- hematocrit
- platelet count
- absolute neutrophil count (ANC)
- white blood cell (WBC) count and differential count
  - — polymorphonuclear leukocytes (neutrophils)
  - — lymphocytes
  - — eosinophils
  - — monocytes
  - — basophils
  - — metamyelocytes

7.2.3 Urinalysis

Urinalysis will include testing for the following:

- protein
- glucose
- ketones
- blood (hemoglobin)
- pH
- specific gravity
- spot protein-creatinine ratio
- creatinine Clearance
- eGRF
- microscopic
  - — bacteria
  - — red blood cells (RBCs)
  - — WBCs

— Casts
— crystals

7.2.4 Other Clinical Laboratory Tests

(a) Serology Tests

Serology tests to be performed at screening will consist of anti-dsDNA, ANA, C3, and C4. Serology tests to be performed at each subsequent visit (visit 2 [week 0; baseline/start of study drug treatment] through visit 16 [week 52], excluding visit 3 [week 2]) will consist of anti-dsDNA Ab, C3, and C4. In addition, the following serology tests will be performed at visit 2 (week 0; baseline/start of study drug treatment), visit 4 (week 4), visit 6 (week 12), visit 9 (week 24), visit 12 (week 36), and the final assessment (or early termination) (visit 16 [week 52]): anti–U1-70K snRNP Ab, ANA, anti-Sm Ab, and CRP, IgG, IgM, IgA and IgE.

(b) Hemolysis Testing

A Coombs' test will be obtained at screening. At subsequent visits, if hemolysis is suspected or confirmed, Coombs' test, haptoglobin, and a peripheral smear will be obtained.

(c) Other Tests

Other clinical laboratory tests will be performed to ensure the safety of the patients, but will not be an assessment of the safety of the study drug.
At screening (visit 1), patients will have serology A tests for HBsAg and HCV Ab. A urine pregnancy test will be performed for all women, regardless of childbearing potential, at screening (visit 1), baseline (visit 2 [week 0]), visits 4 through 15 (weeks 4 through 48), and the final assessment (or early termination) (visit 16 [week 52]). Any patient becoming pregnant during the study will be withdrawn. All pregnancies that occur during the study, or within 14 days of completion of the study, are to be reported immediately to the individual identified in the clinical study personnel contact information section of this protocol, and the investigator must provide ImmuPharma or its designee, by facsimile, with a signed pregnancy tracking form. The facsimile to the sponsor is to be addressed as follows: to be determined. All patients who become pregnant will be monitored to the completion or termination of the pregnancy. If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age) will be reported to the sponsor. Any complication of pregnancy will be reported as an adverse event or serious adverse event, as appropriate.

7.3 Vital Signs

Vital signs will be measured at all study visits. Vital signs include the following:

- pulse
- seated blood pressure (systolic and diastolic)
- temperature

Before pulse and blood pressure are measured, the patient must be in a seated position and resting for at least 5 minutes. (The same position and arm should be used each time vital signs

are measured for a given patient.) Any vital sign value that is judged by the investigator as a clinically significant change (worsening) compared to a baseline value will be considered an adverse event, recorded on the CRF, and monitored as described in section 7.1.2.

7.4 Electrocardiography

A 12-lead ECG will be conducted at screening (visit 1) and at the final assessment (or early termination). A qualified physician will be responsible for providing interpretation of the ECG. Any ECG finding that is judged by the investigator as a clinically significant change (worsening) compared to a baseline value will be considered an adverse event, recorded on the CRF, and monitored as described in section 7.1.2.

7.5 Physical Examinations

Physical examinations (including height to be obtained at the screening visit only) will be performed at screening (visit 1) and at the final assessment (or early termination). Symptom directed physical examination evaluations and the 28-joint count examination for pain and tenderness will be performed at baseline/start of study drug treatment (visit 2) and visits 4 through 16. Body weight will be recorded during all physical examinations. Physical examination findings will be classified using standard categories as listed on the CRFs. Any physical examination finding that is judged by the investigator as a clinically significant change (worsening) compared to a baseline value will be considered an adverse event, recorded on the CRF, and monitored as described in section 7.1.2.

7.6 Other Safety Measures and Variables

7.6.1 Concomitant Therapy or Medication

Concomitant therapy or medication usage will be monitored throughout the study. Details of prohibited medications may be found in section 5.2.

7.6.2 Columbia-Suicide Severity Rating Scale

An evaluation for suicidality will be administered directly to the patient using IRT. (ERT), at baseline and at each visit during the treatment period using the Columbia-Suicide Severity Rating Scale (C-SSRS). The C-SSRS assesses suicidality from ideation to behaviors and monitors the potential emergence of suicidality in clinical studies. The C-SSRS Baseline version will be performed at baseline (visit 2) and the C-SSRS since Last Visit version will be performed at visits 4 through 16 (or final assessment visit).

If the C-SSRS is positive at any visit during the treatment period, the patient will be evaluated by the investigator to determine if a formal evaluation by a trained mental health professional is indicated. If the patient is determined to be a risk to himself or herself or others, the sponsor will be notified and the patient will be withdrawn from the study.

7.6.3 Anaphylaxis Evaluation

Anaphylaxis is defined as a serious allergic reaction that is rapid in onset and may cause death (Sampson et al 2006). Any patient who experiences an adverse event that presents with signs and/or symptoms that are suggestive of an anaphylactic, anaphylactoid, or drug hypersensitivity reaction will be evaluated using the Clinical Criteria for Diagnosing Anaphylaxis. The clinical criteria to be applied for diagnosing anaphylaxis are in Appendix I.

7.7 Methods and Timing of Assessing, Recording, and Analyzing Safety Data

Methods and timing of assessing safety data are discussed in section 3.11. Procedures for recording safety data are discussed in section 13.1, and methods of analyses are discussed in section 9.7.

Furthermore, all adverse events will be reviewed on a periodic basis (eg, scheduled safety reviews for study drug) as interim/preliminary safety databases become available (see section 7).

An independent, external DSMB will oversee the safety of the patients enrolled in the study and monitor the occurrence of flare throughout the study (see section 3.6). This study may be prematurely terminated if, in the opinion of the DSMB or the sponsor, there is sufficient and reasonable cause. Written notification documenting the reason for study termination will be provided by the terminating party to all involved.

8 ASSESSMENT OF PHARMACOKINETICS AND IMMUNOGENICITY

8.1 Pharmacokinetic Assessment

8.1.1 Pharmacokinetic Blood Sampling

Blood samples (5 mL) for pharmacokinetics will be collected from patients at selected North American and Western European study centers via venipuncture or indwelling catheter prior to and 5 minutes and 1, 2, and 24 hours after study drug administration at weeks 0, 16, and 32 (visits 2, 7, and 11, respectively). A blood sample for measurement of the concentration of IPP-201101 will also be obtained from all patients who have a serious adverse event and/or have an adverse event leading to withdrawal from the study. The actual dates and times of study drug administration and the date and time of sampling will be recorded on the CRF.

8.1.2 Processing, Handling, and Shipping of Samples for Pharmacokinetic Analysis

Instructions for processing, handling, and shipping blood samples for pharmacokinetic analysis will be provided to the study centers in the laboratory manual provided by ImmuPharma or its designee..

8.2 Immunogenicity

Anti–IPP-201101 Ab testing will be performed at visit 2 (week 0; baseline/start of study drug treatment), visit 3 (week 2), visit 4 (week 4), visit 6 (week 12), visit 8 (week 20), visit 10 (week 28), visit 12 (week 36), visit 14 (week 44), and the final assessment (or early termination) (visit 16 [week 52]). All samples will be collected prior to administration of study drug at that particular visit.

Any patient with a positive test result in the confirmatory assay at the final study visit will be followed with additional immunogenicity testing at 8-week intervals until the level returns to baseline value or the levels are judged by the investigator to be chronic, or the patient is lost to follow-up.

8.3 Methods and Timing of Pharmacokinetic Blood Sampling and Immunogenicity

Methods and timing of blood sampling for plasma concentrations of IPP-201101 and presence of anti–IPP-201101 Ab are discussed in section 3.11. Procedures for recording blood sampling for plasma concentrations and detection of anti–IPP-201101 Ab are discussed in section 13.1. Methods for analyses of blood samples for concentrations of IPP-201101 and of anti–IPP-201101 Ab (as noted above in section 8.2) are discussed in section 10.8.

9 ASSESSMENT OF IN VITRO INTRACELLULAR AND SECRETED CYTOKINE RESPONSE

9.1 Blood Sampling for in vitro intracellular and secreted cytokine response

Blood samples (5 mL) for in vitro intracellular and secreted cytokine response will be collected from patients at selected study centers via venipuncture or indwelling catheter prior study drug administration at weeks 0, 4, 24, and 48 (visits 2, 4, 9 and 15, respectively). The actual dates and times of study drug administration and the date and time of sampling will be recorded on the CRF.

9.2 Processing, Handling, and Shipping of Samples for in vitro intracellular and secreted cytokine response

Instructions for processing, handling, and shipping blood samples for in vitro intracellular analysis will be provided to the study centers in the laboratory manual provided by ImmuPharma or its designee.

9.3 Methods and Timing of in vitro proliferation and secreted cytokine response

Methods and timing of blood sampling for in vitro intracellular and secreted cytokine response of IPP-201101 are discussed in section 3.11. Procedures for recording blood sampling are discussed in section 13.1. Methods for analyses of blood samples for in vitro proliferation and secreted cytokine response of IPP-201101 are discussed in section 10.9.

10 STATISTICS

10.1 Study Design and Randomization

This is a Phase 3 randomized, double-blind, parallel-group, placebo-controlled study. Treatment assignment will be stratified for the following 3 baseline characteristics (as described in section 3.3): by region, SLEDAI-2K screening total score (6 to 9 or ≥10), and racial-ethnic group classification (black/Hispanic or others). Within each stratum, eligible patients will be randomly

assigned with a 1:1 ratio to receive either 200 mcg of IPP-201101 or placebo sc every 4 weeks for 48 weeks. Study investigators, patients, and ImmuPharma study staff will be blinded to the treatment assignments during the study.

10.2 Sample Size and Power Considerations

This study is designed to estimate and assess the significance of the difference between a 200-mcg dose of IPP-201101 and placebo in the proportion of SRI responders at week 52. With 100 evaluable patients per group (200 in total), this study will have 90% or greater power to detect a 25% or greater difference in the proportion of SRI responders between the IPP-201101 group and the placebo group or to detect a 20% difference with an 80%power. This projection using the Pearson
Chi-square test (2-sided, alpha=0.05) is based on an anticipated placebo effect at week 52 of 40% to 45%. This range covers the placebo effect reported in the literature (Navarra et al 2009, van Vollenhoven et al 2010, Wallace et al 2009) and in a Phase 2b, multicenter, randomized, double-blind, placebo-controlled dose-ranging study of IPP-201101 (study IP-004). The difference between placebo and active which is used in the sample size calculation is 25% based on the results of the Phase IIb study (IP-004) with the same formulation (Zimmer et al. ACR 2012)

10.3 Analysis Sets

The set of randomized patients will include all patients randomly assigned to a treatment at enrollment, regardless of whether or not a patient took any study drug.

The safety analysis set will include all patients who took at least 1 dose of study drug. The full analysis set will include all patients in the safety analysis set.

10.4 Data Handling Conventions

All available data will be included for evaluation. For the purpose of efficacy analysis, missing or invalid values will be imputed using data from the previous visit for individual items and scores in the questionnaires and scales. For a derived score involving multiple items, the missing or invalid individual items will be imputed first before calculating the derived scores based on the complete individual item values. These rules apply only to the visits in which the patient is currently in the study and some data or an individual item is missing. If an assessment is not done at a visit, the missing data will not be imputed. The justification for using data from the previous visit is based on medical judgment. For the SF-36 questionnaire, the Half-Scale Missing Data Estimation (Half-Scale MDE) (Ware et al 2007) method will be used to estimate the missing values for calculating the 8 health domain scales.

Missing or invalid laboratory test results will not be estimated for biomarker analysis or safety analysis.

10.5 Study Population

The set of randomized patients (see section 10.3) will be used for all study population summaries unless otherwise noted. Summaries will be presented by treatment group and for all patients.

10.5.1 Patient Disposition

Data from patients screened, patients screened but not randomized, patients randomized in the study, patients randomized but not treated, patients in the safety analysis set, patients in the full analysis set, patients who complete the study, and patients who withdraw from the study by reason for discontinuation will be summarized using descriptive statistics.

10.5.2 Demographic and Baseline Characteristics

Patient demographic and baseline characteristics, including medical history, prior medications, and physical examination and 12-lead ECG findings, will be summarized by treatment group and stratification factors and overall. For continuous variables, the descriptive summary statistics will include number (n), mean, standard deviation (SD), standard error (SE), median, minimum, and maximum. For categorical variables, patient counts and percentages will be provided. Categories for missing data will be presented if necessary.

10.6 Efficacy Analysis

Efficacy evaluation will be based on the full analysis set (see section 10.3) that includes all patients who received at least 1 dose of the study drug.

10.6.1 Primary Variable

The primary efficacy variable is the proportion of patients achieving a combined clinical response using the SRI assessed at week 52. An SRI response is defined as a reduction from baseline in the SLEDAI-2K score of at least 4 points, no worsening in PhGA (with worsening defined as an increase in PhGA of more than 0.30 point from baseline), no new BILAG A body system score, and no more than 1 new BILAG B body system score from baseline.

10.6.2 Secondary Variables

Secondary efficacy variables and endpoints are as follows:

- proportion of patients achieving an SRI response at each visit during the treatment period
- proportion of patients achieving a reduction of at least 4 points in the SLEDAI-2K total score at each visit during the treatment period
- proportion of patients achieving a clinical SLEDAI-2K response at each visit during the treatment period, where the clinical response is defined as a reduction of at least 4 points in the SLEDAI-2K clinical score
- proportion of patients achieving a BILAG-2004 response at each visit during the treatment period (no new BILAG A body system score and no more than 1 new BILAG B body system score from baseline)
- proportion of patients achieving a BILAG-2004 clinical response at each visit during the treatment period (an improvement in at least 1 category from a B score to a

C or D score, with no worsening in any other category)

- proportion of patients showing no worsening on a PhGA scale at each visit during the treatment period
- proportion of patients achieving a reduction of 5 points in the SLEDAI-2K total score at each visit during the treatment period
- proportion of patients achieving a reduction of 6 points in the SLEDAI-2K total score at each visit during the treatment period
- proportion of patients achieving an SRI-5 response at each visit during the treatment period
- proportion of patients achieving an SRI-6 response at each visit during the treatment period
- proportion of patients showing an improvement in tender and swollen joint counts using the 28-joint count examination for pain and tenderness at each visit during the treatment period
- SFI at each visit during the treatment period
  - time to first mild to moderate flare
  - incidence of mild to moderate flare
  - time to severe flare (NOTE: A severe flare leads to early withdrawal)
- changes in the SDI over time (assessed at screening and weeks 24 and 52 [or final assessment])
- absolute and relative changes in the SF-36 at weeks 12, 24, 36, and 52 (or final assessment)

proportion of patients with changes in steroid dose over time throughout the study.

The exploratory efficacy variables and endpoints for this study are as follows:

- changes in the biomarkers anti-dsDNA Ab, C3, and C4 at each visit during the treatment period
- changes in the following biomarkers at weeks 4, 12, 24, 36, and 52 (or final assessment):
  - ANA
  - anti–U1-70K snRNP Ab
  - anti-Sm Ab
  - CRP
  - IgG, IgM, IgA and IgE
- absolute and relative changes in the FACIT-Fatigue at weeks 12, 24, 36, and 52 (or final assessment)
- in vitro intracellular and secreted cytokine response

10.6.3 Planned Method of Analysis

10.6.3.1 Primary Efficacy Analysis

The efficacy evaluation will be based on the full analysis set, which will include all patients who receive at least 1 dose of study drug. The statistical method to be used for the SRI is the logistic regression model with treatment and stratification factors as main factors. Patients who withdraw from the study are classified as nonresponders as measured by SRI at week 52 in the primary analysis. The SRI is linked to the model factors through the logit function. The

likelihood-ratio–based Chi-square statistics will be used for testing the treatment difference between IPP-201101 and placebo in SRI at week 52 at the significance level 0.05. The odds ratio (active/placebo) and associated 95% confidence interval will be determined from the logistic regression model.

As sensitivity analyses, the primary analysis will be repeated using another 3 imputation methods to estimate missing SRI at week 52 according to the reason for withdrawal. In the 1st method, patients who withdraw because of lack of efficacy will be classified as treatment failures assessed by SRI at week 52. For patients who withdraw because of other reasons, their missing SRI at week 52 will be estimated using the multiple imputation method (Little and Rubin, 2002). The imputation values will be drawn from the categories formed by treatment group and randomization stratum to which the patient belongs. In the 2nd method, the missing SRI at week 52 will be imputed using the last observation carried forward (LOCF) method. In the 3rd method, patients who withdraw and those completers who used prohibited medication within 8 weeks from week 52 will be classified as nonresponders.

10.6.3.2 Secondary Efficacy Analysis

Secondary efficacy variables will be summarized using the descriptive statistics by treatment group and time point. Safety evaluations will include all patients who received at least 1 dose of study drug. Descriptive statistics will be used to summarize the safety variables.

10.7 Safety Variables and Analysis

The safety analysis set (see section 9.3) will be used for all safety analyses.

10.7.1 Study Drug Exposure

Study drug exposure will be summarized by treatment group and stratification factors at baseline for all patients who received at least 1 dose of the study drug (safety analysis set) during the study. The exposure will be characterized by treatment duration and number of injections received. Treatment duration is the number of days from the 1st to the last dose.

10.7.2 Safety Variables

The overall safety and tolerability of IPP-201101 treatment will be assessed throughout the study by evaluating adverse events and the following additional safety variables:

- clinical laboratory (serum chemistry, hematology, and urinalysis) test results at each visit during the treatment period
- vital signs (systolic and diastolic blood pressures, pulse, temperature, and body weight) measurements at each visit during the treatment period
- 12-lead ECG findings at week 24 and the final assessment (or early termination) (week 52)
- suicidality using the C-SSRS at each visit during the treatment period
- adverse events that suggest an anaphylactic reaction to study drug during the treatment period

- physical examination findings, including physical examination symptom directed findings, at selected time points throughout the study
- concomitant medication usage throughout the study

10.7.3 Safety Analysis

For continuous variables, descriptive statistics (n, mean, SD, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point, including endpoint. For categorical variables, patient counts and percentages will be provided. Descriptive summaries of serious adverse events, patient withdrawals because of adverse events, and clinically significant abnormal values (clinical laboratory or vital signs values) on the basis of predefined criteria will also be provided. Summaries will be presented by treatment group and for all patients.

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). A patient will be counted only once in each preferred term or system organ class category for the analyses of safety. Summaries will be presented for all adverse events (overall and by severity), adverse events determined by the investigator to be treatment related (overall and by severity), serious adverse events, and adverse events causing withdrawal from the study. Summaries will be presented by treatment group and for all patients. Patient listings of deaths, other serious adverse events, and adverse events leading to withdrawal will be presented.

Changes in laboratory and vital signs measurement data will be summarized descriptively. All values will be compared to prespecified boundaries in order to identify clinically significant changes or values, and such values will be listed.

Newly occurring physical examination abnormalities will be identified and listed.

The use of concomitant medications will be summarized by therapeutic class using descriptive statistics. Concomitant medications will include all medications taken while the patient is treated with study drug. Concomitant medication usage will be summarized as present at screening, ongoing at baseline/start of study drug treatment
(visit 2 [week 0]), and started any time after visit 2 (week 0) through visit 16 (week 52).

Cumulative positive C-SSRS outcomes during the study will be summarized by treatment group.

10.8 Pharmacokinetic and Immunogenicity Analysis

IPP-201101 plasma concentration data will be summarized by time point. Plasma concentration data may also be included in population pharmacokinetic analyses.

An attempt may be made to establish an exposure-response relationship and/or to correlate systemic exposure with relevant safety parameters. In order to perform the exposure-response analysis successfully, it is extremely important that the actual collection times for pharmacokinetic blood samples be recorded accurately.

The immunogenicity of IPP-201101 will be evaluated by determining any presence of anti–IPP-201101 Ab at weeks 2, 4, 12, 20, 28, 36, and 44 and the final assessment (week 52 or early termination). Testing results will be listed and findings may be summarized as necessary.

10.9 In vitro intracellular and secreted cytokine response

In vitro intracellular and secreted cytokine response data will be summarized by time point.

In vitro intracellular and secreted cytokine response of IPP-201101 will be evaluated to assess secreted cytokine profile and intracellular modification linked to the treatment at weeks 0, 4, 24 and 48.Testing results will be listed and findings may be summarized as necessary.

10.10 Planned Interim Analysis

There is no planned interim analysis.

10.11 Reporting Deviations From the Statistical Plan

Deviations from the statistical plan, along with the reasons for the deviations, will be described in protocol amendments, the complete statistical plan, the clinical study report, or any combination of these, as appropriate.

11 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The medical experts, study monitors, auditors, and health authority inspectors (or their agents) will be given direct access to source data and documentation (eg, medical charts/records, laboratory test results, printouts, videotapes) for source data verification, provided that patient confidentiality is maintained in accordance with local requirements.

Each investigator must maintain, at all times, the primary records (ie, source documents) of each patient's data. Examples of source documents are hospital records, office visit records, examining physician's finding or notes, consultant's written opinion or notes, laboratory reports, drug inventory, study drug label records, and CRFs that are used as the source (see section 3.9).

Each investigator will maintain a confidential patient identification list that allows the unambiguous identification of each patient. All study-related documents must be kept until notification by ImmuPharma.

12 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Protocol Amendments and Protocol Deviations and Violations

12.1.1 Protocol Amendments

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favorable opinion of a written amendment by the IEC/IRB, except when necessary to eliminate immediate safety concerns to the patients or when the change involves only logistics or administration. Each principal investigator and the sponsor will sign the protocol amendment.

12.1.2 Protocol Deviations, Violations, and Exceptions

A **protocol deviation** is nonadherence to protocol-specific study procedures or schedules that does not involve inclusion/exclusion criteria, primary objective variable criteria, and/or GCP guidelines. Deviations are considered minor and do not impact the study. For example, failure to perform scheduled study center visits within the protocol-defined window would be considered a deviation.

A **protocol violation** is any significant divergence from the protocol, ie, nonadherence on the part of the patient, the investigator, or the sponsor to protocol-specific inclusion/exclusion criteria, primary objective variable criteria, and/or GCP guidelines. Protocol violations will be identified and recorded, by study center personnel, on the CRF.

As a matter of policy, ImmuPharma or its designee will not grant **exceptions** to protocol-specific entry criteria to allow patients to enter a study. If under extraordinary circumstances such action is considered ethically, medically, and scientifically justified for a particular patient, prior approval from ImmuPharma or its designee and the responsible IRB/IEC, in accordance with the Standard Operating Procedure (SOP), is required before the patient will be allowed to enter the study. If investigative center personnel learn that a patient who did not meet protocol eligibility criteria was entered in a study (a protocol violation), they must immediately inform ImmuPharma or its designee. Such patients will be discontinued from the study, except in a rare instance following review and written approval by ImmuPharma or its designee and the responsible IRB/IEC, according to the applicable SOP.

12.2 Information to Study Personnel

Each investigator is responsible for giving information about the study to all staff members involved in the study or in any element of patient management, both before starting the practical performance of the study and during the course of the study (eg, when new staff become involved). Each investigator must assure that all study staff members are qualified by education, experience, and training to perform their specific responsibilities. These study staff members must be listed on the study center authorization form, which includes a clear description of each staff member's responsibilities. This list must be updated throughout the study, as necessary..The study monitor is responsible for explaining the protocol to all study staff, including each investigator, and for ensuring their compliance with the protocol. Additional information will be made available during the study when new staff become involved in the study and as otherwise agreed upon with either the investigator or the study monitor.

12.3 Study Monitoring

To ensure compliance with GCP, the study monitor or representative is responsible for ensuring that the study is conducted according to applicable SOPs, the protocol, and other written instructions and regulatory guidelines.

The study monitor is the primary association between the sponsor and each investigator. The main responsibilities of the study monitors are to visit each investigator before, during, and after the study to ensure adherence to the protocol, that all data are correctly and completely recorded

and reported, and that informed consent is obtained and recorded for all patients before their participation in the study.

The study monitors will contact each investigator and visit the study center at regular intervals throughout the study. The study monitor will be permitted to check and verify the various records (CRFs and other pertinent source data records, to include specific electronic source documentation [see section 3.9]) relating to the study to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data being recorded. If electronic case report forms (eCRFs) are used for the study, the study monitor will indicate verification by electronically applying source document verification (SDV) flags to the eCRF and will ensure that all required electronic signatures are being implemented accordingly.

As part of the supervision of study progress, other sponsor personnel may, on request, accompany the study monitor on visits to the study center. Each investigator and assisting staff must agree to cooperate with the study monitor to resolve any problems, errors, or possible misunderstandings concerning the findings detected in the course of these monitoring visits.

12.4 Audit and Inspection

The sponsor may audit the study center to evaluate study conduct and compliance with protocols, SOPs, GCPs, and applicable regulatory requirements. The ImmuPharma or its designee quality assurance unit, independent of the Clinical Research Department, is responsible for determining the need for (and timing of) a study center audit.

Each investigator must accept that regulatory authorities and sponsor representatives may conduct inspections to verify compliance of the study with GCPs.

12.5 Data Quality Assurance

The handling of data, including data quality assurance, will comply with regulatory guidelines (eg, ICH and GCP) and the sponsor's SOPs and working instructions. Data management and control processes specific to this study will be described in a data management plan. All steps and actions taken regarding data management and quality assurance will be documented in a data handling report. When data management is outsourced, the contract organization will be responsible for the development and implementation of the data management plan and preparation of the data handling report according to the sponsor's standards. Incoming completed CRFs will be logged into the CRF tracking system and will be reviewed for completeness, the presence of mandatory values, dated signatures, and consistency. All medication and adverse event terms recorded on the CRF will be automatically encoded in the sponsor's database. All entries rejected by the system will be re-evaluated and corrected as appropriate according to the data on the CRF.

All data on the CRF will be entered into a validated database using double data entry. Edit checks will be implemented in the data entry panel to ensure data quality and accuracy. Responses to requests for further clarification of data recorded on the CRF will be answered, dated, and signed by the investigator. Changes will be implemented in the sponsor's database and the data review and validation procedures will be repeated as needed. All medication and

adverse event information and textual comments will be proofread for consistency between the database and the CRF; the database will be corrected appropriately. In the case when data management is outsourced, the contract organization will be responsible for database quality assurance including, but not limited to, all medication and adverse event terms as described above.

If eCRFs are used, data management at ImmuPharma or its designee will implement edit checks on the eCRF to enforce data entry guidelines, data consistency, and compliance to the protocol and regulatory requirements. Each study center coordinator will be responsible for entering study data on the eCRFs. Data management will track eCRFs and review them for completeness, the presence of mandatory values, consistency, and dated electronic signatures. In addition to checking for SDV flags, data management will electronically attach data clarification queries directly onto the eCRFs during the review process to ensure data quality. Once study center personnel have provided acceptable responses to the queries and implemented the changes on the eCRFs, data management will close the queries with the appropriate resolution status.

At the end of the study, the database will be locked and the data will be released for reporting and statistical analysis.

13 ETHICS

13.1 Informed Consent

Written informed consent will be obtained from each patient before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. The patient's willingness to participate in the study will be documented in writing in a consent form, which will be signed by the patient with the date of that signature indicated. Each investigator will keep the original consent forms, and copies will be given to the patients. It will also be explained to the patients that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

Written and/or oral information about the study in a language understandable by the patient will be given to all patients.

A separate informed consent will also be obtained from each patient for permission to obtain DNA for pharmacogenetic analysis. Entry into the study is not dependent on this separate consent.

13.2 Health Authorities and Independent Ethics Committees/Institutional Review Boards

Before this study starts, the protocol will be submitted to the national/local health authorities and to each IEC/IRB for review. As required, the study will not start at a given center before the IEC/IRB and health authority (where applicable) for each center give written approval or a favorable opinion.

13.3 Confidentiality Regarding Study Patients

Each investigator must assure that the privacy of the patients, including their personal identity and all personal medical information, will be maintained at all times. In CRFs and other documents or image material submitted to the sponsor, patients will be identified not by their names, but by an identification code (eg, initials and identification number).

Personal medical information may be reviewed for the purpose of verifying data recorded on the CRF. This review may be conducted by the study monitor, properly authorized persons on behalf of the sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential.

14 DATA HANDLING AND RECORD KEEPING

14.1 Completing and Signing Case Report Forms

Each investigator must keep a separate patient identification list showing code numbers, names, and dates of birth to allow unambiguous identification of each patient included in the study. A note will be made in the medical records that the patient is participating in a clinical study.

All required data will be recorded on the CRF by study center personnel according to the data entry guidelines provided by ImmuPharma or its designee. All CRFs must be kept in good order and updated so they always reflect the latest observations on the patients participating in the study.

When paper CRFs are used, they will be completed legibly in black ink, with reasons given for missing data. Any corrections to the data will be made in a manner that does not obscure the original entry and will be dated and initialed by the investigator or assigned designee. Each investigator will sign the statement on the last page of the CRF.

When eCRFs are used, electronic signatures of the investigator (or designee) will be provided. Access to the eCRF for data entry and signature is controlled by user identification and password, which are provided ImmuPharma or its designee. Study center personnel will be trained, by ImmuPharma or a designated vendor, in the use of eCRFs and application of electronic signatures before the start of the study.

Because it is extremely important to have proper data collection in a timely manner, the investigator shall complete the CRFs and provide them to the study monitor on an ongoing basis. When the study monitor requests additional data or clarification of data for the CRF, the request must be answered satisfactorily before the next monitoring visit.

14.2 Archiving of Case Report Forms and Source Documents

14.2.1 Investigator Responsibilities

All records related to the study (ie, source data, source documents, CRFs [see section 3.9], copies of protocols and protocol amendments, drug accountability forms, correspondence, patient identification lists, signed informed consent forms, and other essential documents) must

be retained until ImmuPharma notifies the institution, in writing, that records may be destroyed.

If ImmuPharma has not provided written notification of records destruction after 10 years from study completion (or earlier in the case of an institution closing), and the institution determines the study record retention is unduly burdensome, the institution may submit a written request to ImmuPharma at least 60 days before the planned disposition of the study records. No study document or image (eg, scan, radiograph, ECG tracing) should be destroyed without prior written agreement between the sponsor and each investigator. Should an investigator wish to assign the study records to another party or move them to another location, advance written notice will be given to the sponsor.

14.2.2 Sponsor Responsibilities

The sponsor will be responsible for the processing and quality control of the data. Data management and filing will be carried out as described in the sponsor's SOPs for clinical studies.

If data management and filing for this study are delegated to a contract organization, these functions will be carried out as described in the SOPs for clinical studies at that organization. These SOPs will be reviewed by the sponsor prior to the start of data management and filing activities.

The original CRFs will be archived by the sponsor for the lifetime of the product. If eCRFs are used in the study, electronic images will be archived by the sponsor for the lifetime of the product. Center-specific eCRF images will be sent to each study center for archiving.

14.3 Data Collected by Contractors

The sponsor is responsible for the correct collection of all required data according to the protocol and for the archiving of data electronically in ImmuPharma Central File.

Limathon, BLIPS system, is responsible for validation of selected lupus disease activity assessment .

The sponsor is responsible to ensure that the collection and evaluation of data by vendors adheres to protocol specifications. Electronic data from vendors will be archived by the sponsor.

15 FINANCING AND INSURANCE

A separate financial agreement will be made between each principal investigator and ImmuPharma ., before the study drug is delivered.

The study is covered under a liability insurance policy. The certificate of insurance and essential information about the insurance coverage can be provided upon request.

For covered clinical studies in the US (see 21CFR54), each investigator will provide ImmuPharma or its designee with financial information required to complete Form FDA 3454. Each investigator will notify ImmuPharma or its designee of any relevant changes during the conduct of the study and for 1 year after the study has been completed.

16 REPORTING AND PUBLICATION OF RESULTS

The sponsor is responsible for preparing a clinical study report, in cooperation with the coordinating investigator. The final report is signed by the sponsor and, if applicable, by the coordinating investigator.

When ImmuPharma or its designee generates reports from the data collected in this study for presentation to regulatory authorities, drafts may be circulated to the coordinating investigator for comments and suggestions. An endorsement of the final report will be sought from the coordinating investigator when required by local regulatory agencies.

All unpublished information given to each investigator by ImmuPharma or its designee shall not be published or disclosed to a third party without the prior written consent of ImmuPharma or its designee. The primary publication from this study will report the results of the study in accordance with the current "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" as established by the International Committee of Medical Journal Editors (www.ICMJE.org). Authorship will be restricted to parties who have editorial or conceptual input to protocol design, analysis, and manuscript preparation. The publications committee established by ImmuPharma or its designee will oversee this process. Additional publications may follow the first. Policies regarding the publication of the study results are defined in the financial agreement.

No patent application(s) based on the results of the study may be made by any investigator nor may assistance be given to any third party to make such an application without the written authorization of ImmuPharma.

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APPENDIX A
MODIFIED WORLD HEALTH ORGANIZATION TOXICITY CRITERIA

(Sample provided in this appendix is for reference only.)

Modified World Health Organization Toxicity Criteria

MODIFIED WHO RECOMMENDATIONS FOR GRADING OF ACUTE AND SUBACUTE TOXICITIES

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
HAEMATOLOGICAL					
WBC	> 4.0	3.0 - 3.9	2.0 - 2.9	1.0 - 1.9	< 1
PLT	WNL	75.0 - normal	50.0 - 74.9	25.0 - 49.9	< 25.0
Haemoglobin (g/l)	WNL	100 - normal	80 - 100	65 - 79	< 65
mmol/l)	WNL	6.2 - normal	4.95 - 6.2	4.0 - 4.9	< 4.0
(g/100 ml)	WNL	10.0 - normal	8.0 - 10.0	6.5 - 7.9	< 6.5
Granulocytes/bands	≥ 2.0	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	< 0.5
Haematologic – other	none	mild	moderate	severe	life-threatening
HAEMORRHAGE (clinical)	none	mild, no transfusion	gross, 1 - 2 U per episode	gross, 3 - 4 U per episode	massive, > 4 U per episode
INFECTION	none	mild, no active treatment	moderate, PO antibiotic	severe, IV antibiotic, anti- fungal or hospitalization	life-threatening
GASTROINTESTINAL					
Nausea	none	able to eat reasonable intake	intake significantly decreased but can eat	no significant intake	- -
Vomiting	none	once in 24 hrs	2-5 x in 24 hrs	6 - 10 x in 24 hrs	> 10 x in 24 hrs or requiring IV support
Diarrhoea	none	increase of 2 - 3 stools/day over pre-Rx	increase of 4 - 6 stools/ day, or nocturnal stools, or moderate cramping	increase of 7 - 9 stools/ day, or incontinence, or severe cramping	increase of >10 stools/ day or grossly bloody diarrhoea, or need for parenteral support
Stomatitis	none	painless ulcers, erythema, or mild soreness	painful erythema, oedema, or ulcers but can eat	painful erythema, oedema, or ulcers and cannot eat	requires parenteral or enteral support
Oesophagitis/ Obstruction	none	painless ulcers erythema, mild soreness or dysphagia	painful erythema, oedema, or ulcers or moderate dysphagia but can eat without narcotics	complete dysphagia, cannot eat solids or requires narcotics to eat	requires parenteral or enteral support or narcotics or perforation
Anorexia	none	mild	moderate	severe	life-threatening
Gastritis/ulcer	no	antacid	requires vigorous medical management or nonsurgical treatment	uncontrolled by medical management; requires surgery	perforation or bleeding
Small bowel obstruction	no	- -	intermittent, no intervention	requires intervention	requires operation
Intestinal fistula	no	- -	- -	yes	- -
GI – other	none	mild	moderate	severe	life-threatening
OTHER MUCOSAL	none	erythema, or mild pain not requiring treatment	patchy and serosanguinous discharge or non-narcotic for pain	confluent fibrinous mucositis or ulceration or narcotic for pain	necrosis

WHO TOXOCITY GRADING CRITERIA

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
LIVER					
Bilirubin	WNL	- -	< 1.5 x N	1.5 - 3.0 x N	> 3.0 x N
Transaminases (SGOT/AST, SGPT/ALT)	WNL	< 2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	> 20.0 x N
Alk phosphatase or 5'nucleotidase	WNL	< 2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	> 20.0 x N
Liver – clinical	no change from baseline	- -	- -	precoma	hepatic coma
Liver – other	- -	mild	moderate	severe	life-threatening
RENAL & BLADDER					
Creatinine	WNL	<1.5 x N	1.5 - 3.0 x N	3.1 - 6.0 x N	> 6.0 x N
Proteinuria	no change	1+ or <0.3 g% or <3 g/l	2 - 3 + or 0.3 - 1.0 g% or 3 - 10 g/l	4 + or > 1.0 g% or > 10 g/l	nephrotic syndrome
Haematuria	negative	micro only	gross, no clots	gross + clots	requires transfusion
BUN (mg%)	WNL, < 20	21 - 30	31 - 50	> 50	- -
(mmol/l)	WNL, < 7.5	7.6 - 10.9	11 - 18	> 18	- -
Haemorrhagic cystitis	none	blood on microscopic examination	frank blood, no treatment required	bladder irrigation required	requires cystectomy or transfusion
Renal failure	- -	- -	- -	- -	dialysis required
Incontinence	normal	with coughing, sneezing, etc	spontaneous, some control	no control	- -
Dysuria	none	mild pain	painful or burning urination controlled by pyridium	not controlled by pyridium	- -
Urinary retention	none	residue > 100ml or occasional catheter or difficulty initiating stream	self-catheter required for voiding	surgery required(IUR or dilatation)	- -
Increased frequency/ urgency	no change	increase in frequency or nocturia up to 2 x normal	increase > 2 x normal but < hourly	with urgency and hourly or more or requires catheter	- -
Bladder cramps	none	- -	yes	- -	- -
Ureteral obstruction	none	unilateral, no surgery required	bilateral, no surgery required	incomplete bilateral, but stents,nephrostomy tubes or surgery needed	complete bilateral obstruction
GU fistula	none	- -	- -	yes	- -
Kidney/bladder - other	- -	mild	moderate	severe	life-threatening
ALOPECIA	no loss	mild hair loss	pronounced or total hair loss	- -	- -
PULMONARY					
Dyspnoea	none or no change	asymptomatic, with abnormality in PFTs	dyspnoea on significant exertion	dyspnoea at normal level of activity	dyspnoea at rest
pO2 / pCO2	no change or pO2 > 85 and pCO2 < 40	pO2 71-85 pCO2 41-50	pO2 61-70 pCO2 51-60	pO2 51-60 pCO2 61-70	pO2 ≤ 50 or pCO2 > 71

WHO TOXICITY GRADING CRITERIA

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
DLCO	> 90% of pretreatment	76 - 90% of pretreatment	51 - 75% of pretreatment	26 - 50% of pretreatment	≤ 25% of pretreatment
Pulmonary fibrosis	none	radiographic changes, asymptomatic	- -	changes with symptoms	- -
Pulmonary oedema	none	- -	- -	radiographic changes and diuretic needed	requires intubation
Pneumonia (non-infectious)	none	radiographic changes, no steroids needed	steroids required	oxygen required	assisted ventilation required
Pleural effusion	none	present	- -	- -	- -
ARDS	none	mild	moderate	severe	life-threatening
Cough	no change	mild, relieved by OTC medications	requires narcotic antitussive	uncontrolled cough	- -
Pulmonary - other	- -	mild	moderate	severe	life-threatening
ALLERGY	none	transient rash drug fever < 38°C	urticaria, drug fever ≥ 38°C, mild bronchospasm	serum sickness, bronchospasm, parenteral medication	anaphylaxis
CARDIAC					
Cardiac dysrhythmias	none	asymptomatic, transient, no therapy required	recurrent or persistent, no therapy required	requires treatment	requires monitoring; or hypotension or ventricular tachycardia or fibrillation
Cardiac function	none	asymptomatic, decline of resting LVEF < 20% of baseline	asymptomatic decline of resting LVEF > 20% of baseline	mild CHF, responsive CHF to therapy	severe or refractory
Cardiac ischaemia	none	non-specific T wave flattening	asymptomatic ST and T wave changes for ischaemia	angina without evidence for infarction	acute myocardial infarction
Cardiac-pericardial	none	asymptomatic effusion, no intervention	pericarditis (rub, chest pain, ECG changes)	symptomatic effusion; drainage	tamponade; drainage urgently required
Cardiac - other	none	mild	moderate	severe	life-threatening
Hypertension	none or no change	asymptomatic, transient increase by > 20mm Hg (D) or to > 150/100 if previously WNL. No treatment	recurrent or persistent increase by > 20 mm Hg (D) or to >150/100 if previously WNL. No treatment	requires therapy	hypertensive crisis
Hypotension	none or no change	changes not requiring therapy (including transient orthostatic hypotension)	requires fluid replacement or other therapy but not hospitalisation	requires therapy and hospitalisation; resolves within 48 hrs of stopping the agent	requires therapy and hospitalisation for > 48hrs the agent
Phlebitis/thrombosis embolism	- -	- -	superficial phlebitis(not local)	deep vein thrombosis	major event (cerebral/hepatic/ pulmonary/other infarction) or pulmonary embolism
Oedema	none	1+ or dependent in evening only	2+ or dependent throughout day	3+	4+, generalized anasarca

WHO TOXICITY GRADING CRITERIA

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
NEUROLOGIC					
Neurosensory	none or no change	mild paraesthesias loss of deep tendon reflexes	mild or moderate objective loss; moderate paraesthesias	severe objective sensory loss or paraesthesias that interfere with function	- -
Neuromotor	none or no change	subjective weakness; no objective findings	mild objective weakness but no significant impairment of function	objective weakness with impairment of function	paralysis
Neurocortica	none	mild somnolence or agitation	moderate somnolence or agitation	severe somnolence, agitation, confusion, disorientation, hallucinations	coma, seizures, toxic psychosis
Neurocerebellar	none	slight incoordination dysdiadochokinesis	intention tremour, dysmetria slurred speech, nystagmus	locomotor ataxia	cerebellar necrosis
Neuromood	no change	mild anxiety or depression	moderate anxiety or depression	severe anxiety or depression	suicidal ideation
Neuroheadache	none	mild	moderate or severe but transient	unrelenting and severe	- -
Neuroconstipation	none or no change	mild	moderate	severe	ileus > 96 hours
Neurohearing	none or no change	asymptomatic, hearing loss on audiometry only	tinnitus	hearing loss interfering with function, correctable with hearing aid	deafness not correctable
Neurovision	none or no change	- -	- -	symptomatic subtotal loss of vision	blindness
Pain	none	mild	moderate	severe	intolerable
Behavioural change	none	change, not disruptive to subjects or family	disruptive to subjects or family	harmful to others or self	psychotic behavior
Dizziness/vertigo	none	non-disabling	- -	disabling	- -
Taste	normal	slightly altered taste, metallic taste	markedly altered taste	- -	- -
Insomnia	normal	occasional difficulty sleeping, may need pills	- -	difficulty sleeping despite medication	- -
Neurologic - other	- -	mild	moderate	severe	life-threatening
DERMATOLOGIC					
Skin	none or no change	scattered macular or papular eruption or erythema that is asymptomatic	scattered macular or macular or papular eruption or erythema with pruritus or other associated symptoms	generalized symptomatic macular, papular, or vesicular eruption	exfoliative dermatitis or ulcerating dermatitis
Local	none	pain	pain and swelling with inflammation or phlebitis	ulceration	plastic surgery indicated

WHO TOXICITY GRADING CRITERIA

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
FLU-LIKE SYMPTOMS					
Fever in absence of infection	none	37.1 - 38.0°C 98.7 - 100.4°F	38.1 - 40.0°C 100.5 - 104.0°F	> 40.0°C (104.0°F) for < 24 hrs	> 40.0°C (104.0°F) for> 24 hrs or with hypotension
Chills	none	mild or brief	pronounced or prolonged	- -	- -
Myalgia/arthralgia	normal	mild	decrease in ability to move	disabled	- -
Sweats	normal	mild and occasional	frequent or drenching	- -	- -
Malaise	none	mild, able to continue normal activities	impaired normal daily activity or bedrest <50% of waking hours	in bed or chair > 50% of waking hours	bed ridden or unable to care for self
Flu-like symptoms	- -	mild	moderate	severe	life-threatening
WEIGHT GAIN	< 5%	5.0 - 9.9%	10.0 - 19.9%	≥ 20%	- -
WEIGHT LOSS	< 5%	5.0 - 9.9%	10.0 - 19.9%	≥ 20%	- -
METABOLIC					
Hyperglycaemia	< 116 mg/dl < 6.2 mmol/l	116 – 160 6.2 - 8.9	161 – 250 9.0 - 13.9	251 – 500 14.0 - 27.8	> 500 or ketoacidosis > 27.8 or ketoacidosis
Hypoglycaemia	> 64 mg/dl > 3.6 mmol/l	55 – 64 3.1 - 3.6	40 – 54 2.2 - 3.0	30 – 39 1.7 - 2.1	< 30 < 1.7
Amylase	WNL	< 1.5 x N	1.5 - 2.0 x N	2.1 - 5.0 x N	> 5.1 x N
Hypercalcaemia	< 10.6 mg/dl < 2.65 mmol/l	10.6 - 11.5 2.65 - 2.87	11.6 - 12.5 2.88 - 3.12	12.6 - 13.5 3.13 - 3.37	≥ 13.5 ≥ 3.37
Hypocalcaemia	> 8.4 mg/dl > 2.1 mmol/l	8.4 - 7.8 2.1 - 1.95	7.7 - 7.0 1.94 - 1.75	6.9 - 6.1 1.74 - 1.51	≤ 6.0 ≤ 1.50
Hypomagnaesia	> 1.4 mmol/l	1.4 - 1.2	1.1 - 0.9	0.8 - 0.6	≤ 0.5
Hyponatraemia	WNL or > 135	131 - 135	126 - 130	121 - 125	≤ 120
Hypokalaemia	WNL or > 3.5	3.1 - 3.5	2.6 - 3.0	2.1 - 2.5	≤ 2.0
Metabolic - other	- -	mild	moderate	severe	life-threatening
COAGULATION					
Fibrinogen	WNL	0.99 - 0.75 x N	0.74 - 0.50 x N	0.49 - 0.25 x N	≤ 0.24
Prothrombin time	WNL	1.01 - 1.25 x N	1.26 - 1.50 x N	1.51 - 2.00 x N	> 2.00 x N
Partial thromboplastin time	WNL	1.01 - 1.66 x N	1.67 - 2.33 x N	2.34 - 3.00 x N	> 3.00 x N
Coagulation - other	- -	mild	moderate	severe	life-threatening

WHO TOXICITY GRADING CRITERIA

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
ENDOCRINE					
Impotence/libido	normal	decrease in normal function	- -	absence of function	- -
Sterility	- -	- -	yes	- -	- -
Amenorrhoea	no	yes	- -	- -	- -
Gynaecomastia	normal	mild	pronounced or painful	- -	- -
Hot flushes	none	mild or < 1/day	moderate and ≥ 1/day	frequent and interferes with normal function	- -
Cushingoid	normal	mild	pronounced	- -	- -
Endocrine - other	- -	mild	moderate	severe	life-threatening
EYE					
Conjunctivitis/keratitis	none	erythema or chemosis, no steroids or antibiotics	steroids or antibiotics required	corneal ulceration or visible opacification	- -
Dry eye	normal	- -	requires artificial tears	- -	requires enucleation
	no change	- -	- -	yes	- -
Glaucoma	- -	mild	moderate	severe	life-threatening
Eye - other					

APPENDIX B
CONCOMITANT SYSTEMIC LUPUS ERYTHEMATOSUS MEDICATIONS

(Sample provided in this appendix is for reference only.)

Concomitant Systemic Lupus Erythematosus Medications[a]

Medication	Start date	Stop date	Stable date
DMARDS/immunosuppressants[b]			
Antimalarials Hydroxychloroquine sulfate Chloroquine	3 months prior to 1st dose	4 weeks prior to 1st dose	4 weeks prior to 1st dose
Methotrexate	3 months prior to 1st dose	4 weeks prior to 1st dose	4 weeks prior to 1st dose
Leflunomide	3 months prior to 1st dose	8 weeks prior to 1st dose unless an adequate cholestyramine washout has been completed.[c] If cholestyramine washout is performed, the last use of leflunomide must be at least 4 weeks before the 1st dose of study drug.	4 weeks prior to 1st dose
Mycophenolate mofetil	3 months prior to 1st dose	4 weeks prior to 1st dose	4 weeks prior to 1st dose
Azathioprine	3 months prior to 1st dose	4 weeks prior to 1st dose	4 weeks prior to 1st dose
Steroids			
Prednisone or prednisolone (most likely to be used)	NA	NA	4 weeks prior to 1st dose

[a] Changes in background therapies, including use of steroids, should not occur after week 44.
[b] Dosages of these medications should remain stable during the study. Patients will be withdrawn from the study if there is an increase in the dose of immunosuppressive agents (methotrexate, azathioprine, mycophenolate mofetil [MMF], leflunomide) above the baseline level or if any new immunosuppressive agents are introduced.
[c] Cholestyramine washout (per ARAVA package insert) is 8 grams administered 3 times daily for 11 days (days do not need to be consecutive). Compliance for this washout is low. DMARDS=disease-modifying antirheumatic drugs; NA=not applicable.

Excluded medications[a]	**Must stop by:**
iv pulse steroids (methylprednisolone)	>4 weeks prior to 1st dose
Tacrolimus	>3 months prior to 1st dose
Cyclosporin A	>3 months prior to 1st dose IVIG (intravenous immunoglobulin
therapy)	>3 months prior to 1st dose
Cyclophosphamide	>6 months prior to 1st dose
Biologic agents	>6 months prior to 1st dose
Fusion proteins (eg, atacicept, abatacept, etanercept)	
Therapeutic proteins	
Monoclonal antibodies[b] (eg, ocrelizumab, alemtuzumab, rituximab, epratuzumab, belimumab)	
B-cell depleting agents[b] (eg, rituximab, epratuzumab, belimumab)	B-cell count and ALC ≥ normal ranges >3 months prior to 1st dose[a]
Live or live-attenuated vaccines (eg, nasal flu vaccine; measles, mumps and rubella vaccine; oral polio vaccine, etc.)	
Investigational drug for the treatment of lupus	>6 months prior to 1st dose
Investigational drug for the treatment of a condition other than lupus	>4 weeks prior to 1st dose

[a] Patients will be withdrawn from the study if there is an initiation of new immunosuppressive therapy (eg, cyclophosphamide, cyclosporin, tacrolimus) or if there is an initiation of therapy with biologics for the treatment of systemic lupus erythematosus (SLE).
[b] For B-cell depleting agents that are also monoclonal antibodies, the most conservative restriction applies.
iv=intravenous; IVIG=intravenous immuneglobulin; ALC=absolute lymphocyte count.

Prednisone Equivalent Conversion Sheet

Steroid type in milligrams (mg)	Betametasone	Cortisol (Hydrocortisone)	Cortisone	Deflazacort	Dexamethasone	Methylprednisolone	Prednisolone	Triamcinolone
To convert to prednisone equivalent dose, divide steroid dose by factor in this row	0.12	4	5	1.2	0.15	0.8	1	0.8
Dose of prednisone (mg)								
80	9.6	320	400	96	12	64	80	64

APPENDIX C
SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY INDEX 2000

Centre:_____ Patient:_____ Visit No:_____ Scheduled:____ Date:_____ Investigator:_____
dd-mmm-yy

- ♦ Only record manifestations/items due to SLE Disease Activity
- ♦ Score manifestations occurring in **the last 4 weeks**
- ♦ TO BE USED IN CONJUCTION WITH THE SLEDAI 2000 GLOSSARY

Physicians Global Assessment	0 None	1 Mild	2 Med	3 Severe

Descriptor	YES	No	Not Known
1. Seizure			
2. Psychosis			
3. Organic brain syndrome			
4. Visual disturbance			
5. Cranial nerve disorder			
6. Lupus headache			
7. CVA			
8. Vasculitis			
9. Arthritis			
10. Myositis			
11. Urinary casts			
12. Hematuria			
13. Proteinuria			
14. Pyuria			
15. Rash			
16. Alopecia			
17. Mucosal ulcers			
18. Pleurisy			
19. Pericarditis			
20. Low complement			
21. Increased DNA binding			
22. Fever			
23. Thrombocytopenia			
24. Leukopenia			

SLEDAI FLARE INDEX	YES		NO	Not Known
25. Increase in Prednisone (mg/kg/day)	Not done	No Increase	To < 0.5g	To > 0.5
26. Added NSAID or Plaquenil				
27. New Cytoxan, Azathioprine, Methotrexate, Hospitalization (SLE)				
28. Discoid Rash, new/worse				
29. Photosensitive Rash, new/worse				
30. Lupus Profundus, new/worse				
31. Cutaneous vasculitis, new/worse				

32. Bullous lupus, , new/worse			
33. Nasopharyngeal ulcers, new/worse			
34. Pleuritis, new/worse			
35. Pericarditis, new/worse			
36. Arthritis , new/worse			
37. Fever (SLE), new/worse			
38. CNS-SLE, new/worse, requiring double prednisone or hospitalization			
39. Vasculitus, new/worse, requiring double prednisone or hospitalization			
40. Nephritis, new/worse, requiring double prednisone or hospitalization			
41. Myositis, new/worse, requiring double prednisone or hospitalization			
42. Platelets < 60.000, new/worse, req. double prednisone or hospitalization			
43. Heme-anaemia: Hb <7% req. double prednisone or hospitalization			
44. Decrease in Hb >3% requiring double prednisone or hospitalization			

SLEDAI 2000 GLOSSARY	
Seizure	*Recent onset (last 28 days). Exclude metabolic, infectious or drug cause, or seizure due to past irreversible CNS damage.*
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 behaviour. Exclude uraemia and drug causes.*
Organic brain syndrome	*Altered mental function with impaired orientation, memory or other intellectual function, with rapid onset and fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus, and inability to sustain attention to environment, plus at least two of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes.*
Visual disturbance	*Retinal and eye changes of SLE. Include cytoid bodies, retinal haemorrhages, serous exudate or haemorrhages in the choroid, optic neuritis, Exclude hypertension, infection or drug causes.*
Cranial nerve disorder	*New onset of sensory or motor neuropathy involving cranial nerves. Include vertigo due to lupus.*
Lupus headache	*Severe persistent headache: may be migrainous, but must be non-responsive to narcotic analgesia.*
CVA	*New onset of cerebrovascular accident (s). Exclude arteriosclerosis or hypertensive causes.*
Vasculitis	*Ulceration, gangrene, tender finger nodules, periungual infarction, splinter haemorrhages, or biopsy, or angiogram proof of vasculitis.*
Arthritis	*More than two joints with pain and signs of inflammation, i.e., tenderness, swelling, or effusion.*
Myositis	*Proximal muscle aching/weakness, associated with elevated creatine phosphokinase (CK) / aldolase, or electromyogram changes or a biopsy showing myositis.*
Urinary casts	*Haeme-granular or red blood cell casts.*
Haematuria	*>5 red blood cells/high power field. Exclude stone, infection or other cause.*
Proteinuria	*> 0.5 g/24 hours.*
Pyuria	*>5 white blood cells/high power field. Exclude infection.*

Rash	*Ongoing inflammatory lupus rash.*
Alopecia	*Ongoing abnormal, patchy or diffuse loss of hair due to active lupus.*
Mucosal ulcers	*Ongoing oral or nasal ulcerations due to active lupus.*
Pleurisy	*Classic and severe pleuritic chest pain or pleural rub or effusion or new pleural thickening due to lupus.*
Pericarditis	*Classic and severe pericardial pain or rub or effusion, or electrocardiogram, or echo confirmation.*
Low complement	*Decrease in CH50, C3 or C4 below the lower limit of normal for testing laboratory.*
Increased DNA binding	*>25% binding by Farr assay or above normal range for testing laboratory.*
Fever	*>38°C. Exclude infectious cause.*
Thrombocytopenia	*100,000 platelets/mm^3 (or* < 100 x 10^9 platelets/L)
Leukopenia	*<3,000 white blood cells/mm^3. Exclude drug causes.(*or < 3 x 10^9 WBC/L)

APPENDIX D
BRITISH ISLES LUPUS ASSESSMENT GROUP 2004

(Sample provided in this appendix is for reference only.)

British Isles Lupus Assessment Group 2004

Only record items due to SLE Disease Activity & assessment refers to manifestations occurring in the last 4 weeks (compared with the previous 4 weeks). ♦♦ TO BE USED WITH THE GLOSSARY ♦♦

Scoring: **ND** Not Done
1 Improving
2 Same
3 Worse
4 New
Yes/No OR Value (where indicated)
❑ **indicate if not due to SLE activity**
(default is 0 = not present)

CONSTITUTIONAL
1. Pyrexia - documented > 37.5°C ( )
2. Weight loss - unintentional > 5% ( )
3. Lymphadenopathy/splenomegaly ( )
4. Anorexia ( )

MUCOCUTANEOUS
5. Skin eruption - severe ( )
6. Skin eruption - mild ( )
7. Angio-oedema - severe ( )
8. Angio-oedema - mild ( )
9. Mucosal ulceration - severe ( )
10. Mucosal ulceration - mild ( )
11. Panniculitis/Bullous lupus - severe ( )
12. Panniculitis/Bullous lupus - mild ( )
13. Major cutaneous vasculitis/thrombosis ( )
14. Digital infarcts or nodular vasculitis ( )
15. Alopecia - severe ( )
16. Alopecia - mild ( )
17. Peri-ungual erythema/chilblains ( )
18. Splinter haemorrhages ( )

NEUROPSYCHIATRIC
19. Aseptic meningitis ( )
20. Cerebral vasculitis ( )
21. Demyelinating syndrome ( )
22. Myelopathy ( )
23. Acute confusional state ( )
24. Psychosis ( )
25. Acute inflammatory demyelinating polyradiculoneuropathy ( )
26. Mononeuropathy (single/multiplex) ( )
27. Cranial neuropathy ( )
28. Plexopathy ( )
29. Polyneuropathy ( )
30. Seizure disorder ( )
31. Status epilepticus ( )
32. Cerebrovascular disease (not due to vasculitis) ( )
33. Cognitive dysfunction ( )
34. Movement disorder ( )
35. Autonomic disorder ( )
36. Cerebellar ataxia (isolated) ( )
37. Lupus headache - severe unremitting ( )
38. Headache from IC hypertension ( )

MUSCULOSKELETAL
39. Myositis - severe ( )
40. Myositis - mild ( )
41. Arthritis (severe) ( )
42. Arthritis (moderate)/Tendonitis/Tenosynovitis ( )
43. Arthritis (mild)/Arthralgia/Myalgia ( )

Weight (kg): **Serum urea (mmol/l):**
African ancestry: Yes/No **Serum albumin (g/l):**

CARDIORESPIRATORY
44. Myocarditis - mild ( )
45. Myocarditis/Endocarditis + Cardiac failure ( )
46. Arrhythmia ( )
47. New valvular dysfunction ( )
48. Pleurisy/Pericarditis ( )
49. Cardiac tamponade ( )
50. Pleural effusion with dyspnoea ( )
51. Pulmonary haemorrhage/vasculitis ( )
52. Interstitial alveolitis/pneumonitis ( )
53. Shrinking lung syndrome ( )
54. Aortitis ( )
55. Coronary vasculitis ( )

GASTROINTESTINAL
56. Lupus peritonitis ( )
57. Abdominal serositis or ascites ( )
58. Lupus enteritis/colitis ( )
59. Malabsorption ( )
60. Protein losing enteropathy ( )
61. Intestinal pseudo-obstruction ( )
62. Lupus hepatitis ( )
63. Acute lupus cholecystitis ( )
64. Acute lupus pancreatitis ( )

OPHTHALMIC
65. Orbital inflammation/myositis/proptosis ( )
66. Keratitis - severe ( )
67. Keratitis - mild ( )
68. Anterior uveitis ( )
69. Posterior uveitis/retinal vasculitis - severe ( )
70. Posterior uveitis/retinal vasculitis - mild ( )
71. Episcleritis ( )
72. Scleritis - severe ( )
73. Scleritis - mild ( )
74. Retinal/choroidal vaso-occlusive disease ( )
75. Isolated cotton-wool spots (cytoid bodies) ( )
76. Optic neuritis ( )
77. Anterior ischaemic optic neuropathy ( )

RENAL
78. Systolic blood pressure (mm Hg) value ( ) ❑
79. Diastolic blood pressure (mm Hg) value ( ) ❑
80. Accelerated hypertension Yes/No ( )
81. Urine dipstick protein (+=1, ++=2, +++=3) ( ) ❑
82. Urine albumin-creatinine ratio mg/mmol ( ) ❑
83. Urine protein-creatinine ratio mg/mmol ( ) ❑
84. 24 hour urine protein (g) value ( ) ❑
85. Nephrotic syndrome Yes/No ( )
86. Creatinine (plasma/serum) µmol/l ( ) ❑
87. GFR (calculated) ml/min/1.73 m^2 ( ) ❑
88. Active urinary sediment Yes/No ( )
89. Active nephritis Yes/No ( )

HAEMATOLOGY
90. Haemoglobin (g/dl) value ( ) ❑
91. Total white cell count (x 10^9/l) value ( ) ❑
92. Neutrophils (x 10^9/l) value ( ) ❑
93. Lymphocytes (x 10^9/l) value ( ) ❑
94. Platelets (x 10^9/l) value ( ) ❑
95. TTP ( )
96. Evidence of active haemolysis Yes/No ( )
97. Coombs' test positive (isolated) Yes/No ( )

Revision: 12/Jan/2007

APPENDIX E
MEDICAL OUTCOME SURVEY SHORT FORM 36

(Sample provided in this appendix is for reference only.)

Medical Outcome Survey Short Form 36

Your Health and Well-Being

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. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

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

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	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 hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b. Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c. Were limited in the kind of work or other activities	☐1	☐2	☐3	☐4	☐5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐1	☐2	☐3	☐4	☐5

5. During the past 4 weeks, how much of the time 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)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b. Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c. Did work or other activities less carefully than usual	☐1	☐2	☐3	☐4	☐5

6. **During the <u>past 4 weeks</u>, to what extent has your <u>physical health or emotional problems</u> interfered with your normal social activities with family, friends, neighbors, or groups?**

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

7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**

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

8. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**

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

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐1	☐2	☐3	☐4	☐5
b. Have you been very nervous?	☐1	☐2	☐3	☐4	☐5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐1	☐2	☐3	☐4	☐5
d. Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
e. Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
f. Have you felt downhearted and depressed?	☐1	☐2	☐3	☐4	☐5
g. Did you feel worn out?	☐1	☐2	☐3	☐4	☐5
h. Have you been happy?	☐1	☐2	☐3	☐4	☐5
i. Did you feel tired?	☐1	☐2	☐3	☐4	☐5

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 friends, relatives, etc.)?

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

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	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

THANK YOU FOR COMPLETING THESE QUESTIONS!

APPENDIX F
28-JOINT COUNT EXAMINATION FOR PAIN AND TENDERNESS

(Sample provided in this appendix is for reference only.)

28-Joint Count Examination for Pain and Tenderness

ASSESSMENT OF JOINT TENDERNESS AND SWELLING AND JOINT COUNT

		Right side			Left Side		
Upper Extremity	**Joint Number**	Tenderness*	Swelling**	Not Assessed***	Tenderness*	Swelling**	Not Assessed***
Shoulder	1						
Elbow	2						
Wrist	3						
(includes radiocarpal, carpal, carpometacarpal considered as single unit)							
MCP I	4						
MCP II	5						
MCP III	6						
MCP IV	7						
MCP V	8						
IP	9						
PIP II	10						
PIP III	11						
PIP IV	12						
PIP V	13						
Lower Extremity							
Knee	14						
Joint Count							

***Tenderness Response**	****Swelling Response**	*****Not Assessed**
0 = Not Tender 1 = Positive response to questioning (tender), spontaneous response elicited (tender and winced) or withdrawal by subject on examination (tender, winced, and withdrew)	0 = None 1 = Detectable synovial thickening with or without loss of bony contours, or bulging synovial proliferation with or without cystic characteristics	Do not score artificial or ankylosed joints; enter as NA For missing joints enter NA

APPENDIX G
FUNCTIONAL ASSESSMENT OF CHRONIC ILLNESS THERAPY–FATIGUE

(Sample provided in this appendix is for reference only.)

Functional Assessment of Chronic Illness Therapy–Fatigue FACIT-Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
An4	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

SOURCE: http://www.facit.org/FACITOrg/Questionnaires.

APPENDIX H
SYSTEMIC LUPUS INTERNATIONAL COLLABORATIVE CLINICS/AMERICAN COLLEGE OF RHEUMATOLOGY DAMAGE INDEX

(Sample provided in this appendix is for reference only.)

Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index

Item	Score
Ocular (either eye, by clinical assessment)	
Any cataract ever	1
Retinal change *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 >1)	1 (2)
Cranial or peripheral neuropathy (excluding optic)	1
Transverse myelitis	1
Renal	
Estimated or measured glomerular filtration rate <50%	1
Proteinuria ≥3.5 gm/24 hours	1
or	
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 (radiograph)	1
Pleural fibrosis (radiograph)	1
Pulmonary infarction (radiograph)	1
Cardiovascular	
Angina *or* coronary artery bypass	1
Myocardial infarction ever (score 2 if >1)	1 (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) (score 2 if >1 site)	1 (2)
Venous thrombosis with swelling, ulceration, *or* venous stasis	1
Gastrointestinal	
Infarction or resection of bowel below duodenum, spleen, liver, or gall bladder ever, for cause any (score 2 if >1 site)	1 (2)
Mesenteric insufficiency	1
Chronic peritonitis	1
Stricture *or* upper gastrointestinal tract surgery ever	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 >1)	1 (2)
Osteomyelitis	1
Skin	
Scarring chronic alopecia	1
Extensive scarring or panniculum other than scalp and pulp space	1
Skin ulceration (excluding thrombosis) for >6 months	1
Premature gonadal failure	1
Diabetes (regardless of treatment)	1
Malignancy (exclude dysplasia) (score 2 if >1 site)	1 (2)

* Damage (nonreversible change, not related to active inflammation) occurring since onset 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.

APPENDIX I
CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS

(Sample provided in this appendix is for reference only.)

Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

   And at least one of the following:

   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):

   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)

   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)

   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced BP after exposure *to known allergen for that patient* (minutes to several hours):

   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP[a]

   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

[a] Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

PEF=peak expiratory flow; BP=blood pressure.
SOURCE: Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J All Clin Immunol 2006;117(2):391–7.