Neovacs SA
3-5 Impasse Reille
75014 Paris
France

CLINICAL STUDY PROTOCOL

Study product	IFNα-Kinoid emulsified with ISA 51 VG adjuvant
IND	016840
Study number and abbreviated title	IFN-K-002: Phase IIb study of IFN-K in Systemic Lupus Erythematosus
EudraCT number	2015-001341-86
Version	6.0 Amendment #4
Version date	11 April 2016
Title	A Phase IIb, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Neutralization of the Interferon Gene Signature and the Clinical Efficacy of IFNα-Kinoid in Adult Subjects with Systemic Lupus Erythematosus
Coordinating author	Thérèse Croughs, MD Chief Medical Officer, Neovacs SA
Sponsor	Neovacs S.A., 3-5 Impasse Reille, 75014 Paris, France Neovacs Inc., 50 Milk Street, Boston MA 02109, USA

- CONFIDENTIAL –

NEOVACS SA APPROVAL

Date: 11 April 2016

Thérèse Croughs
(Chief Medical Officer)

T. Croughs, MD
CMO

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75014 Paris

INVESTIGATOR PROTOCOL AGREEMENT PAGE

Protocol Number and Abbreviated Title:	IFN-K-002 Phase IIb study of IFN-K in Systemic Lupus Erythematosus
EudraCT number	2015-001341-86
IND	016840

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments, and with any other study conduct procedures provided by Neovacs SA.
- To ensure that all persons assisting me with the study are adequately informed about the Neovacs SA study product(s) and other study-related duties and functions as described in the protocol.
- Not to implement any changes to the protocol without agreement from Neovacs SA and prior review and written approval from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard to the patients, or where permitted by all applicable regulatory requirements (for example, for administrative aspects of the study).
- That I am thoroughly familiar with the appropriate use of the study product(s), as described in this protocol, and any other information provided by Neovacs SA, including, but not limited to, the following: the current Investigator's Brochure (IB) or equivalent document, IB supplement (if applicable).
- That I am aware of, and will comply with, "Good Clinical Practice" (GCP) and all applicable regulatory requirements.
- That I have been informed that certain regulatory authorities require Neovacs SA to obtain and supply, as necessary, details about the Investigator's ownership interest in Neovacs SA or the investigational product, and more generally about his/her financial ties with Neovacs SA. Neovacs SA will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply Neovacs SA with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that Neovacs SA may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide Neovacs SA with an updated Curriculum Vitae.

Agreed by:

FREDERIC HOUSSIAU 11 APR 2016.

Study Chairman Name, Signature and Date

Investigator Name, Signature and Date

LIST OF CONTACTS

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2. STUDY SYNOPSIS

Title of Study:	A Phase IIb, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Neutralization of the Interferon Gene Signature and the Clinical Efficacy of IFNα-Kinoid in Adult Subjects with Systemic Lupus Erythematosus
Protocol Number:	IFN-K-002
Phase of Development:	IIb
Study Rationale:	Neovacs has prepared an adjuvanted interferon (IFN)α-kinoid (IFN-K) formulation to induce polyclonal anti-IFNα antibodies. In a Phase I-II, randomized, double-blind, placebo-controlled dose escalation study, IFN-K has been evaluated in patients with mild to moderate Systemic Lupus Erythematosus (SLE). The kinoid was generally well tolerated; few local (including tenderness, swelling, erythema and itching) or systemic reactions were reported, and were mild to moderate in severity and transient in nature. The safety profile was considered acceptable by independent boards of experts. At baseline, patients were subdivided in two subgroups based on the expression of SLE and IFN related genes. Patients with a high gene expression, i.e. with a high IFN gene signature, accounted for two thirds of the patients and their biological markers of disease (anti-double-stranded DNA [dsDNA] antibodies, C3 and C4 levels) indicated a more active disease than patients with a low IFN gene signature. All patients developed an antibody response against IFNα, and antibody levels were significantly higher in patients with a positive IFN gene signature than in patients with a negative signature. In addition, 3out of 6 patients and 4 out of 5 patients immunized with 120 mcg and 240 mcg, respectively, developed neutralizing antibodies. Furthermore, IFNα-mediated and SLE-associated gene expression was more reduced in patients immunized with IFN-K than in patients treated with the placebo. This decrease in the expression of SLE-associated genes significantly correlated with anti-IFNα antibody levels and was more pronounced in patients with the highest IFN gene signature before immunization. Furthermore, the increase in C3 complement from baseline significantly correlated with the anti-IFNα antibody level.
Objectives:	**Primary Objective** The primary objective of this study is to evaluate the neutralization of the IFN gene signature following treatment with IFN-K, as measured by the change from baseline of the expression of IFN-induced genes **and** to evaluate the efficacy of treatment with IFN-K using the British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) response criteria. The study will be considered as positive if a statistically significant better effect of IFN-K compared to placebo is observed on the neutralization of the IFN gene signature and if at least a trend favoring IFN-K is observed on the BICLA response. **Secondary Objectives** The secondary objectives of this study are: • To evaluate the efficacy of treatment with IFN-K using: – The SLE Responder Index [(SRI)-4 and above] – The SLE Disease Activity Index-2000 (SLEDAI-2K) – The BILAG-2004 index – The Safety of Estrogen in Lupus Erythematosus National Assessment-SLEDAI (SELENA-SLEDAI) Flare index

	– The Systemic Lupus International Collaborating Clinics/American College of Rheumatology-Damage Index for Systemic Lupus Erythematosus (SLICC/ACR DI) – The Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) in patients with cutaneous lesions at baseline • To evaluate the immune response induced by IFN-K – Anti-IFNα antibody response – Anti-Keyhole Limpet Hemocyanin (KLH) antibody response – Anti-IFNα antibody neutralizing capacities • To assess the safety of IFN-K emulsified with ISA 51 VG **Exploratory Objectives** The exploratory objectives of this study are: • To assess disease activity using: – The Physician's Global Assessment (PGA) score – The 28-Tender and Swollen joint counts – A Joint Pain Visual Analog Scale (VAS) – The flare description – The changes in Lupus therapy • To assess quality of life using: – The Short Form (SF)-36 questionnaire – The Functional Assessment of Chronic Illness Therapy (FACIT) fatigue score • To assess biological parameters: – Levels of lupus related serum auto-antibodies and biomarkers – Neutralizing capacity against IFNα subtypes – Anti-IFNα and Anti-KLH antibody isotyping – IFNβ cross-neutralization – Antibody response to influenza vaccination • To assess correlations between immune responses, IFN gene signature and clinical responses
Study Design:	This will be a Phase IIb, randomized, double-blind, placebo-controlled, multicenter study. Study patients will be enrolled into one of the two treatment groups and allocated in a 1:1 randomization ratio to receive IFN-K or placebo as outlined below: • Group 1: IFN-K emulsified in ISA 51 VG • Group 2: placebo emulsified in ISA 51 VG A total of 178 patients (89 patients in each group) will be enrolled. The main study is comprised of 12 visits occurring over a period of 40 weeks. The main study will be divided into four periods: a 4-week Screening Period that will be performed to determine eligibility of the patients for randomization into the study, a 12-week Induction Period, a 12-week Maintenance Period and a 12-week Follow-up Period. Study patients will then enter in an Extended Follow-up study period for a duration of additional 240 weeks (60 months).

The total duration of the study will be 69 months (276 weeks).

Screening Period (from Study Week -4 to 0)

Patient eligibility will be determined over the course of a Screening Period.

In order to determine their eligibility, candidate patients will undergo a series of assessments and procedures as outlined in the table of study procedures. Whenever possible, screening samples should be collected before any new SLE related treatment is initiated.

Randomization will be minimized by:

- Ethnic Origin: Black, Asian, Caucasian/Hispanic, other
- Age: 18-40 & 41-65 years old
- Presence or absence of renal BILAG at screening
- With or without corticosteroids (CS) treatment at randomization
- With or without hydroxychloroquine (HCQ) treatment at randomization
- With or without Mycophenolate Mofetil (MMF) treatment at randomization

Induction Period (Week 0 to Week 12)

Eligible patients will be randomized (according to a 1:1 randomization ratio) and will enter the 12-week Induction Period during which each patient will receive three administrations of IFN-K (240 mcg, as two injections) or placebo emulsified in ISA 51 VG at Week 0 (Visit 2), Week 1 (Visit 3), Week 4 (Visit 4).

The patients will undergo planned assessments and procedures as outlined in the table of study procedures (Table 1).

The key efficacy evaluations include repeated assessments of disease activity with various scoring metrics, as well as laboratory analysis of blood and urine samples.

Maintenance Period (Week 12 to Week 24)

After the Induction Period, patients will be followed during the 12-week Maintenance Period.

During the Maintenance Period, patients will undergo planned assessments and procedures as outlined in the table of study procedures.

Two booster doses (120 mcg of IFN-K or placebo emulsified in ISA 51 VG) will be administered at Week 12 (Visit 6) and at Week 24 (Visit 9).

Follow-up Period (Week 24 to Week 36)

After the Maintenance Period, patients will be followed during the 12-week Follow-up Period.

Patient will not receive any study treatment during this period.

During the Follow-up Period, patients will undergo planned assessments and procedures as outlined in the table of study procedures.

Extended Follow-up Period (Week 36 to Week 276)

After the Follow-up Period of the main study, all patients who have completed the study during the blinded period will enter into an Extended Follow-up Period. Then, when the study results are available, only patients who have received IFN-K will continue the Extended Follow-up Period for up to 60 months (240 weeks) after Visit 12 (Week 36).

Patient will not receive any study treatment during this period.

During the Extended Follow-up Period, patients will undergo planned assessments and procedures as outlined in the table of study procedures. The

	visit at Week 276 (Month 69) (FU10 Visit) will be considered as the last planned visit. If patients remain positive for anti-IFNα neutralizing antibodies after this Extended Follow up Period, they will be proposed to be enrolled in another 5-year follow up study to confirm the favorable safety profile of IFN-K. **Planned analyses** The primary analysis will be performed at Week 36 of the main study. A follow-up analysis will be performed at year 5 (week 276 - Month 69) when all patients have completed the extended follow up. For safety purpose, a descriptive analysis will be performed at regular intervals, according to Development Safety Update Report (DSUR) timelines. **Independent Data Safety Monitoring Board (iDSMB)** An iDSMB will oversee the conduct of the study and ensure the safety of participating patients. The role and responsibilities of the iDSMB will be outlined in detail in a separate iDSMB charter.

Main Eligibility Criteria:	A patient will need to meet the following eligibility criteria at study entry to be eligible for this study. **Inclusion Criteria** A patient meeting all of the following inclusion criteria at screening will be eligible for participation in the study: 1. Has had a diagnosis of SLE according to current ACR criteria (4 of 11 ACR criteria) 2. Has SLEDAI-2K ≥ 6 3. Has at least 1 BILAG A and/or at least 2 BILAG B 4. Has a positive IFN gene signature by RT-qPCR as assessed on a limited number of genes 5. Has anti-nuclear antibodies (ANA) ≥ 1:160 and/or anti-dsDNA antibodies ≥ 7.0 IU/mL 6. Be a male or female, aged between 18 and 65 years, inclusive, at the time of the screening visit 7. Agrees to receive influenza vaccination during each influenza season of the study period 8. Currently receiving at least one of the following treatment: • Corticosteroids (CS) at a dose of ≤ 20 mg of prednisone equivalent/day • Antimalarial drugs (hydroxychloroquine [HCQ] or chloroquine [CQ]); the patient must have been treated since at least 8 weeks and on stable dose for at least 4 weeks prior to first planned administration of the study product • Methotrexate (MTX); the patient must have been treated and be on stable dose (≤ 20 mg/week) for at least 12 weeks prior to the first planned administration of the study product • Azathioprine (AZA); the patient must have been treated and be on stable dose (≤ 2.5 mg/kg/day) for at least 12 weeks prior to the first planned administration of the study product • Mycophenolate mofetil (MMF), the patient must have been treated and be on stable dose (≤ 2 g/day) for at least 12 weeks prior to the first planned administration of the study product 9. Study patient and his/her partner has to use effective method of contraception for the duration of the study including the Extended Follow-up Period. Note: If of child-bearing potential, effective contraception methods include: – *Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least 6 weeks prior to the first planned administration of the study product. In case of oophorectomy alone, the reproductive status of the woman must be confirmed by follow up hormone level assessment.* – *Male sterilization (at least 6 months prior to Screening).* – *Combination of the following:* • *Oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception* ***or*** • *Placement of an intrauterine device (IUD) or intrauterine system (IUS)* • ***And*** *Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository*

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, she is considered not of child bearing potential only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

10. Is able and willing to comply with the requirements of the study protocol (e.g., completion of the diary cards, return for follow-up visits), in the opinion of the Investigator
11. Has provided written informed consent

Exclusion Criteria

A patient meeting any of the following exclusion criteria at study entry will not be eligible for the study:

1. Has active, severe lupus nephritis as defined either by the immediate need for cyclophosphamide treatment or by renal BILAG A
2. Has active, severe, neuropsychiatric SLE, defined as neuropsychiatric BILAG A
3. During the 4 months prior to the first planned administration of the study product, has been treated with corticosteroids (CS) at a dose of >20 mg of prednisone equivalent/day for > 7 consecutive days
4. Is currently receiving or has received pulse dose CS (≥ 250 mg prednisone equivalent/day) within 3 months prior to the first planned administration of the study product
5. Has received potent immunosuppressive drugs such as cyclophosphamide, cyclosporine A, oral tacrolimus within 3 months prior to the first planned administration of the study product
6. Has received abatacept, sifalimumab, rontalizumab, anifrolumab, belimumab, TNF antagonists or another registered or investigational biological therapy within 6 months prior to the first planned administration of the study product
7. Has received anti-B-cell therapy (e.g., rituximab, epratuzumab) within 12 months prior to the first planned administration of the study product
8. Has significant electrocardiogram (ECG) abnormalities that are clinically relevant and preclude study eligibility in the Investigator's opinion
9. Has inflammatory joint or skin disease other than SLE that may interfere with study assessments
10. Has any laboratory abnormality that is clinically relevant and precludes study entry in the Investigator's opinion
11. Has a history of malignant cancer, except the following treated cancers: cervical carcinoma in situ, basal cell carcinoma, or dermatological squamous cell carcinoma.

    For US patients only: Has a history of malignant cancer, except the following treated cancer: basal cell carcinoma. Note: only patients with negative screening tests for malignancy according to The American Cancer Society guidelines (see Appendix 12), documented within the 12 months prior screening visit will be enrolled.
12. Has frequent recurrences of oral or genital herpes simplex lesions (≥ 6 occurrences during the 12 months prior to first study product administration)
13. Has had an episode of shingles during the 12 months prior to the first planned administration of the study product

	14. Has no IgG against herpes simplex virus (HSV-1 and HSV-2), varicella zoster virus (VZV), cytomegalovirus (CMV) or Epstein-Barr virus (EBV) 15. Is positive for HTLV 1-2 antibodies, HIV antibodies, Hepatitis C (HCV) antibodies, or Hepatitis B surface antigen (HBsAg) 16. Is at high risk of significant infection and/or has any current signs or symptoms of infection at entry or has received intravenous antibiotics within 2 months prior to the first planned administration of the study product 17. Has received any live vaccine within 3 months prior to the first planned administration of the study product (e.g. nasal flu vaccine, oral poliomyelitis vaccine, measles-mumps-rubella vaccine, yellow fever vaccine, Japanese encephalitis vaccine, dengue vaccine, rotavirus vaccine, varicella vaccine, zoster vaccine, Bacillus Calmette-Guérin [BCG] vaccine, oral typhoid vaccine) 18. Has used any investigational or non-registered product within 30 days or 5 half-lives, whichever is longer, or any investigational or non-registered vaccine within 30 days prior to the first planned administration of the study product 19. Has a history of chronic alcohol and/or drug abuse within 6 months prior to the first planned administration of the study product 20. Is breastfeeding, pregnant, or planning to become pregnant during the study period 21. Has known hypersensitivity to any component of the study product 22. Is high-risk human papilloma virus (HPV) positive by reverse transcription polymerase chain reaction (RT-qPCR) on a cervical swab at Screening or within 3 months prior to the first planned study product administration 23. Has cytological abnormalities ≥ HSIL on a cervical swab at Screening or within 3 months prior to the first planned study product administration
Investigational Therapy:	The study product IFN-K has been developed by Neovacs SA. All study materials, prepared in compliance with current Good Manufacturing Practice (GMP) requirements and guidelines for injectable products, will be provided by Neovacs SA. The investigational therapy is composed of IFN-K/placebo emulsified in ISA-51 VG to be administered by intramuscular injection. IFN-K is a conjugated immunotherapeutic agent. It is a complex between recombinant human (rhu)-IFNα2b and KLH subunit obtained by conjugation with glutaraldehyde and subsequent inactivation/stabilization with formaldehyde and glycine treatment. It is then formulated as a solution for injection in phosphate buffer. Placebo is a sterile physiological saline solution (0.9% NaCl). ISA 51 VG is the oil-based adjuvant Montanide® ISA 51 VG. It is a sterile clear yellow liquid composed of Montanide® 80 VG, a non-ionic surfactant of plant origin in highly purified mineral oil Drakeol® 6VR. Two vials of IFN-K are emulsified in ISA 51 VG to obtain a dose of 240 mcg in a volume of 1.2 mL. The volume of study product to be injected will be adapted to the dose to be administered. One ampoule of placebo will be prepared and injected in the same way.
Treatment Duration:	Each patient will receive a dose of 240 mcg of IFN-K/placebo (1.2 mL of study product administered in two injections) at 3 visits during the Induction Period (at Week 0 [Visit 2], Week 1 [Visit 3], and Week 4 [Visit 4]). Each patient will be administered a dose of 120 mcg of IFN-K/placebo (0.6 mL of study product administered in one injection) at 2 visits during the Maintenance Period (at Week 12 [Visit 6] and Week 24 [Visit 9]). The

	duration of the intermittent study treatment will be 24 weeks from the first (Week 0 [visit 2]) to the last administration (Week 24 [visit 9]).
Allowed Prior and Concomitant therapies	During the Induction Period, standard therapy will be allowed within the study protocol limits, in particular the maximum CS dose will be 20 mg prednisone equivalent/day. From Visit 2, CS tapering will be encouraged as soon as clinically possible with a target dose ≤ 10 mg prednisone equivalent/day at Week 12 (Visit 6) and with a mandatory target dose ≤ 5 mg prednisone equivalent/day at Week 24 (Visit 9). Patients who need a dose > 10 mg prednisone equivalent/day at Week 12 will continue the study. In addition, no CS increase will be allowed between Week 12 and Week 36. Patients who have reached a CS dose ≤ 10 mg prednisone equivalent/day at Week 12 or later will be further encouraged to taper the dose of other immunosuppressive drugs. There is no particular guidance regarding permitted medications for the duration of the Extended Follow up Period.
Study Endpoints:	**<u>Primary Efficacy Endpoint</u>** Two co-primary endpoints will be evaluated in the trial: • Change from baseline in the expression of IFN-induced genes at Week 36. • Response to treatment with IFN-K as measured by the British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) response criteria at Week 36: - All BILAG A scores at baseline improve to B/C/D and all BILAG B scores improve to C/D at Week 36 *and* - No BILAG worsening in other body systems: no new BILAG A or ≥ 2 new BILAG B scores at Week 36 *and* - No worsening in SLEDAI-2K total score at Week 36 compared with baseline *and* - No deterioration in PGA (< 10% worsening) on VAS 100 mm at Week 36 compared with baseline *and* - No addition or increased dose level of anti-malarial drugs or immunosuppressive drugs or corticosteroids between Week 24 and Week 36 **<u>Secondary Endpoints</u>** *<u>Clinical secondary Endpoints</u>* • Response to treatment with IFN-K, as measured by the SLE Responder Index (SRI)-4 response criteria at Week 36: - Reduction ≥ 4 points in SELENA-SLEDAI *and* - No new BILAG A *and* - No more than 1 new BILAG B *and* - No deterioration in PGA (< 10% worsening) on VAS 100 mm compared with baseline • Response to treatment with IFN-K, as measured by SLEDAI response, defined as a reduction of the SLEDAI-2K score of at least 4 points at Week 36 compared to baseline • Response to treatment with IFN-K, as measured by BILAG grade changes by body system • Response to treatment with IFN-K, as measured by incidence of SLE flare (SELENA SLEDAI flare index, BILAG flares)

- Response to treatment with IFN-K, as measured by SLICC/ACR-DI
- Response to treatment with IFN-K, as measured by Cutaneous LE Disease Area and Severity Index (CLASI)

Immunogenicity secondary Endpoints

At timepoints specified on the flow chart, Geometric Mean Titers (GMT) and seroconversion rates for:

- Anti-IFNα binding antibody titers
- Anti-IFNα neutralizing antibody titers
- Anti-KLH binding antibody titers

Safety Endpoints

- Occurrence, intensity and relationship of any solicited local and systemic AEs during a 7-day follow-up period (i.e. day of study product administration and 6 subsequent days) after each IFN-K or placebo dose
- Occurrence, intensity and relationship of unsolicited local and systemic AEs occurring throughout the study period
- Occurrence and relationship of all SAEs occurring throughout the study period
- Occurrence and intensity of solicited injection site reactions 1 hour post study product administration
- Occurrence and intensity of solicited systemic reactions 1 hour post study product administration
- Hematological and biochemical levels within or outside the normal ranges and percent change from baseline at each visit
- Occurrence, intensity and relationship of any abnormality in physical examination, vital signs, 12-lead ECG, clinical laboratory evaluations
- Rate and severity of viral infections

Exploratory Endpoints

- Evaluation of clinical response by assessing disease activity using: PGA scores, Number of SLE flares, Time to first SLE flare in patients, 28-Tender and Swollen Joint Counts, Joint Pain VAS and incidence of patient requiring change in lupus therapy (intensification and/or addition of drugs)
- Quality of life using:
  - Changes in the SF-36 score: Physical Component Summary (PCS) and Mental Component Summary (MCS) scores
  - FACIT fatigue score
- Evaluation of biological response by assessing :
  - Changes in the levels of auto-antibodies (anti-dsDNA, anti-Smith antigen [anti-Sm], anti-RNP, anti-SSA/Ro, anti-SSB/La, anti-cardiolipin, and anti-β2-glycoprotein I antibodies)
  - Changes in the levels of biomarkers (C3, C4, CH50)
  - Neutralizing Anti-IFNα antibodies towards IFNα subtypes
  - Anti-IFNα and anti-KLH antibody isotyping
  - IFNβ cross neutralization
  - Anti-hemagglutinin antibody response

Statistical Design and Sample Size:	The primary objective of the main study (at Week 36) is to evaluate the neutralization of the IFN gene signature following treatment with IFN-K, as measured by the change from baseline of the expression of IFN-induced genes **and** to evaluate the efficacy of treatment with IFN-K using the British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) response criteria. The following assumptions were made for the sample size calculation: • The error probability for a 2-sided t-test should not exceed 5%; • The power should be 80% or higher; • The change of the expression of IFN-induced genes in patients treated with IFN-K is assumed to be -22.6% (data from study IFN-K-001); • The change of the expression of IFN-induced genes in patients treated with placebo is assumed to be 10% (data from study IFN-K-001); • The common standard deviation of the change is 68 . (data from study IFN-K-001) The assumptions for the change in expression of IFN gene signature and the standard deviation are based on the original data of study IFN-K-001 as presented in Lauwerys *et al*., 2013. With 80 evaluable patients per group, i.e. a total of 160 evaluable patients, the study will have a power of 85% to detect a difference of 32.6% in the expression of IFN-induced genes in patients treated with IFN-K compared to patients treated with placebo, assuming that the common standard deviation is 68% and using a two group t-test with a 0.050 two-sided significance level. Assuming a BICLA response of 20.6% in placebo patients and 40.6% in IFN-K treated patients, with 80 evaluable patients per group, there will be a 73% power to detect a difference of 20% in the BICLA response criterion. Assuming a rate of 10% drop-out patients, 178 patients should be enrolled in order to have 160 evaluable patients at Week 36 (80 evaluable patients in each treatment arm=90% of the enrolled patients). A follow-up analysis will be performed at the end of the Extended Follow up (Week 276) to evaluate the clinical efficacy, safety and immunogenicity.

Table 1 List of Study Procedures

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**FU1***	**FU2***
Week	**max -4**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**60** **108** **156** **204** **252**	**84** **132** **180** **228** **276**
		Dose 1 240 mcg	Dose 2 240 mcg	Dose 3 240 mcg		Dose 4 120 mcg			Dose 5 120 mcg					
Informed consent	●													
Demographic data	●													
SLE-specific and general medical history including alcohol, drug, and tobacco use. For US patient ONLY, screening for malignancy within the previous 12 months according to ACS	●													
Complete physical examination[1]	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Gynecological examination[2]	●											●		
ECG (12-lead)	●	●				●			●			●		
Chest X-ray		●										●		
Vital signs[3]	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Evaluation of eligibility	●	●												

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**FU1***	**FU2***
Week	**max -4**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**60** **108** **156** **204** **252**	**84** **132** **180** **228** **276**
		Dose 1 240 mcg	Dose 2 240 mcg	Dose 3 240 mcg		Dose 4 120 mcg			Dose 5 120 mcg					
Randomization		●												
Check contraindications		●	●	●		●			●					
Administration of study product[4]		●	●	●		●			●					
Hematology, coagulation and biochemistry (complete)[5]	●	●		●		●			●			●		
Hematology, coagulation and biochemistry (disease-oriented)[5]					●		●	●		●	●		●	●
Lymphocytes count (Total, CD4+, CD8+)		●				●			●			●	●	●
Viral serology[6]	●													
Anti-IFNα binding antibodies		●		●	●	●	●		●	●		●	●	●
Anti-IFNα neutralizing antibodies		●				●	●		●	●		●	●	●

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**FU1***	**FU2***
Week	**max -4**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**60** **108** **156** **204** **252**	**84** **132** **180** **228** **276**
		Dose 1 240 mcg	Dose 2 240 mcg	Dose 3 240 mcg		Dose 4 120 mcg			Dose 5 120 mcg					
Neutralizing Anti-IFNα antibodies towards IFNα subtypes		●				●	●		●	●		●		●[11]
Anti-IFNα and anti-KLH antibody isotyping		●				●			●			●		
IFNβ cross neutralization		●				●			●			●		
Anti-KLH binding antibodies		●				●	●		●	●		●	●	●
Anti-dsDNA antibodies	●	●				●			●			●	●	●
ANA	●	●				●			●			●	●	●
Other auto-antibodies (anti-Sm, anti-RNP, anti-SSA/Ro, anti-SSB/La, anti-cardiolipin and anti-β_2-glycoprotein I antibodies)		●				●			●			●		●[11]
Inflammatory markers (C3, C4, CH50)	●	●		●	●	●	●		●	●		●	●	●
IFN gene signature (RT-qPCR)	●													●

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**FU1***	**FU2***
Week	**max -4**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**60** **108** **156** **204** **252**	**84** **132** **180** **228** **276**
		Dose 1 240 mcg	Dose 2 240 mcg	Dose 3 240 mcg		Dose 4 120 mcg			Dose 5 120 mcg					
IFN gene signature (Affymetrix)		●				●			●			●		●[11]
Serum pregnancy test[7]	●													
Urine pregnancy test[7]		●	●	●	●	●	●	●	●	●	●	●	●	●
Urine analysis including dipstick and microscopic examination	●	●		●	●	●	●	●	●	●	●	●	●	●
SLEDAI-2K	●	●				●			●			●	●	●
PGA	●	●				●			●			●	●	●
BILAG-2004 index	●	●		●	●	●	●	●	●	●	●	●		
SELENA-SLEDAI flare index		●							●			●	●	●
SLICC/ACR DI		●										●		
28-Tender and Swollen joint counts		●				●			●			●		
Joint Pain VAS		●				●			●			●	●	●

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**FU1***	**FU2***
Week	**max -4**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**60** **108** **156** **204** **252**	**84** **132** **180** **228** **276**
		Dose 1 240 mcg	Dose 2 240 mcg	Dose 3 240 mcg		Dose 4 120 mcg			Dose 5 120 mcg					
CLASI		●				●			●			●		
SF-36 survey score		●				●			●			●	●	●
FACIT fatigue score		●				●			●			●	●	●
Record prior medication and vaccination	●													
Record concomitant medication		●	●	●	●	●	●	●	●	●	●	●	●	●
Influenza vaccination	As needed from Visit 5 at each influenza season except within 7 days before or after study product administration													
Anti-Influenza antibody response	Should be performed 28 days +/-7 days after each flu vaccination													
Record solicited injection site reactions 1 hour post study product administration[8]		●	●	●		●			●					
Record solicited systemic AEs 1 hour post study product administration[9]		●	●	●		●			●					
Provision of diary card for daily recording of solicited AEs by patients[10]		●	●	●		●			●					

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**FU1***	**FU2***
Week	**max -4**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**60** **108** **156** **204** **252**	**84** **132** **180** **228** **276**
		Dose 1 240 mcg	Dose 2 240 mcg	Dose 3 240 mcg		Dose 4 120 mcg			Dose 5 120 mcg					
Return, checking and transcription of diary card			●	●	●		●			●				
Record all AEs		●	●	●	●	●	●	●	●	●	●	●	●	●

ACR = American College of Rheumatology; ACS = American Cancer Society; AE = Adverse event; ANA = Anti-nuclear antibodies; BILAG = British Isles lupus assessment group; CLASI = Cutaneous lupus erythematosus disease area and severity index; CRP = C-reactive protein; CS = corticosteroids; DNA = Deoxyribonucleic acid; ECG = Electrocardiogram; FACIT = Functional assessment of chronic illness therapy; IFN = Interferon; KLH = Keyhole limpet hemocyanin; PGA = Physician's global assessment; RT qPCR = Reverse transcription quantitative polymerase chain reaction; SELENA = Safety of estrogen in lupus erythematosus national assessment; SF-36 = Short form-36 questionnaire; SLE = Systemic lupus erythematosus; SLEDAI = SLE disease activity index; SLICC = System Lupus International Collaborating Clinics; VAS = Visual analog scale.

[1] Including body temperature, weight and height; height being measured only during screening.

[2] Including examination of the cervix, and detection of high risk HPV (by RT qPCR) on PAP smear; unless performed and documented 3 months prior to the first planned study product administration.

[3] Vital signs include brachial pulse and blood pressure. They will be performed after patient has been in a supine position for 3 minutes. At Visits 2, 3, 4, 6 and 9, vital signs will be performed prior to and 1 hour post study product administration.

[4] 240 mcg study product administration at Visit 2, 3 and 4. 120 mcg study product administration at Visit 6 and 9.

[5] Blood samples are to be taken prior to administration of the study product, when applicable.

- Complete means Hemoglobin, complete blood cell count and differential (Red Blood Cells, White Blood Cells, Neutrophil, Lymphocyte, Platelet), INR, PT, PTT, fibrinogen, serum Urea, serum Albumine, serum creatinine level, serum Total protein, Creatinine clearance GFR, Serum Alanine Aminotransferase, Aspartate Aminotransferase, Alkaline Phosphatase, Coombs test, Circulating Anti-Coagulant, Creatine Phospho Kinase. CD19 counts will be performed at Visit 2.
- Disease oriented means Hemoglobin, complete blood cell count and differential (Red Blood Cells, White Blood Cells, Neutrophil, Lymphocyte, Platelet), INR, PT, PTT, fibrinogen, serum Urea, serum Albumine, serum creatinine level, serum Total protein, Creatinine clearance GFR, Coombs test, Circulating Anti-Coagulant, Creatine Phospho Kinase

[6] Screening virology testing at Visit 1: HBV [HBsAg], HCV, HIV, CMV, VZV, EBV, HTLV 1-2, and HSV-1, HSV-2.

[7] Serum and urine pregnancy tests for female patients of childbearing potential only.

[8] Solicited injection site reactions will be recorded by study staff 1 hour post study product administration by asking the patient about his/her perception of pain and itching sensation and via visual assessment of redness, swelling and induration.

[9]Solicited systemic AE will be recorded by study staff 1 hour post study product administration, in particular headache, fatigue, myalgia, nausea, and fever.

[10] Daily recording by patients of the presence or absence and severity of solicited local and systemic reactions on the day of the injection and the six subsequent days (i.e., 7 days in total)
[11] At extended follow-up, to be tested at patient's last visit only.

* The extended follow-up period will last for 5 years (i.e. 60 additional months, 69 months since 1st injection), with one visit every 6 months.

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4. LIST OF ABBREVIATIONS

˚C	Degrees Celsius
ACR	American College of Rheumatology
ACS	American Cancer Society
AE	Adverse Event
ALT	Alanine aminotransferase
ANA	Anti-Nuclear Antibodies
ANCOVA	Analysis of Covariance
Anti-RNP	Anti-Ribonucleoprotein
Anti-SSA	Anti-Sjögren's-syndrome A
Anti-SSB	Anti-Sjögren's-syndrome B
APECED	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy
AST	Aspartate aminotransferase
AZA	Azathioprine
BCG	Bacillus Calmette-Guérin vaccine
BICLA	British Isles Lupus Assessment Group-based Composite Lupus Assessment
BILAG	British Isles Lupus Assessment Group
CA	Competent Authorities
CI	Confidence Interval
CIN	Cervical intraepithelial neoplasia
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CMV	Cytomegalovirus
CPK	Creatine PhosphoKinase
CQ	Chloroquinine
CRA	Clinical Research Associate
CrCl GFR	Creatinine Clearance (Glomular Filtration Rate)
CRO	Contract Research Organization
CRP	C-Reactive Protein
CS	Corticosteroid
CVS	Cardio Vascular System
CXCL	Chemokine (C-X-C motif) ligand
DNA	Deoxyribonucleic acid
dsDNA	Double-stranded DNA
DSUR	Development Safety Update Report
EBV	Epstein Barr Virus

EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
FACIT	Functional Assessment of Chronic Illness Therapy
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GMT	Geometric Mean Titer
HIA	Hemagglutination Inhibition Assay
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
hCG	human Chorionic Gonadotropin
HCQ	Hydroxychloroquinine
HCV	Hepatitis C Virus
Hg	Mercury
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HSIL	High Grade Squamous Intraepithelial Lesions
HSV	Herpes Simplex Virus
huIFN-α	Human interferon α
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
iDSMB	Independent Data and Safety Monitoring Board
IEC	Independent Ethics Committee
IFN	Interferon
IFN-K	Interferon α-kinoid
Ig	Immunoglobulin
IL	Interleukin
IM	Intramuscular
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional review board
ITT	Intention-to-treat
IUD	Intrauterine Device

IUS	Intrauterine system
IV	Intravenous
IWRS	Interactive Web Response System
KLH	Keyhole Limpet Hemocyanin
Mcg	micrograms
MCID	Minimum Clinically Important Difference
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
mm	millimeter
MMF	Mycophenolate mofetil
MTX	Methotrexate
muIFN-K	Murine Interferon-Kinoid
NSAID	Non-Steroidal Anti-Inflammatory Drug
PBMCs	Peripheral Blood Mononuclear Cells
PCS	Physical Component Summary
PGA	Physician Global Assessment
PI	Principal Investigator
PP	Per Protocol
PT	Prothrombin time
PTT	Partial Thromboplastin Time
RBC	Red Blood Cell
Rhu	Recombinant human
mRNA	Messenger ribonucleic acid
RNP	Ribonucleoprotein
RTX	Rituximab
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SC	Subcutaneous
SELENA	Safety of Estrogen in Lupus Erythematosus National Assessment
SF-36	Short Form-36
SJC	Swollen Joint Count
SLE	Systemic Lupus Erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index-2000
SLICC/ACR-DI	Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus

Sm	Smith antigen
SOP	Standard Operating Procedures
SP	Safety Population
SS	Sjögren's Syndrome
SUSAR	Suspected Unexpected Serious Adverse Reaction(s)
TJC	Tender Joint Count
TNF	Tumor Necrosis Factor
UCP	Urine C-peptide creatinine
VAS	Visual Analog Scale
WBC	White Blood Cell
WHO	World Health Organization
WMA	World Medical Association

5. BACKGROUND AND RATIONALE

5.1 Introduction

Systemic Lupus Erythematosus (SLE) is a chronic systemic autoimmune disease that can affect virtually any part of the body (Tsokos, 2011). Like in other autoimmune diseases, the immune system attacks the body's self-cells and tissues, resulting in inflammation and tissue damage. The course of the disease is unpredictable, with periods of illness (called flares) alternating with remissions. There is no definitive cure for SLE. The disease is currently treated with immunosuppression, mainly with hydroxychloroquine, cyclophosphamide, corticosteroids (CS) and other immunosuppressive drugs, all accompanied with significant debilitating side effects. Kinoids may offer an alternative treatment by induction of self-polyclonal antibodies anti-IFNα. IFNα-Kinoid has been evaluated in SLE patients in a phase I-II study (Grouard-Vogel *et al*., 2014; Lauwerys *et al*., 2013 and 2014). The present trial aims at confirming the promising preliminary biological results and further evaluates the clinical efficacy.

5.2 Background on Systemic Lupus Erythematosus

SLE is a complex autoimmune disease of unknown origin that can affect virtually every organ in the human body but more frequently the skin and mucosa, muscles and joints, the kidneys, the hematopoietic system and the central nervous system. The clinical course of SLE can be highly variable, ranging from a relatively benign illness to a rapidly progressive disease with fulminant organ failure and death. Hallmarks are the accumulation of symptoms and affected organs over time and the undulating disease course characterized by remissions and flares. The prognosis varies in function of the type and severity of the clinical complications, but overall patients with SLE have a nearly 5-fold increased risk of death compared to the general population. The disease is characterized by the presence of numerous autoantibodies against nucleic acid and associated proteins, several of them being associated with the severity of the disease activity.

Worldwide epidemiology studies reported large variations in incidence and prevalence of SLE, reflecting influences of race, ethnicity and socio-economic status (Lisnevskaia *et al*., 2014; Shim *et al*., 2014; Nasonov *et al*., 2014). In 2006, a higher prevalence and incidence were reported for Europe and Australia compared to the USA or to Japan and for individuals of African-American or African-Caribbean descent compared to the white racial group (Danchenko *et al*., 2006). The worldwide range of incidence (per 100 000 per year) and of prevalence (per 100 000 per year) was 1.6 to 21.9 and 7.4 to 159.4, respectively (Danchenko *et al*., 2006). In South Korea, the prevalence is approximately 18.8-21.7 per 100 000 (Ju *et al*., 2014). In France, in 2010, the annual incidence of SLE was 3.3 per 100 000 and the prevalence was 47.0 per 100 000, with higher rates observed in the Caribbean overseas areas than in north-western metropolitan territories (Arnaud *et al*., 2014).

SLE primarily affects women of childbearing age with a female to male ratio of 9:1 commonly reported, but this predominance is less striking in juvenile and elderly populations.

Treatment of SLE remains unsatisfactory. In many patients, the disease is inadequately controlled, resulting in the progression to end-stage organ failure. Current therapies, such as CS and potent immunosuppressive drugs, which must be administered at high doses, can also lead to serious side effects.

Elevated levels of interferon (IFN)-α in serum have long been recognized to be associated with SLE, both in terms of disease activity and severity (Rönnblom *et al*., 2006, Bauer *et al*., 2006, Bauer *et al*., 2009). Accordingly, patients with SLE also have a dominant pattern of type-1 IFN-inducible gene expression or IFN gene signature (Baechler *et al*., 2003; Bennett *et al*., 2003). Yao *et al*. have identified IFNα/β-inducible gene transcripts that are significantly up-regulated in the whole blood of SLE patients (Yao *et al*., 2009a). By subsequent neutralization with anti-IFNAR or anti-IFNα mabs of healthy mononuclear cells stimulated by SLE serum, they demonstrated that IFNα is mainly responsible for the type I IFN gene signature in SLE patients. They also showed that scoring the IFN gene signature by transcriptomic analyses could serve as biomarker to evaluate the impact of IFNα neutralization. Since then, Phase I and Phase II clinical trials with sifalimumab (an anti-IFNα monoclonal antibody [mab]) (CT.gov# NCT00299819; NCT01283139; NCT01559090), rontalizumab (another anti-IFNα mab) and anifrolumab (an anti-IFNAR mab) have been reported (McBride *et al*., 2012; Petri *et al*, 2013; Khamashta *et al*., 2014; Morehouse *et al*, 2014). The safety assessment did not reveal any safety concern, there was some indication of positive clinical effect and a significant neutralization of over-expressed IFNα-inducible genes was measured (Yao *et al*., 2009b; Merrill *et al*., 2011).

In addition, among a variety of auto-immune and immune-related disorders, SLE has been reported following long term administration of IFNα in patients with malignancies or chronic viral infections (Rönnblom *et al*., 1991; Ioannou and Ysenberg, 2000; IFNα product information). There is also a correlation between serum IFNα levels and several markers of immune activation typical for SLE such as anti-double-stranded deoxyribonucleic acid (dsDNA) levels, interleukin (IL)-10 levels and a degree of complement activation (Park *et al*., 1998; Kalsi *et al*., 1999; Truedsson *et al*., 2007).

Therefore, this observed association between IFNα and SLE suggests that down-regulation of this cytokine may be beneficial in patients suffering from SLE. An attractive therapeutic strategy is active immunization against IFNα to induce anti-IFNα antibodies to neutralize IFNα biological activity.

5.3 Background on CS and Response to Vaccination

Response to classical vaccination has been reported to be decreased during concomitant CS therapy, although reports are controversial and few well conducted evaluations exist. A non-significant trend towards a lower humoral response to influenza vaccine in patients taking prednisone at a dose > 10 mg/day was reported (Abu-Shakra *et al*., 2002). In another study a decrease seroconversion rate to the first dose of H1N1 influenza vaccination but not to the second injection was reported in SLE patients who receive prednisone at a dose ≥ 0.15 mg/kg/day (Mathian *et al*., 2011b). On the other hand, response to vaccination with H3N2 classical influenza vaccine in lupus patients was altered by corticoid use (dose level of 10.8 +/- 5.9 mg/day) only for the production of antibodies to the B/M antigen, but not to the A/W and A/NC strains (Wallin *et al*., 2009). Similarly, prednisone use reduced, but not significantly, the antibody response to pneumococcal, tetanus toxoid and *Haemophilus influenza* type B vaccines (Battafarano *et al*., 1998). In that study no difference was shown between patients treated with < or > 10 mg/day of prednisone, but the number of patients receiving > 10 mg/day was small. H1N1 influenza vaccination has been evaluated in 555 SLE patients and 170 healthy controls. Seroconversion in SLE patients taking prednisone at a dose ≥ 20 mg/day was significantly reduced when compared to SLE patients with no therapy. However response was restored by co-administration of chloroquine (CQ) (Borba *et al*, 2012).

5.4 Background on IFN-Kinoid

5.4.1 Product Description

IFNα Kinoid (IFN-K) is an immunotherapeutic agent developed by Neovacs SA to treat the deleterious effects consequent to over-expression of the cytokine IFNα. The generation of polyclonal neutralizing antibodies directed against IFNα following the administration of IFN-K is relevant to diseases mediated by IFNα over-production, such as SLE, dermatomyositis, polymyositis, and Sjögren's syndrome (SS).

IFN-K is a heterocomplex consisting of recombinant human (rhu)-IFNα2b coupled to a T-helper carrier protein, Keyhole Limpet Hemocyanin (KLH). The finished product consists of a solution of IFN-K emulsified with ISA 51 VG at a 1:1 (v/v) ratio which will be administered as an intramuscular injection.

5.4.2 Non-clinical Experience

Both IFN-K and a murine surrogate compound (muIFN-K) have been employed in non-clinical studies and were shown to elicit antibody production against human and murine IFNα, respectively. Anti-KLH antibody production and anti-IFNα neutralization were also observed. A

T cell memory response was induced against the KLH component of IFN-K but not against IFNα, suggesting that IFN-K is able to break B-cell tolerance to IFNα without breaking T-cell tolerance. In addition, IFN-K induces antibodies that cross-react with all IFNα subtypes but not with IFNβ or IFNγ.

The administration of muIFN-K in a murine model of lupus reduced mortality and resulted in protection against the development of proteinuria and histological lesions of glomerulonephritis (Zagury, 2009).

Numerous studies have been performed in mice (Balb/c with muIFN-K, huIFNα2b transgenic mice with IFN-K), with no safety issue being identified. A follow-up of nearly one year was achieved in Balb/c mice immunized with different doses of muIFN-K as an emulsion with ISA 51 VG. The animals survived through to the end of the study, confirming the safety of the murine IFN-K in a relevant species.

Two studies were conducted in cynomolgus macaques, a species considered relevant for IFN-K studies (i.e. anti-IFNα antibodies induced by human IFN-K neutralize simian IFNα).

- A dose-range finding study was performed in 12 cynomolgus macaques. Three dose levels of IFN-K were tested (50 µg, 200 µg and 400 µg). Five doses were administered intramuscularly (IM) or subcutaneously (SC) as an emulsion with ISA 51 VG. All animals were followed-up to Day 220. Animals receiving 200 µg or 400 µg doses IM were followed-up to Day 304. Minimal to mild local reactions were observed in animals after the third IM dose of IFN-K. The severity of the local reaction in the IM group did not go beyond 'mild'. Following the first SC immunization IFN-K (Day 0), minimal local symptoms were observed in 3/6 animals. Local symptoms (minimal, mild or moderate) were observed in all animals who had received the second SC dose of IFN-K (Day 7). By the third immunization (IM and SC) at Day 28, all animals exhibited local reactions mostly associated with transient lymph node swelling close to the administration site. There were no clinical signs related to the administration of IFN-K. Blood cell counts remained within the normal range and no abnormal values were recorded for serum biochemistry. No differences in terms of body weight or temperature were observed in this study. There were no infections. No animals died during the study.

- In another study (GLP-toxicity study), 14 cynomolgus macaques were administered 400 µg IFN-K or saline (0.9% NaCl) as an emulsion with ISA 51 VG in a series of 5 intramuscular administrations (days 0, 7, 28, 49 and 70) followed by a 13-week observation period (total 23 weeks). No local reactions were observed immediately following the first IFN-K administration. Injection site edema (slight to severe) was observed up to 1 week following the second dose, but no local symptoms occurred thereafter. No local reactions were seen following the third, fourth and fifth doses. There were no notable general effects on body weight, body

temperature, food consumption, cardiovascular parameters (including ECG and systolic blood pressure), organ weight, biochemistry or hematology. There were no macroscopic findings (the necropsy report showed that the organs appeared normal) or ophthalmological findings. The only histological observations were the retention of injected materials in vacuoles near the administration site with a discernible multinuclear giant cell response and neofibrosis, with no obvious differences between the control and the IFN-K. No deaths were recorded in this study. For further details, see the current version of the Investigator Brochure (IB).

These studies have demonstrated immunogenicity and innocuity of IFN-K in relevant species.

5.4.3 Clinical Experience

In a Phase I-II, randomized, double-blind, placebo-controlled dose escalation study, IFN-K has been evaluated in patients with mild to moderate SLE (EudraCT# 2009-012059-47, CT.gov# NCT01058343, Lauwerys *et al*., 2013). Twenty-eight patients were enrolled and distributed among 4 parallel groups receiving 30, 60, 120 or 240 µg IFN-K or placebo at days 0, 7 and 28 with a conditional fourth injection at month 3 for 50% of the patients in the 60, 120, and 240 µg dose groups. A total of 21 patients were exposed to IFN-K, and 7 patients received the placebo.

For the patients receiving IFN-K, major conclusions on biologic effect were:

- An immunogenic effect of IFN-K is observed after 3 immunizations irrespective of the dose. Neutralization of the IFN gene signature is already visible 10 days after completion of the 3-dose course, and it peaks at 8 weeks post-dose 3.

- All patients developed an antibody response against IFNα, and antibody levels were significantly higher in patients with a positive IFN gene signature than in patients with a negative signature. Also, IFNα-mediated and SLE-associated gene expression was reduced more in patients immunized with IFN-K than in patients treated with the placebo. This decrease in the expression of SLE-associated genes significantly correlated with anti-IFNα antibody levels and was more pronounced in patients with the highest IFN gene signature before immunization. Furthermore, the increase in C3 complement from baseline significantly correlated with the anti-IFNα antibody level.

- Two patients in the phase I-II study were taking prednisone at 15 and 20 mg/day, with no indication of a decreased anti-IFNα antibody response.

- Patients with a positive IFN gene signature at baseline developed higher antibody titers and a more pronounced neutralization of the IFN gene signature, together with an impact on disease

biomarkers than patients with a negative IFN gene signature. IFNα-neutralizing activity was detected in 3 out of 6 subjects treated with 60 µg IFN-K, in 3 out of 6 subjects treated with 120 µg IFN-K, and in 4 out of 5 subjects treated with 240 µg IFN-K, but was not detected in subjects treated with 30 µg IFN-K or with placebo or at baseline in any subjects.

No significant difference was observed on any of the clinical scores for SLE. This is most likely due to the polymorphism of the disease, the limited sample size with the multiplicity of small groups and the inadequacy of the scoring systems, such as the SLEDAI.

In comparison with the patients receiving the placebo, IFN-K administration was generally well tolerated. Few local or systemic reactions were reported, and were mild to moderate in severity and transient in nature. A total of 8 serious adverse events (SAEs) were reported in 5 patients:

During the main study period, only 2 SAEs were reported in 2 patients and both were lupus flares. One was qualified as a serious unexpected suspected adverse reaction or SUSAR (i.e. one flare of underlying lupus occurred for a patient receiving only one injection of IFN-K at 240 µg).

During the extended follow-up period, 6 SAEs were reported in 4 patients:

- One patient who received 4 injections of IFN-K at 120 µg experienced a SUSAR (colon cancer and liver metastasis). This patient died due to septicemia.
- One patient experienced one lupus flare, pregnancy and spontaneous abortion
- One patient experienced lupus flare
- One patient experienced bronchial hyper reactivity.

Further details and narrative are provided in the current version of the IB.

5.5 Rationale for Population, Dose Selection and Design

The previous Phase I-II study has shown that IFN-K is able to decrease gene signature. The primary endpoint of this study will confirm the neutralization of the IFN gene signature so that only patients with a positive signature will be enrolled in this Phase IIb trial. The study will enroll only individuals with active SLE so that only patients with SLEDAI ≥ 6 will be eligible.

A major constraint in designing the present study was that SLE patients are likely to be administered concomitant CS treatment (at least during a certain period of time) which may impact both the IFN gene signature and the antibody response induced by the kinoid. Response to classical vaccines is potentially decreased when the prednisone dose is ≥ 10 mg/day. However a large study performed in SLE patients showed that the immunogenicity of influenza vaccine could be altered if administered to patients treated with prednisone at a dose ≥ 20 mg/day (Saad *et al*., 2011). In

addition, since IFN-K is a conjugated adjuvanted vaccine, it will be more immunogenic than non-adjuvanted vaccines; indeed, several studies have demonstrated that H1N1 vaccines adjuvanted with an emulsion were significantly more immunogenic than non-adjuvanted vaccines (Leroux-Roels *et al*., 2007). Therefore, dose levels of CS and immunosuppressive drugs will be monitored for eligible patients in order to avoid a negative effect on the response to IFN-K.

In the Phase I/II study, no neutralizing antibodies were detected in the 30 µg group. IFNα-neutralizing activity was detected in 3 out of 6 subjects treated with 60 µg IFN-K. This response was weak and very transient indicating that this dose was insufficient to induce a robust immune response. In the 120 µg IFN-K group, neutralizing antibodies were only observed in the 3 patients that received 4 administrations. Four out of 5 subjects treated with 240 µg IFN-K developed neutralizing antibodies among which one subject received only 3 injections. Therefore, the dose of 240 µg was chosen as it resulted in the highest number of patients developing neutralizing capacities (4 out 5 patients). At least four administrations of IFN-K should be given since all patients in the 120 and 240 µg groups who received the fourth administration developed IFNα neutralizing antibodies. The fourth and fifth injections should be at 120 µg of IFN-K, since all patients in 120 µg group with 4 administrations displayed neutralizing capacity.

The proposed study is designed as a three phase study with induction, maintenance and follow-up periods. The study is a randomized, double-blind, placebo-controlled study, which will ensure the robustness of its results. A 1:1 randomization ratio was chosen to ensure robustness of the primary endpoint at Week 36 with a sufficient number of patients in the placebo arm compared to the IFN-K arm.

Validated research instruments (such as SLEDAI-2K, SELENA-SLEDAI, BILAG and BICLA) will be used to assess the severity of the disease and therefore to adequately evaluate the potential benefit of the IFN-K treatment. An Adjudication Committee will review and validate BILAG scores. The study is designed according to precedents in the field of clinical research in patients with SLE, and takes into consideration applicable guidelines published by relevant expert bodies and competent authorities (van Vollenhoven *et al*., 2014).

As the eligible population is patients with active SLE (SLEDAI $\geq$ 6), and with the objective to demonstrate a significant difference between the treatment with IFN-K versus placebo, the following treatment periods have been proposed in accordance with the standard practices:

- at screening, patient's active SLE will be adequately treated with either CS and/or permitted immunosuppressive drugs;
- if eligible to the study, patients will be randomized and receive IFN-K or placebo all along the 12-week induction period during which tapering of CS will be recommended;

- if not previously initiated, tapering of CS will be mandatory and immunosuppressive drugs tapering recommended in the next 12-week maintenance period during which patients will receive a booster of IFN-K or placebo;
- the patients will then continue the 12-week follow up period during which CS will be minimal and immunosuppressive drugs tapering recommended if not yet initiated.

The time points for assessing the primary and secondary endpoints have also been selected to balance the chance of success and to guarantee the security of the patients. There will be more frequent visits than the standard practices, and this will offer the patients to be carefully followed up for their SLE, specifically in case of flare during the CS and/or immunosuppressive drugs tapering, to be adequately treated before the disease worsened.

Since the clinical experience with IFN-K in SLE patients is limited, it is important to confirm the preliminary clinical and safety information before initiating a confirmatory study in several hundreds of patients.

5.6 Benefit-Risk Assessment

The down-regulation of IFNα has been suggested to be possibly beneficial in patients suffering from SLE (Yao *et al*., 2009b). IFN-K acting as active immunization against IFNα has the capability to induce anti-IFNα antibodies to neutralize IFNα biological activity and therefore has the potential to treat the deleterious effects consequent to over-expression of the cytokine IFNα observed in patients with SLE.

Preclinical data in lupus mice injected with IFN-K, have shown that treatment with IFN-K elicit production of anti-IFN neutralizing antibodies, and significantly reduced progression of the disease, as demonstrated by an increased survival rate, and a reduction in proteinuria. In long term treatment administration in mice models and in repeat toxicity studies in monkeys, IFN-K was well tolerated at the dose, and with the route and the schedule of administration equivalent to the ones proposed in the planned clinical trial (see current version of the IB).

Over the 28 patients enrolled in the previous Phase I-II clinical study, 21 patients with SLE were administered with IFN-K as an intramuscular injection (Lauwerys *et al*., 2013). IFN-K was generally well tolerated. Few local (including tenderness, swelling, erythema and itching) or systemic reactions were reported, and were mild to moderate in severity and transient in nature. Eight serious adverse events (SAEs) were reported in 5 patients across the whole study (main and extended Follow-up). Two of the SAEs were SUSARs (one flare of underlying lupus occurred for a patient who had received only one injection of IFN-K at 240 µg and one colon cancer with liver metastasis in a patient who received 4 injections of IFN-K at 120 µg) (for further details see the current version of the IB).

Although the presence of anti-IFNα antibodies may raise the question of antibody persistence and therefore the potential difficulty of controlling viral infections, there may not necessarily be a need for concern. Data showed that the antibodies induced by IFN-K immunization neutralized all 13 subtypes of IFNα but not IFNβ or IFNγ. Thus, a level of defense against viral infections is maintained. Indeed, in the long term immunogenicity and toxicology studies performed in non-human primates whose IFNα is neutralized by anti-human IFNα antibodies, none of the animals developed a severe or unusual infection. In humans, the use of IFNα as a treatment for chronic HCV or HBV infections and some cancers may result in the generation of anti-IFN antibodies able to neutralize IFNα without increasing the incidence of viral infection (Ehrenstein *et al*;, 1993; Okanoue *et al*., 1996; Rönnblom *et al*., 1991; Kalkner *et al*., 1998; Rönnblom *et al*., 1990; Ioannou *et al*., 2000). In addition, patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) and myasthenia gravis have high serum concentrations of neutralizing anti-IFNα antibodies but are not at higher risk of viral infection despite the corticosteroid treatment (Kisand *et al*., 2008; Meager *et al*., 2008). Recent publications have demonstrated that blocking IFNα could help control chronic viral infections (Teijaro *et al*., 2013; Wilson *et al*., 2013).

The safety of a previous formulation of an IFNα immunotherapeutic agent was evaluated in over 200 Human Immunodeficiency Virus (HIV)-infected patients during the early 1990's. Some patients were treated and followed-up for over 5 years without raising any safety concerns (Gringeri *et al*., 1999).

In contrast to mab, anti-IFNα antibodies can neutralize all IFNα subtypes and consequently these antibodies should be more effective in reducing the IFN gene signature. Indeed, also in the patients in the Phase I/II who exhibited neutralizing antibodies more than two years after immunization, neutralization of IFN gene signature was still observed (non published data). In addition, significantly higher anti-IFN titers were found in signature-positive patients than in signature-negative patients. In IFN gene signature–positive patients, IFN-K significantly reduced the expression of IFN-induced genes. The decrease in IFN score correlated with the anti-IFN antibody titer. Serum complement C3 levels were significantly increased in patients with high anti-IFN antibody titers (Lauwerys *et al*., 2013).

These results show that IFN-K is well tolerated, immunogenic, and significantly improves disease biomarkers in SLE patients, and are in favor of proceeding with the clinical development.

In the proposed clinical study, treatment with IFN-K or placebo is added in addition to standard therapy, with the exception of potent immunosuppressive agents, such as cyclophosphamide, oral tacrolimus, and cyclosporine A; and biological agents such as rituximab.

The study population will enroll patients with active SLE (SLEDAI ≥ 6) and positive IFN gene signature, treated with either CS and/or immunosuppressive drug at screening. In accordance with

the current standard treatments of such patients with active SLE, appropriate guidances are provided in the protocol for the tapering of CS and immunosuppressive drugs along the study, all of this to allow the detection of a significant immunological activity and clinical efficacy of IFN-K while ensuring adequate patients' safety.

In the proposed study, in addition to monitoring of standard safety parameters (ie, physical examination findings, clinical laboratory tests, ECGs, and vital signs), an independent DSMB will oversee the safety of the patients enrolled in the study and monitor the occurrence of flare throughout the study. The iDSMB 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.

Although the clinical experience with IFN-K in SLE patients is limited, the preliminary clinical and safety information together with the preclinical information are promising and warrant obtaining further clinical evaluation before initiating a confirmatory study in several hundreds of patients.

The benefit-risk-balance is, therefore, considered to be favorable for treatment with IFN-K. Consequently, participation in this clinical study is not associated with unacceptable risks and, in fact, may provide significant clinical benefits over the extended treatment period.

5.7 Amendment #2 rationale (protocol version 4.0)

In the study protocol Version 3.0, section 7.4, it is written that the study patients will be proposed at the end of the study to enter in a separate Extended Follow up study protocol. As pointed out by few Medicine Agencies, this extended FUP should be detailed and included within the IFN-K 002 study protocol due to the persistence of the anti-IFNα antibodies as shown in the study IFN-K-001. Therefore, Neovacs is amending the study protocol to integrate an Extended Follow up Period up to a total duration of 5 years (60 months, 240 weeks) after the last visit of the main study (V12). The visit at Week 276 (Month 69) (FU10 Visit) will be considered as the last planned visit.

Because of the double-blind study design, all patients who have completed the main study (up to visit 12) during the blinded period will enter into the extended follow up period. Then, when the results become available, only patients having received IFN-K and having produced anti-IFNα antibodies (neutralizing) will continue the extended follow up. Patients will remain into the extended follow-up period until they become negative for anti-IFNα neutralizing antibodies (below 200 Dil-1) or for up to 60 months (240 weeks) after V12, whichever comes first.

During this extended follow up period, the patients will be followed every 6 months (see section 10.9.14 for more details on the visit schedule) as in the IFN-K-001 study. For safety purpose, a descriptive analysis will be performed at regular intervals, according to DSUR timelines.

5.8 Amendment #3 rationale (protocol version 5.0)

On one hand, worldwide epidemiology studies reported large variations in incidence and prevalence of SLE, reflecting influences of race, ethnicity and socio-economic status (Danchenko *et al*, 2006; Lisnevskaia *et al*., 2014; Shim *et al*., 2014; Nasonov *et al*., 2014; Housey *et al*, 2015; Gómez-Puerta et al, 2015). Please also refer to section 5.2 of the study protocol.

On the other hand, several studies have demonstrated an overexpression of IFNα-inducible genes in SLE patients and a possible correlation between their expression and the disease activity notably the serological markers (Baechler *et al*, 2003; Bennett *et al*., 2003; Yao *et al,* 2009a; Kennedy *et al*, 2015)

The proposed Phase 2b, designed to evaluate the neutralization of the IFN gene signature following treatment with IFN-K, as measured by the change from baseline of the expression of IFN-induced genes **and** to evaluate the efficacy of treatment with IFN-K using the British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) response criteria. was originally planned to be conducted in 3 geographic areas (Europe, Asia-Pacific and Latin-America) reflecting different ethnicities. Therefore, the proposed amended study protocol plans to expand the study in USA to provide results on an overall population and better cover the specificities of the different ethnicities.

The relationship between the ethnicity and the expression of the IFN gene signature is taken into account in the randomization (minimization factor) and the sample size calculation has been revised to ensure statistical power on the primary end-points.

5.9 Amendment #4 rationale (protocol version 6.0)

In the study protocol Version 5.0 section 7.5, it is written that after un-blinding of the treatment arm has been performed, only patients having received IFN-K and having produced anti-IFNα antibodies (neutralizing) will continue the 60 months' extended follow up period. As requested by FDA, all patients having received IFN-K will be followed up for up to 60 months, irrespective of the production of anti-IFNα antibodies at month 9 and during the whole extended follow-up period.

As requested by FDA:

- inclusion criterion #8 has been modified. The time on treatment and time on stable dose has been increased to 3 months (12 weeks) prior to study product injection for patients taking Methotrexate, Azathioprine and Mycophenolate Mofetil.

- for US patients only, exclusion criterion #11 has been modified to ensure that patients have had documented negative screening tests for malignancy according to the American Cancer Society Guidelines within 12 months before screening visit. Moreover, for US patients with history of treated cancers, only treated basal cell carcinoma is not preventing enrolment.

- section 10.6.3 has been modified to include "the occurrence of bronchospasm after administration of study product must be considered as a criterion for study product discontinuation.". The revised sentence is as follows: "…., Bronchospasm or anaphylactic reaction following the administration of the study product. …."

Since not all countries have the same requirements for reporting of fatal, life-threatening events and all other SAEs to Regulatory Health Authorities, the possibility to follow local requirements was added in section 12.3.1.

6. STUDY OBJECTIVES

6.1 Primary Objective

The primary objective of this study is to evaluate the neutralization of the IFN gene signature following treatment with IFN-K, as measured by the change from baseline of the expression of IFN-induced genes **and** to evaluate the efficacy of treatment with IFN-K using the British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) response criteria. The study will be considered as positive if a statistically significant better effect of IFN-K compared to placebo is observed on the neutralization of the IFN gene signature and if at least a trend favoring IFN-K is observed on the BICLA response.

6.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the efficacy of treatment with IFN-K using:
  - The SLE Responder Index [(SRI)-4 and above]
  - The SLE Disease Activity Index-2000 index (SLEDAI-2K)

  - The BILAG-2004 index
  - The Safety of Estrogen in Lupus Erythematosus National Assessment-SLEDAI (SELENA-SLEDAI) Flare index
  - The Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus (SLICC/ACR-DI)
  - The Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) in patients with cutaneous lesions at baseline
- To evaluate the immune response induced by IFN-K:
  - Anti-IFNα antibody response
  - Anti-IFNα antibody neutralizing capacities
  - Anti-KLH antibody response
- To assess the safety of IFN-K emulsified with ISA 51 VG

6.3 Exploratory Objectives

The exploratory objectives of this study are:

- To assess disease activity using:
  - The Physician Global Assessment (PGA) score
  - The 28-Tender and Swollen joint counts
  - A Joint Pain Visual Analog Scale (VAS)
  - The flare description
  - The changes in Lupus therapy
- To assess quality-of-life using:
  - The Short Form-36 (SF-36) questionnaire
  - The Functional Assessment of Chronic Illness Therapy (FACIT) fatigue score.
- To assess biological parameters:
  - Levels of lupus-related serum auto-antibodies and biomarkers
  - Neutralizing Anti-IFNα antibodies towards IFNα subtypes
  - Anti-IFNα and anti-KLH antibody isotyping
  - IFNβ cross neutralization

  - Antibody response to influenza vaccination
- To assess correlations between immune responses, IFN gene signature and clinical responses

7. INVESTIGATIONAL PLAN

This will be a Phase IIb, randomized, double-blind, placebo-controlled, multicenter study assessing intramuscular (IM) administration of IFN-K against a adjuvanted placebo. Study patients will be enrolled into one of two treatment groups and allocated in 1:1 randomization ratio to receive the study product: IFN-K or placebo as outlined below:

- Group 1: IFN-K emulsified in ISA 51 VG
- Group 2: placebo emulsified in ISA 51 VG

The study will consist in a main study followed by an Extended Follow up Period.

During the main study, each patient will receive two injections of study product (corresponding to 240 mcg of IFN-K or placebo) at three visits during the Induction Period (at Week 0 [Visit 2], Week 1 [Visit 3], and Week 4 [Visit 4]). Each patient will be administered one injection of study product (corresponding to 120 mcg of IFN-K or placebo) during the Maintenance Period (at Week 12 [Visit 6] and Week 24 [Visit 9]).

The main study comprises a total of 12 visits occurring over a period of 40 weeks. The study will be divided into four periods: a 4-week Screening Period that will be performed to determine eligibility of the patients for randomization into the study, a 12-week Induction Period, a 12-week Maintenance Period and a 12-week Follow-up Period.

The Extended Follow up Period applies to all patients who have completed the main study. Then, when the results of the main study are available, only patients who have received IFN-K will continue the Extended Follow-up Period for up to 60 months (240 weeks) after Visit 12 (Week 36).

7.1 Screening Period (from Study Week -4 to 0)

Patient eligibility will be determined over the course of the Screening Period.

In order to determine their eligibility, candidate participants will undergo a series of assessments and procedures as outlined in Table 1 and in Section 10.9.1. All relevant samples should be collected before any new SLE related treatment is initiated.

Randomization will be minimized according to the criteria described in Section 9.2.2.

7.2 Induction Period (Week 0 to Week 12)

When screening results are available and should all entry criteria be fulfilled, the patients will be allocated to receive IFN-K or a placebo, according to a 1:1 randomization ratio, and enter the 12-week Induction Period during which each patient will receive three administrations of study product on Visit 2 (Week 0), Visit 3 (Week 1), and Visit 4 (Week 4).

The patients will undergo planned assessments and procedures as outlined in Table 1 and in Sections 10.9.2 to 10.9.6.

Note that Visit 6 (Week 12) is the last visit of the Induction Period and the first visit of the Maintenance Period.

7.3 Maintenance Period (Week 12 to Week 24)

Following the Induction Period, patients will be followed during the 12-week Maintenance Period.

During the Maintenance Period, patients will undergo planned assessments and procedures as outlined in Table 1 and in Sections 10.9.6 to 10.9.9.

A booster dose will be administered at Visit 6 (Week 12) and at Visit 9 (Week 24).

Visit 9 (Week 24) is the last visit of the Maintenance Period and the first visit of the Follow-up Period.

7.4 Follow-up Period (Week 24 to Week 36)

Following the Maintenance Period, patients will be followed during the 12-week Follow-up Period.

During the Follow-up Period, patients will undergo planned assessments and procedures outlined in Table 1 and sections 10.9.9 to 10.9.12.

Patients will not receive any study treatment during this period.

7.5 Extended Follow-up Period (Week 36 to Week 276)

All patients who have completed the Follow-up Period before un-blinding of treatment arm is performed will enter into an extended follow up period for up to 60 months (240 weeks) after Visit 12 (Week 36). Then, when the study results are available, only patients who have received IFN-K will be followed for up to 60 months.

Patient will not receive any study treatment during this period.

During this extended follow up period, the patients will be followed every 6 months for 5 years and will undergo planned assessments and procedures as outlined in Table 1 and section 10.9.14.

The visit at Week 276 (Month 69) (FU10 Visit) will be considered as the last planned visit.

If patients remain positive for anti-IFNα neutralizing antibodies after this Extended Follow up Period, they will be proposed to be enrolled in another 5-year follow up study to confirm the favorable safety profile of IFN-K.

7.6 Planned Analyses

The primary analysis will be performed at Week 36.

A follow-up analysis will be performed at year 5 (week 276 - Month 69) when all patients have completed the extended follow up. For safety purpose, a descriptive analysis will be performed at regular intervals, according to Development Safety Update Report (DSUR) timelines.

8. STUDY POPULATION

8.1 Number of Patients

The target number of eligible patients to be enrolled in this study is 178 (89 patients in each treatment group).

8.2 Recruitment Method

This study will be performed in multiple centers worldwide. There will be competitive recruitment.

8.3 Eligibility Criteria

Patients will need to meet the following eligibility criteria at study entry to be eligible for this study.

8.3.1 Inclusion criteria

A patient meeting all of the following inclusion criteria at screening will be eligible for participation in this study:

1. Has had a diagnosis of SLE according to current ACR criteria (4 of 11 ACR criteria) (list of criteria provided in Appendix 1)

2. Has SLEDAI ≥ 6
3. Has at least 1 BILAG A and/or at least 2 BILAG B
4. Has a positive IFN gene signature by RT-qPCR as assessed on a limited number of genes
5. Has anti-nuclear antibodies (ANA) ≥ 1:160 and/or anti-dsDNA antibodies ≥ 7.0 IU/mL
6. Be a male or female, aged between 18 and 65 years, inclusive, at the time of the screening visit
7. Agrees to receive influenza vaccination during each influenza season of the study period
8. Currently receiving at least one of the following treatment:
    - Corticosteroids (CS) at a dose of ≤ 20 mg of prednisone equivalent/day
    - Antimalarial drugs (hydroxychloroquine [HCQ] or chloroquine [CQ]); the patient must have been treated since at least 8 weeks and on stable dose for at least 4 weeks prior to first planned administration of the study product
    - Methotrexate (MTX); the patient must have been treated and be on stable dose (≤ 20 mg/week) for at least 12 weeks prior to the first planned administration of the study product
    - Azathioprine (AZA); the patient must have been treated and be on stable dose (≤ 2.5 mg/kg/day) for at least 12 weeks prior to the first planned administration of the study product
    - Mycophenolate mofetil (MMF), the patient must have been treated and be on stable dose (≤ 2 g/day) for at least 12 weeks prior to the first planned administration of the study product
9. Study patient and his/her partner has to use effective method of contraception for the duration of the study including the Extended Follow up Period.

Note: If of child bearing potential, effective contraception methods include:

- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least 6 weeks prior to the first planned administration of the study product. In case of oophorectomy alone, the reproductive status of the woman must be confirmed by follow up hormone level assessment.
- Male sterilization (at least 6 months prior to Screening).
- Combination of the following:
    - Oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception **or**
    - Placement of an intrauterine device (IUD) or intrauterine system (IUS)
    - **And** barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In

the case of oophorectomy alone, she is considered not of child bearing potential only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

10. Is able and willing to comply with the requirements of the study protocol (e.g., completion of the diary cards, return for follow-up visits), in the opinion of the Investigator
11. Has provided written informed consent

8.3.2 Exclusion criteria

A patient meeting any of the following exclusion criteria at study entry will not be eligible for the study:

1. Has active, severe lupus nephritis as defined either by the immediate need for cyclophosphamide treatment or by renal BILAG A
2. Has active, severe, neuropsychiatric SLE, defined as neuropsychiatric BILAG A
3. During the 4 months prior to the first planned study product administration, has been treated with corticosteroids (CS) at a dose of >20 mg of prednisone equivalent/day for > 7 consecutive days
4. Is currently receiving or has received pulse dose CS (≥ 250 mg prednisone equivalent/day) within 3 months prior to the first planned administration of the study product.
5. Has received potent immunosuppressive drugs such as cyclophosphamide, cyclosporine A, oral tacrolimus within 3 months prior to the first planned administration of the study product
6. Has received abatacept, sifalimumab, rontalizumab, anifrolumab, belimumab, TNF antagonists or another registered or investigational biological therapy within 6 months prior to the first planned administration of the study product
7. Has received anti-B-cell therapy (e.g., rituximab, epratuzumab) within 12 months prior to the first planned administration of the study product
8. Has significant electrocardiogram (ECG) abnormalities that are clinically relevant and preclude study eligibility in the Investigator's opinion
9. Has inflammatory joint or skin disease other than SLE that may interfere with study assessments
10. Has any laboratory abnormality other than SLE related that is clinically relevant and precludes study entry in the Investigator's opinion.
11. Has a history of malignant cancer, except the following treated cancers: cervical carcinoma in situ, basal cell carcinoma, or dermatological squamous cell carcinoma.

For US patients only: Has a history of malignant cancer, except the following treated cancer: basal cell carcinoma. Note: only patients with negative screening tests for malignancy according to The American Cancer Society guidelines (see Appendix 12), documented within the 12 months prior screening visit will be enrolled.

12. Has frequent recurrences of oral or genital herpes simplex lesions (≥ 6 occurrences during the 12 months prior to first study product administration)
13. Has had an episode of shingles during the 12 months prior to the first planned administration of the study product
14. Has no IgG against herpes simplex virus (HSV-1 and HSV-2), varicella zoster virus (VZV), cytomegalovirus (CMV) or Epstein-Barr virus (EBV)
15. Is positive for HTLV 1-2 antibodies, HIV antibodies, Hepatitis C (HCV) antibodies, or Hepatitis B surface antigen (HBsAg)
16. Is at high risk of significant infection and/or has any current signs or symptoms of infection at entry or has received intravenous antibiotics within 2 months prior to the first planned administration of the study product
17. Has received any live vaccine within 3 months prior to the first planned administration of the study product (e.g. nasal flu vaccine, oral poliomyelitis vaccine, measles-mumps-rubella vaccine, yellow fever vaccine, Japanese encephalitis vaccine, dengue vaccine, rotavirus vaccine, varicella vaccine, zoster vaccine, Bacillus Calmette-Guérin [BCG] vaccine, oral typhoid vaccine)
18. Has used any investigational or non-registered product within 30 days or 5 half-lives, whichever is longer, or any investigational or non-registered vaccine within 30 days prior to the first planned administration of the study product
19. Has a history of chronic alcohol and/or drug abuse within 6 months prior to the first planned administration of the study product
20. Is breastfeeding, pregnant, or planning to become pregnant during the study period
21. Has known hypersensitivity to any component of the study product
22. Is high-risk human papilloma virus (HPV) positive by reverse transcription polymerase chain reaction (RT-qPCR) on a cervical swab at Screening or within 3 months prior to the first planned study product administration
23. Has cytological abnormalities ≥ HSIL (High Grade squamous intraepithelial lesions) on a cervical swab at Screening or within 3 months prior to the first planned study product administration

9. INVESTIGATIONAL PRODUCT AND ADMINISTRATION

9.1 Study Products

The IFN-K study product has been developed by Neovacs SA. and manufactured by a designated contract manufacturing organization (CMO) in compliance with current Good Manufacturing Practice (GMP) requirements and guidelines for injectable products.

All study materials required for the study product preparation and administration will be supplied by Neovacs SA and are listed in Table 2.

IFN-K is provided as a liquid formulation in single-use vials to be emulsified with ISA 51 VG, as described in Section 9.1.3.

IFN-K is a conjugated immunotherapeutic agent. It is a complex between rhu-IFNα2b and KLH subunit obtained by conjugation with glutaraldehyde and subsequent inactivation/stabilization with formaldehyde and glycine treatment. The formulation is a sterile clear solution for injection. Each DIN 2R vial contains at least 150 mcg of IFN-K in a volume of 0.4 mL of phosphate buffer.

ISA 51 VG is the oil-based adjuvant Montanide® ISA 51 VG. It is a sterile clear yellow liquid composed of Montanide® 80 VG, a non-ionic surfactant of plant origin in highly purified mineral oil Drakeol® 6VR. Each DIN 2R vial contains 3.0 mL ISA 51 VG.

Placebo is provided as an ampoule of 2 mL of sterile sodium chloride solution (0.9% NaCl) to be emulsified with ISA 51 VG as adjuvant.

Note: Refer to the current version of the IB for further information about study products and their components.

Table 2 Study Products and Materials

Study product	Formulation/Vial	Presentation	Volume
IFN-K	At least 150 mcg of IFNα conjugated with KLH (IFN-K)	Solution for injection in single-use vial to be emulsified with ISA 51 VG	0.4 mL (DIN 2R vials)
Placebo	0.9% Sodium Chloride solution	Solution for injection in single-use vial to be emulsified with ISA 51 VG	2 mL (ampoule)
Adjuvant	Montanide® ISA 51 VG	Liquid formulation	3 mL (DIN 2R vials)
Ancillaries		Syringes, syringe caps, needles, connector with filter	

IFN-K = Interferon-kinoid; KLH = Keyhole limpet hemocyanin.

9.1.1 Packaging and Labelling

All clinical trial packaging and labelling operations will be performed according to current GMP. The contents of the label will be in accordance with all applicable regulatory requirements specified by each country participating in the trial.

Each treatment kit will be identified by a unique treatment number and will consists of:

- two vials of IFN-K or one ampoule of placebo,

- one vial of ISA 51 VG,

- two syringes, two syringe caps, one connector and four needles.

9.1.2 Kit Storage, Preparation, and Return

The study products and the materials will be supplied to the Investigational site packed in one kit with appropriate vials and outer-packaging labels and an "Instructions for use" leaflet.

The study product should be stored under refrigerated conditions at (+2 - +8˚C).

When kits are received at the site, Pharmacist or authorized designee shall check for accurate delivery, ensure that the study product is in good condition, verify that it arrived within the specified temperature ranges and place it in a refrigerator (+2 - +8˚C) as soon as possible.

Study kits will be stored away from light in a securely locked area that is accessible only to authorized personnel until they are administered to the patients. The site will maintain a temperature log to ensure that study kits are stored within the correct temperature range. They should be removed from the refrigerator at least 1 hour before preparation. The emulsion ideally will be prepared extemporaneously, immediately prior to use.

The unblinded study pharmacist or authorized designee will prepare each dose of IFN-K or placebo and provide the syringe(s) containing the emulsion to the Investigator. The same standard procedure for the emulsion preparation will be used for all doses. It will be communicated to each Investigational site in the provided Pharmacy Manual. Briefly, the procedure for one emulsion preparation comprises the following steps:

The volume of the 2 vials of IFN-K is transferred in a 2 mL syringe. The same volume of adjuvant is loaded into a second syringe. Both syringes must be attached to the connector after clearing as much air as possible from the system.

The emulsion process takes place in two steps:

- Emulsion starts by transferring alternatively the formulation from one syringe to the other very slowly.

- After the first 20 cycles performed slowly over 2 minutes, the speed is increased for 40 additional cycles performed in less than 50 seconds. When the emulsion starts to form, resistance will be felt and the mixture develops as a creamy viscous appearance. For the Placebo, 0.8 mL of 0.9% NaCl solution is transferred in a 2 mL syringe. Then, the emulsion process is the same as described above for IFN K emulsion.

After completion of the preparation, the total volume emulsion should be equally distributed with an equivalent volume of IFN-K (or placebo) in each syringe, each corresponding to an ultimate IFN-K dose of 120 mcg. The two syringes should then be disconnected from the connector and a sterile needle for IM administration or syringe cap should be attached to each syringe. The prepared syringes will be labelled with the study number, the subject number and the date and time of reconstitution/preparation of the study treatment. Labels prepared for IFN-K and placebo doses will be identical to ensure blind procedures.

The Pharmacist or authorized designee will maintain study products accountability and the return to Neovacs SA of unused test materials. This will include receipt, preparation, return dates, quantities, batch numbers, product name, vial numbers and the numbers of the vials allocated to the patients. The Pharmacist or authorized designee will maintain records that adequately document that the patients were provided with the dose specified by the protocol and reconcile all investigational products received from Neovacs SA. After completion of the study, all unused study products will be returned to designated CMO, unless otherwise requested by Neovacs SA in writing.

9.1.3 Dosage and Administration

The study products will be injected by suitably trained clinical staff. The covered syringes containing IFN-K and placebo will be indistinguishable. Please refer to the Pharmacy Manual provided separately.

Administration methods of IFN-K and placebo throughout the study are outlined in Table 3:

1- Each patient will receive two injections of study product (corresponding to 240 mcg of IFN-K or placebo) at 3 visits during the induction period (at Week 0 [visit 2], Week 1 [visit 3] and Week 4 [visit 4]).

2- Each patient will then be administered one injection of study product (corresponding to 120 mcg of IFN-K or placebo) at 2 visits during the maintenance period (at Week 12 [visit 6], Week 24 [visit 9]).

The duration of this intermittent study treatment will be 24 weeks from the first (Week 0 [visit 2]) to the last administration (Week 24 [visit 9]).

The study drug will be administered by intramuscular route in various body muscles (deltoid, buttock or thigh muscles) as displayed in the Table 3, to minimize the injection site reactions. Patients will be required to stay in the clinic for 1 hour post-dose for evaluation of any adverse reactions/events (see Section 11.2).

Table 3 Dosage and Administration of Study Products

Visit	Study Week	Injection	Groups IFN-K	Group Placebo	Study product	Route	Site	Side
2	Week 0	1	IFN-K		IFN-K 240 mcg + ISA 51 VG	IM	D	R/L
				Placebo	Sodium Chloride solution + ISA 51 VG	IM	D	R/L
3	Week 1	2	IFN-K		IFN-K 240 mcg + ISA 51 VG	IM	B	R/L
				Placebo	Sodium Chloride solution + ISA 51 VG	IM	B	R/L
4	Week 4	3	IFN-K		IFN-K 240 mcg + ISA 51 VG	IM	T	R/L
				Placebo	Sodium Chloride solution + ISA 51 VG	IM	T	R/L
6	Week 12	Booster 1	IFN-K		IFN-K 120 mcg + ISA 51 VG	IM	D	L
				Placebo	Sodium Chloride solution + ISA 51 VG			
9	Week 24	Booster 2	IFN-K		IFN-K 120 mcg + ISA 51 VG	IM	D	R
				Placebo	Sodium Chloride solution + ISA 51 VG			

D = deltoid muscles B = buttock muscles; T = thigh muscles; IFN-K = interferon-kinoid; IM = intramuscular; R/L = Right / Left;

9.2 Treatment Allocation and Randomization

A total of 166 patients will be enrolled in the study and randomly assigned into each cohort sequentially in a 1:1 ratio between the IFN-K group and the placebo group as described in Section 9.2.2.

Randomized patients who do not receive any study product will not be replaced and will be handled as drop-out patients (see Section 13.6).

9.2.1 Treatment Supply

A packaging list will be computer-generated using a standard Statistical Analysis System (SAS)® program and will be used to number the treatment kits.

IFN-K and placebo treatment kits will be distributed to each Investigational site.

9.2.2 Randomization of Patients

Treatment allocation at each site will be performed using central randomization via an Interactive Web Response System (IWRS). The randomization algorithm was developed using a stochastic minimization with a minimization probability parameter of 0.80. Randomization will be minimized by:

- Ethnic Origin: Black, Asian, Caucasian/Hispanic, other
- Age: 18-40 & 41-65 years old
- Presence or absence of renal BILAG at screening
- With or without CS treatment at randomization
- With or without HCQ treatment at randomization
- With or without MMF treatment at randomization

At the time of randomization, the IWRS will assign the patient to a treatment arm and will provide the number of the treatment kit for the first injection. The actual treatment numbers administered to the patient will be recorded in the eCRF.

Please refer to Section 10.1 for details about patient identification.

10. STUDY PROCEDURES

10.1 Patient Identification

Patients will be screened for eligibility for the study. The identification number will consist of six digits (two digits to represent the country, two to represent the site, and two to represent the patient's order of inclusion at the site).

Patients will be identified by their unique identification number throughout the study.

10.2 Method of Blinding and Breaking the Study Blind

10.2.1 Blinding rules

The study will be conducted with a double-blind design (patient and investigator will be blinded). As the placebo is not identical to the IFN-K, blinding rules will be set up and maintained during the whole study:

Treatment

The injected study product is an emulsion indistinguishable whether it has been prepared with IFN-K or placebo.

The pharmacist or the authorized designated person in charge of study product preparation will prepare the emulsion and deliver the blinded ready to use syringes in order that neither the patient nor the investigator will know the allocated treatment. He/she will be the only person knowing treatment allocation during the whole study.

The randomization list is centralized and treatment allocation will be through IWRS. At randomization and at each treatment visit, a blinded kit number is allocated to the patient.

Outcome used to evaluate endpoints

IFN gene signature, assessed as primary endpoint will be performed blind on anonymized samples, by a central specialized laboratory *a posteriori* when the patient will have completed the study. Procedures for assessment of immunogenicity (secondary endpoints) will be identical.

An independent adjudication committee will review and validate the BILAG on blinded data for consistency in the scoring.

Laboratory results will not be expected to reveal the treatment allocation.

Monitoring and study product accountability

Monitoring visits at pharmacy will be performed by an unblinded CRA who is different from the site designated CRA. Drug accountability will be performed at regular interval and potential issues/discrepancies will be reported in a separate « monitoring report » sent to reviewer independent from the Sponsor or a contractor involved in the study.

During the monitoring visit on site, the allocated treatment group will remain blinded for the site designated CRA.

10.2.2 Unblinding procedure

If knowledge of the study product (IFN-K or placebo) is necessary for optimal emergency treatment, the Investigator may break the treatment code through the IWRS. If possible, the Neovacs SA Clinical Safety Physician or Delegate Medical Monitor assigned to the investigational site should be consulted before breaking the study blind. In case of pregnancy, the investigator will be asked to break the treatment code and inform Neovacs SA Clinical Safety physician. The investigator will also have to notify the Pharmacovigilance Department of the contracted CRO by filling the Pregnancy form.

In any case, the Investigator must record the reason for breaking the study blind in the eCRF, and the site designated CRA must be notified as soon as possible.

Neovacs Clinical Safety Physician
Tel: +33153109300
Fax: +33153109303
Mobile phones for 7/7 day availability: +33 6 86907565
Medical Monitor
Mobile phone for 7/7 day availability: +39 345 2271297

10.3 Independent Data and Safety Monitoring Board

An iDSMB consisting of experts in the appropriate disciplines will ensure the safety of participating patients. The role and responsibilities of the iDSMB, as well as the data review process are outlined in detail in a separate iDSMB Charter.

In addition to planned iDSMB reviews, unscheduled meeting may be triggered in case of emerging safety concerns. Specifically, unscheduled meetings may be called at the request of any iDSMB member, the Study Chairman, or the Sponsor at any time during the study. The iDSMB will meet if any of the following occur during the study:

- A death or a medically significant and immediately life-threatening condition is sustained by one patient enrolled in the study, regardless of the study treatment causality;
- Two consecutive treatment-related SAEs;
- An unanticipated significant safety issue is newly identified during the development program of IFN-K that could expose treated patients to unnecessary risk;
- Any other concern regarding patient safety raised by any iDSMB member, the Study Chairman, or the Sponsor at any time during the study.

The available safety, immune responses and clinical data will be reviewed by the iDSMB through ad-hoc meetings. Rules for reviewing data will be described in the charter. iDSMB may recommend an amendment to the study protocol, or premature termination of the study. Such iDSMB recommendations will be submitted to the Sponsor. If applicable, they will be submitted to Independent Ethics Committees (IECs) and Competent Authorities.

10.4 Steering Committee

A steering committee consisting of Study Chairman, co-chairmen, CRO Project Manager, and Sponsor representatives will oversee the conduct of the study. A charter will describe missions and rules of this Committee.

10.5 Adjudication Committee

An Adjudication Committee consisting of independent SLE experts will ensure the consistency of BILAG scoring. A charter will describe missions and rules of this Committee.

10.6 Treatment Modification and Discontinuation Criteria

10.6.1 Study hold

The administration of IFN-K within the study will be put on hold if:

- Neovacs SA, Study Chairman and/or the iDSMB believe that the number and/or severity of adverse events (AEs) justify halting the study.
- New data raises concerns about the safety of the study material and continued administration of study product would pose potential risks to the patients.

10.6.2 Patient withdrawal from the study

A patient will be considered to have completed the main study when he or she completes the final assessment visit (Visit 12 at Week 36), after which he or she will complete the Extended Follow up up to the last visit FU10. A termination eCRF page should be completed for every patient who received study product, whether or not the patient completed the study (applicable for both main study and Extended Follow up study).

If a patient is discontinued prematurely at any time after entering the study, the Investigator will make every effort to see the patient and complete an early termination visit.

The reason for any early discontinuation should be indicated on the termination page. The primary reason for a patient withdrawing prematurely should be selected from the following standard categories of early termination:

- **Medical decision**: Clinical or laboratory events occurred that in the medical judgment of the Investigator for the best interest of the patient are grounds for discontinuation. This includes serious and non-serious AEs regardless of relation to study medication.
- **Death**: The patient died.
- **Pregnancy**: The patient became pregnant.
- **Withdrawal of Consent:** The patient desired to withdraw from further participation in the study in the absence of an Investigator-determined medical need to withdraw. If the patient gave a reason for withdrawal, it should be recorded in the eCRF.
- **Lost to Follow-Up:** The patient stopped coming for visits, and study personnel were unable to contact the patient.
- **Other:** The patient was terminated for a reason other than those listed above, such as termination of the study by the Sponsor.

10.6.3 Study Product Discontinuation

If any of these AEs or conditions occur during the study, the patient must not receive additional doses of study product but should be encouraged to continue other study procedures until Week 36. The patient must be followed until resolution of the event or condition:

- Bronchospasm or anaphylactic reaction following the administration of study product.
- Any confirmed or suspected immunosuppressive or immunodeficient condition.
- Medications leading to discontinuation of study product (list in Section 10.7.2).

10.7 Prior and Concomitant Medications

10.7.1 Permitted medications

Table 4 provides a list of the medications permitted prior to and during the main study.

Table 4 Permitted Medications

Drug	Screening Period	Induction Period	Maintenance Period	Follow-up Period
Visit	From Visit 1 (Week -4) to Visit 2 (Week 0)	From Visit 2 (Week 0) to Visit 6 (Week 12)	From Visit 6 (Week 12) to Visit 9 (Week 24)	From Visit 9 (Week 24) to Visit 12 (Week 36)
CS	During the last 3 preceding months and the screening period, ≤20 mg/day. Note: 1 episode >20 mg/day during ≤7 consecutive days is allowed	− ≤20 mg/day − Tapering encouraged to reach ≤10mg/day at Week 12 − 1 increase episode >20 mg/day during ≤ 7 consecutive days is allowed	− ≤10 mg/day recommended − Tapering mandatory to reach ≤5mg/day at Week 24 − No increase allowed	− ≤5 mg/day − No increase allowed
HCQ – CQ	At least ≥8 weeks, and stable dose ≥4 weeks	No initiation Stable dose	No initiation Stable dose	No initiation Stable dose
MTX **or** AZA	MTX dose ≤20mg/week AZA ≤2.5 mg/kg/day At least ≥12 weeks, and stable dose	MTX dose ≤20mg/week AZA ≤2.5mg/kg/day No initiation Variations allowed	MTX dose≤20mg/week AZA≤2.5mg/kg/day No initiation Tapering encouraged	MTX dose ≤20mg/week AZA ≤2.5mg/kg/day No initiation Tapering encouraged
MMF	Maintenance dose ≤2 g/day At least ≥12 weeks, and stable dose	No initiation Maintenance dose ≤2 g/day	No initiation Maintenance dose ≤2g/day Tapering encouraged	No initiation Maintenance dose ≤2g/day Tapering encouraged
Topical agents (steroids, tacrolimus)	Allowed	Allowed	Allowed if initiated before Week 12 Tapering encouraged	Allowed if initiated before Week 12 Tapering encouraged
NSAIDs	Allowed	Allowed	Allowed if initiated before Week 12 Tapering encouraged	Allowed if initiated before Week 12 Tapering encouraged

AZA = azathioprine; CQ = chloroquine; CS = corticosteroids; HCQ = hydroxychloroquine; MMF = mycophenolate mofetil; MTX = methotrexate; NSAID = non-steroidal anti-inflammatory drug.

Note: there is no particular guidance regarding permitted medications for the duration of the Extended Follow up Period.

10.7.2 Medications leading to study product discontinuation

The following medications will result in study product discontinuation. As described in Section 10.6.3, the patient should however continue other study procedures until Week 36 for the primary analysis and as much as possible in the Extended Follow up if applicable.

- Pulse dose CS (≥ 250 mg prednisone equivalent/day)
- Potent immunosuppressive drugs such as cyclophosphamide, cyclosporine A, oral tacrolimus
- Biological disease modifying products, including belimumab, anti-IFN monoclonal antibodies
- Anti-B-Cell therapy, such as rituximab (RTX) and epratuzumab,
- Any investigational or non-registered product (drug or vaccine) other than the study product
- Any live vaccine (e.g., nasal influenza vaccine, oral poliomyelitis vaccine, measles-mumps-rubella vaccine, yellow fever vaccine, Japanese encephalitis vaccine, dengue vaccine, rotavirus vaccine, varicella vaccine, zoster vaccine, BCG, oral typhoid vaccine)

10.8 Outline of Study Procedures

The list of the study procedures is provided in Table 1.

It is the Investigator's responsibility to ensure that the intervals between visits are strictly followed per Table 5. If a patient withdraws from the study before the final visit, the early termination visit procedures will be conducted.

Table 5 Intervals Between Study Visits

Visit	Interval	Visit window
V2	4 Weeks after V1	
V3	1 week after V2	+/- 1 day
V4	4 weeks after V2	+/- 4 days
V5	8 weeks after V2	+/- 4 days
V6	12 weeks after V2	+/- 4 days
V7	16 weeks after V2	+/- 4 days
V8	20 weeks after V2	+/- 4 days
V9	24 weeks after V2	+/- 4 days
V10	28 weeks after V2	+/- 4 days
V11	32 weeks after V2	+/- 4 days
V12	36 weeks after V2	+/- 4 days
FU visits*	Every 6 months from V12	+/- 14 days

* applies to all extended follow up visits

10.9 Detailed Description of Study Procedures

When materials are provided by Neovacs SA or its designated laboratory, it is mandatory that all clinical samples (including serum samples) are collected and stored exclusively using these materials in the appropriate manner. The Investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when Neovacs SA or its designated laboratory does not provide material for collecting and storing clinical samples, then appropriate materials from the Investigator's site are to be used and this should be duly documented.

Visit procedures as planned per protocol are described below. If deemed necessary, unscheduled visits may be performed.

10.9.1 Screening visit (Visit 1; Week -4 to 0)

Patients will undergo a screening visit to be evaluated for eligibility. Rescreening is not allowed.

At the screening visit, after patients have provided signed informed consent to participate in the study, the following activities will be carried out:

- Collect demographic data, including race
- Record SLE-specific and general medical history, including history of alcohol, drug, and tobacco use. In addition, for US patient ONLY, screening test(s) for malignancy within the previous 12 months according to ACS (please refer to appendix 12) has(ve) to be documented in the medical record
- Record prior medication and vaccination
- Assess disease activity scores:
  - SLEDAI-2K
  - PGA
  - BILAG-2004 index
- Perform complete physical examination, including body temperature, weight and height
- Measure vital signs – brachial pulse and blood pressure to be taken after 3 minutes of rest in a supine position

- Perform a gynecological examination, including examination of the cervix, cervical swabbing for cytological examination (PAP smear) and detection of high risk HPV (by RT qPCR); unless performed and documented within 3 months prior to first study product administration
- Perform a 12-lead ECG
- Perform urinalysis, including dipstick and microscopic examination
- Obtain blood sample for:
  - Serum pregnancy test for female patients of childbearing potential
  - Hematology, coagulation (INR, PT, PTT, fibrinogen), biochemistry (complete)
  - Viral serology (screening for HBV [HBsAg], HCV, HIV, CMV, VZV, EBV, HTLV-1, HTLV-2, and HSV-1, HSV-2)
  - Inflammatory markers (C3, C4, CH50)
  - Anti-dsDNA antibodies
  - ANA
  - IFN gene signature (by RT-qPCR)
- Evaluate eligibility

10.9.2 Visit 2 (Week 0) = baseline

Eligible patients will return to the clinic no later than 4 weeks (28 days) after completing the Screening Visit. The following assessments and evaluations will be carried out during this study visit:

- Collect quality of life questionnaires:
  - SF-36 health survey score
  - FACIT fatigue score
- Assess disease activity scores:
  - SLEDAI-2K
  - PGA
  - BILAG-2004 index
  - SELENA-SLEDAI flare index

  - SLICC/ACR-DI
  - 28- Tender & Swollen Joint Counts
  - Joint Pain VAS
  - CLASI
- Record all AEs
- Record concomitant medication
- Perform complete physical examination, including body temperature and weight
- Measure vital signs – brachial pulse and blood pressure to be taken after 3 minutes of rest in a supine position prior to and 1 hour post study product administration
- Evaluate eligibility
- Randomization by IWRS
- Perform a 12-lead ECG
- Obtain a Chest X-Ray where allowed by local regulation
- Perform urine pregnancy test for female patients of childbearing potential
- Perform urinalysis, including dipstick and microscopic examination
- Obtain blood sample for:
  - Hematology, coagulation (INR, PT, PTT, fibrinogen), biochemistry (complete)
  - Lymphocytes count (Total, CD4+, CD8+)
  - Anti-IFNα binding antibodies
  - Anti-KLH binding antibodies
  - Anti-IFNα neutralizing antibodies
  - Neutralizing Anti-IFNα antibodies towards IFNα subtypes
  - Anti-IFNα and anti-KLH antibody isotyping
  - IFNβ cross-neutralization
  - Anti-dsDNA antibodies

- ANA
- Other autoantibodies (anti-Sm, anti-RNP, anti-SSA/Ro, anti-SSB/La, anti-cardiolipin and anti-β_2-glycoprotein I antibodies)
- Inflammatory markers (C3, C4, CH50)
- IFN gene signature (by Affymetrix)

- Check contraindications
- Administer study product (two syringes)
- Record solicited injection site reactions during one hour following study product administration
- Record solicited systemic AEs during one hour following study product administration
- Provide diary card for daily recording by the patient of solicited AEs (Day 1 to Day 7)

10.9.3 Visit 3 (Week 1)

Enrolled patients will return to the clinic 7 days (+/- 1 day) after completing Visit 2. The following assessments and evaluations will be carried out during this study visit:

- Collect, check and transcribe diary card into eCRF
- Record all AEs
- Record concomitant medication
- Perform complete physical examination, including body temperature and weight
- Measure vital signs – brachial pulse and blood pressure to be taken after 3 minutes of rest in a supine position prior to and 1 hour post study product administration
- Perform urine pregnancy test for female patients of childbearing potential
- Check contraindications
- Administer study product (two syringes)
- Record solicited injection site reactions during one hour following study product administration
- Record solicited systemic AEs during one hour following study product administration

- Provide diary card for daily recording by the patient of solicited AEs (Day 1 to Day 7)

10.9.4 Visit 4 (Week 4)

Enrolled patients will return to the clinic 4 weeks (+/- 4 days) after completing Visit 2. The following assessments and evaluations will be carried out during these study visits:

- Assess disease activity scores:
  - BILAG-2004 index
- Collect, check and transcribe diary card into eCRF
- Record all AEs
- Record concomitant medication
- Perform complete physical examination, including body temperature and weight
- Measure vital signs – brachial pulse and blood pressure to be taken after 3 minutes of rest in a supine position prior to and 1 hour post study product administration
- Perform urinalysis, including dipstick and microscopic examination
- Perform urine pregnancy test for female patients of childbearing potential
- Obtain blood sample for:
  - Hematology, coagulation (INR, PT, PTT, fibrinogen), biochemistry (complete)
  - Anti-IFNα binding antibodies
  - Inflammatory markers (C3, C4, CH50)
- Check contraindications
- Administer study product (two syringes)
- Record solicited injection site reactions during one hour following study product administration
- Record solicited systemic AEs during one hour following study product administration
- Provide diary card for daily recording by the patient of solicited AEs (Day 1 to Day 7)

10.9.5 Visit 5 (Week 8)

Enrolled patients will return to the clinic 8 weeks (+/- 4 days) after completing Visit 2. The following assessments and evaluations will be carried out during this study visit:

- Assess disease activity scores:
  - BILAG-2004 index
- Collect, check and transcribe diary card into eCRF
- Record concomitant medication
- Record all AEs
- Perform complete physical examination, including body temperature and weight
- Measure vital signs – brachial pulse and blood pressure to be taken after 3 minutes of rest in a supine position
- Perform urine pregnancy test for female patients of childbearing potential
- Perform urinalysis, including dipstick and microscopic examination
- Obtain blood sample for:
  - Hematology, coagulation (INR, PT, PTT, fibrinogen), biochemistry (disease-oriented)
  - Anti-IFNα binding antibodies
  - Inflammatory markers (C3, C4, CH50)

10.9.6 Visit 6 (Week 12)

Enrolled patients will return to the clinic 12 weeks (+/- 4 days) after completing Visit 2. The following assessments and evaluations will be carried out during this study visit:

- Collect quality of life:
  - SF-36 health survey score
  - FACIT fatigue score
- Assess disease activity scores:
  - SLEDAI-2K

  - PGA
  - BILAG-2004 index
  - 28 Tender & Swollen Joint counts
  - Joint Pain VAS
  - CLASI
- Record all AEs
- Record concomitant medication
- Perform complete physical examination, including body temperature and weight
- Measure vital signs – brachial pulse and blood pressure to be taken after 3 minutes of rest in a supine position prior to and 1 hour post study product administration
- Perform a 12-lead ECG
- Perform urine pregnancy test for female patients of childbearing potential
- Perform urinalysis, including dipstick and microscopic examination
- Obtain blood sample for:
  - Hematology, coagulation (INR, PT, PTT, fibrinogen), biochemistry (complete)
  - Lymphocytes count (Total, CD4+, CD8+)
  - Anti-IFNα binding antibodies
  - Anti-KLH binding antibodies
  - Anti-IFNα neutralizing antibodies
  - Neutralizing Anti-IFNα antibodies towards IFNα subtypes
  - Anti-IFNα and anti-KLH antibody isotyping
  - IFNβ cross-neutralization
  - Anti-dsDNA antibodies
  - ANA
  - Other autoantibodies (anti-Sm, anti-RNP, anti-SSA/Ro, anti-SSB/La, anti-cardiolipin and anti-β_2-glycoprotein I antibodies)
  - Inflammatory markers (C3, C4, CH50)

  - IFN gene signature (by Affymetrics)

- Check contraindications
- Administer study product (one syringe)
- Record solicited injection site reactions during one hour following study product administration
- Record solicited systemic AEs during one hour following study product administration
- Provide diary card for daily recording by the patient of solicited AEs (Day 1 to Day 7)

10.9.7 Visit 7 (Week 16)

Enrolled patients will return to the clinic 16 weeks (+/- 4 days) after completing Visit 2. The following assessments and evaluations will be carried out during this study visit:

- Assess disease activity scores:
  - BILAG-2004 index
- Collect, check and transcribe diary card into eCRF
- Record all AEs
- Record concomitant medication
- Perform complete physical examination, including body temperature and weight
- Measure vital signs – brachial pulse and blood pressure to be taken after 3 minutes of rest in a supine position
- Perform urine pregnancy test for female patients of childbearing potential
- Perform urinalysis, including dipstick and microscopic examination
- Obtain blood sample for:
  - Hematology, coagulation (INR, PT, PTT, fibrinogen), biochemistry (disease-oriented)
  - Anti- IFNα binding antibodies
  - Anti-KLH binding antibodies
  - Anti-IFNα neutralizing antibodies

- Neutralizing Anti-IFNα antibodies towards IFNα subtypes
- Inflammatory markers (C3, C4, CH50)

10.9.8 Visit 8 (Week 20)

Enrolled patients will return to the clinic 20 weeks (+/- 4 days) after completing Visit 2. The following assessments and evaluations will be carried out during this study visit:

- Assess disease activity scores:
  - BILAG-2004 index
- Record all AEs
- Record concomitant medication
- Perform complete physical examination, including body temperature and weight
- Measure vital signs – brachial pulse and blood pressure to be taken after 3 minutes of rest in a supine position
- Perform urine pregnancy test for female patients of childbearing potential
- Perform urinalysis, including dipstick and microscopic examination
- Obtain blood sample for:
  - Hematology, coagulation (INR, PT, PTT, fibrinogen), biochemistry (disease-oriented)

10.9.9 Visit 9 (Week 24)

Enrolled patients will return to the clinic 24 weeks (+/- 4 days) after completing Visit 2. The following assessments and evaluations will be carried out during this study visit:

- Collect quality of life:
  - SF-36 health survey score
  - FACIT fatigue score
- Assess disease activity scores:
  - SLEDAI-2K
  - PGA

  - BILAG-2004 index
  - SELENA-SLEDAI flare index
  - 28-Count of Tender & Swollen Joints
  - Joint Pain VAS
  - CLASI
- Record all AEs
- Record concomitant medication
- Perform complete physical examination, including body temperature and weight
- Measure vital signs – brachial pulse and blood pressure to be taken after 3 minutes of rest in a supine position prior to and 1 hour post study product administration
- Perform a 12-lead ECG
- Perform urine pregnancy test for female patients of childbearing potential
- Perform urinalysis, including dipstick and microscopic examination
- Obtain blood sample for:
  - Hematology, coagulation (INR, PT, PTT, fibrinogen), biochemistry (complete)
  - Lymphocytes count (Total, CD4+, CD8+)
  - Anti-IFNα binding antibodies
  - Anti-KLH binding antibodies
  - Anti-IFNα neutralizing antibodies
  - Neutralizing Anti-IFNα antibodies towards IFNα subtypes
  - Anti-IFNα and anti-KLH antibody isotyping
  - IFNβ cross-neutralization
  - Anti-dsDNA antibodies
  - ANA
  - Other autoantibodies (anti-Sm, anti-RNP, anti-SSA/Ro, anti-SSB/La, anti-cardiolipin and anti-β_2-glycoprotein I antibodies)
  - Inflammatory markers (C3, C4, CH50)

  - IFN gene signature (by Affymetrix)

- Check contraindications
- Administer study product (one syringe)
- Record solicited injection site reactions during one hour following study product administration
- Record solicited systemic AEs during one hour following study product administration
- Provide diary card for daily recording by the patient of solicited AEs (Day 1 to Day 7)

10.9.10 Visit 10 (Week 28)

Enrolled patients will return to the clinic 28 weeks (+/- 4 days) after completing Visit 2. The following assessments and evaluations will be carried out during this study visit:

- Assess disease activity scores:
  - BILAG-2004 index
- Collect, check and transcribe diary card into eCRF
- Record all AEs
- Record concomitant medication
- Perform complete physical examination, including body temperature and weight
- Measure vital signs – brachial pulse and blood pressure to be taken after 3 minutes of rest in a supine position
- Perform urine pregnancy test for female patients of childbearing potential
- Perform urinalysis, including dipstick and microscopic examination
- Obtain blood sample for:
  - Hematology, coagulation (INR, PT, PTT, fibrinogen), biochemistry (disease-oriented)
  - Anti-IFNα binding antibodies
  - Anti-KLH binding antibodies
  - Anti-IFNα neutralizing antibodies

- Neutralizing Anti-IFNα antibodies towards IFNα subtypes
- Inflammatory markers (C3, C4, CH50)

10.9.11 Visit 11 (Week 32)

Enrolled patients will return to the clinic 32 weeks (+/- 4 days) after completing Visit 2. The following assessments and evaluations will be carried out during this study visit:

- Assess disease activity scores:
  - BILAG-2004 index
- Record all AEs
- Record concomitant medication;
- Perform complete physical examination, including body temperature and weight
- Measure vital signs – brachial pulse and blood pressure to be taken after 3 minutes of rest in a supine position
- Perform urine pregnancy test for female patients of childbearing potential
- Perform urinalysis, including dipstick and microscopic examination
- Obtain blood sample for:
  - Hematology, coagulation (INR, PT, PTT, fibrinogen), biochemistry (disease-oriented)

10.9.12 Visit 12 (Week 36)

Enrolled patients will return to the clinic 36 weeks (+/- 4 days) after completing Visit 2. The following assessments and evaluations will be carried out during this study visit:

- Collect quality of life:
  - SF-36 health survey score
  - FACIT fatigue score
- Assess disease activity scores:
  - SLEDAI-2K
  - PGA

  - BILAG-2004 index
  - SELENA-SLEDAI flare index
  - SLICC/ACR-DI
  - Count of Tender & Swollen Joints
  - Joint Pain VAS
  - CLASI
- Record all AEs
- Record concomitant medication
- Perform complete physical examination, including body temperature and weight
- Measure vital signs – brachial pulse and blood pressure to be taken after 3 minutes of rest in a supine position
- Perform a gynecological examination, including examination of the cervix, cervical swabbing for cytological examination (PAP smear) and detection of high risk HPV (by RT qPCR)
- Perform a 12-lead ECG
- Obtain Chest X-Ray where allowed by local regulation
- Perform urine pregnancy test for female patients of childbearing potential
- Perform urinalysis, including dipstick and microscopic examination
- Obtain blood sample for:
  - Hematology, coagulation (INR, PT, PTT, fibrinogen), biochemistry (complete)
  - Lymphocytes count (Total, CD4+, CD8+)
  - Anti-IFNα binding antibodies
  - Anti-KLH binding antibodies
  - Anti-IFNα neutralizing antibodies
  - Neutralizing Anti-IFNα antibodies towards IFNα subtypes
  - Anti-IFNα and anti-KLH antibody isotyping
  - IFNβ cross-neutralization

- Anti-dsDNA antibodies
- ANA
- Other autoantibodies (anti-Sm, anti-RNP, anti-SSA/Ro, anti-SSB/La, anti-cardiolipin and anti-β_2-glycoprotein I antibodies)
- Inflammatory markers (C3, C4, CH50)
- IFN gene signature (by Affymetrics)

10.9.13 Early Termination Visit

If the patient exits the study before Week 36 after having received at least one injection of study product, the following assessments and evaluations will be carried out whenever possible:

- Collect quality of life:
  - SF-36 health survey score
  - FACIT fatigue score
- Assess disease activity scores:
  - SLEDAI-2K
  - PGA
  - BILAG-2004 index
  - SELENA-SLEDAI flare index
  - SLICC/ACR-DI
  - Count of Tender & Swollen Joints
  - Joint Pain VAS
  - CLASI
- Record all AEs
- Record concomitant medication
- Perform complete physical examination, including body temperature and weight
- Measure vital signs – brachial pulse and blood pressure to be taken after 3 minutes of rest in a supine position

- Perform a gynecological examination, including examination of the cervix, cervical swabbing for cytological examination (PAP smear) and detection of high risk HPV (by RT qPCR)
- Perform a 12-lead ECG
- Obtain chest X-Ray where allowed by local regulation
- Perform urine pregnancy test for female patients of childbearing potential
- Perform urinalysis, including dipstick and microscopic examination
- Obtain blood sample for:
  - Hematology, coagulation (INR, PT, PTT, fibrinogen), biochemistry (complete)
  - Lymphocytes count (Total, CD4+, CD8+)
  - Anti-IFNα binding antibodies
  - Anti-KLH binding antibodies
  - Anti-IFNα neutralizing antibodies
  - Neutralizing Anti-IFNα antibodies towards IFNα subtypes
  - Anti-IFNα and anti-KLH antibody isotyping
  - IFNβ cross-neutralization
  - Anti-dsDNA antibodies
  - ANA
  - Other autoantibodies (anti-Sm, anti-RNP, anti-SSA/Ro, anti-SSB/La, anti-cardiolipin and anti-β_2-glycoprotein I antibodies)
  - Inflammatory markers (C3, C4, CH50)
  - IFN gene signature (by Affymetrix)

10.9.14 Extended Follow up visits

During the extended follow up period, the patients will be followed every 6 months for 5 years. The assessments and evaluations are described below.

The last Follow up Visit will be the last visit FU10. The assessments and evaluations are described in a separate section as they defer from the 6 and 12 month repeated pattern.

10.9.14.1 Follow up Visit FU1 (week 60), FU3 (week 108), FU5 (week 156), FU7 (week 204) and FU9 (week 252)

The following assessments and evaluations will be carried out during these study visits:

- Collect quality of life:
  - SF-36 health survey score
  - FACIT fatigue score
- Assess disease activity scores:
  - SLEDAI-2K
  - PGA
  - SELENA-SLEDAI flare index
  - Joint Pain VAS
- Record all AEs
- Record concomitant medication
- Perform complete physical examination, including body temperature and weight
- Measure vital signs – brachial pulse and blood pressure to be taken after 3 minutes of rest in a supine position
- Perform urine pregnancy test for female patients of childbearing potential
- Perform urinalysis, including dipstick and microscopic examination
- Obtain blood sample for:
  - Hematology, coagulation (INR, PT, PTT, fibrinogen), biochemistry (complete)
  - Lymphocytes count (Total, CD4+, CD8+)
  - Anti-IFNα binding antibodies
  - Anti-KLH binding antibodies
  - Anti-IFNα neutralizing antibodies
  - Anti-dsDNA antibodies
  - ANA

- Inflammatory markers (C3, C4, CH50)

10.9.14.2 Follow up Visit FU2 (Week 84), FU4 (week 132), FU6 (week 180) and FU8 (week 228)

The following assessments and evaluations will be carried out during this study visit:

- Collect quality of life:
  - SF-36 health survey score
  - FACIT fatigue score
- Assess disease activity scores:
  - SLEDAI-2K
  - PGA
  - SELENA-SLEDAI flare index
  - Joint Pain VAS
- Record all AEs
- Record concomitant medication
- Perform complete physical examination, including body temperature and weight
- Measure vital signs – brachial pulse and blood pressure to be taken after 3 minutes of rest in a supine position
- Perform urine pregnancy test for female patients of childbearing potential
- Perform urinalysis, including dipstick and microscopic examination
- Obtain blood sample for:
  - Hematology, coagulation (INR, PT, PTT, fibrinogen), biochemistry (complete)
  - Lymphocytes count (Total, CD4+, CD8+)
  - Anti-IFNα binding antibodies
  - Anti-KLH binding antibodies
  - Anti-IFNα neutralizing antibodies
  - Anti-dsDNA antibodies

- ANA
- Inflammatory markers (C3, C4, CH50)
- IFN gene signature (by RT-qPCR)

10.9.14.3 Follow up Visit FU10 (Week 276) or Visit when the patient becomes negative for anti-IFNα neutralizing antibodies

The following assessments and evaluations will be carried out during this study visit:

- Collect quality of life:
  - SF-36 health survey score
  - FACIT fatigue score
- Assess disease activity scores:
  - SLEDAI-2K
  - PGA
  - SELENA-SLEDAI flare index
  - Joint Pain VAS
- Record all AEs
- Record concomitant medication
- Perform complete physical examination, including body temperature and weight
- Measure vital signs – brachial pulse and blood pressure to be taken after 3 minutes of rest in a supine position
- Perform urine pregnancy test for female patients of childbearing potential
- Perform urinalysis, including dipstick and microscopic examination
- Obtain blood sample for:
  - Hematology, coagulation (INR, PT, PTT, fibrinogen), biochemistry (complete)
  - Lymphocytes count (Total, CD4+, CD8+)
  - Anti-IFNα binding antibodies
  - Anti-KLH binding antibodies

- Anti-IFNα neutralizing antibodies
- Neutralizing Anti-IFNα antibodies towards IFNα subtypes*
- Anti-dsDNA antibodies
- ANA
- Other autoantibodies (anti-Sm, anti-RNP, anti-SSA/Ro, anti-SSB/La, anti-cardiolipin and anti-β_2-glycoprotein I antibodies)*
- Inflammatory markers (C3, C4, CH50)
- IFN gene signature (by Affimetrix)*

* If a patient is tested negative for anti-IFN neutralizing antibodies prior to FU10 visit, the 3 following tests, i.e. neutralizing Anti-IFNα antibodies towards IFNα subtypes, other autoantibodies (anti-Sm, anti-RNP, anti-SSA/Ro, anti-SSB/La, anti-cardiolipin and anti-β_2-glycoprotein I antibodies) and IFN gene signature by Affimetrix, will be performed on the blood samples collected, if possible.

11. DESCRIPTION OF ASSESSMENTS

11.1 Informed Consent

Before performing any study procedure, the signed informed consent of the patient must be obtained.

11.2 Eligibility Criteria

All applicable **inclusion** and **exclusion** criteria as described in Sections 8.3 must be checked after informed consent has been given at the Screening Visit (Visit 1, Week -4 to 0) and again at Visit 2 (Week 0) before randomization.

11.3 Administration of Study Product

The study product will be administered IM in various body muscles (deltoid, buttock or thigh muscles) by the Investigator or a medically qualified designated person, according to schedule allocation at Visit 2 (Week 0), Visit 3 (Week 1), Visit 4 (Week 4), Visit 6 (Week 12), and Visit 9 (Week 24). The injection site must be rotated as described in Table 3, Section 9.1.3; the actual site of injection will be recorded in the eCRF.

The patients will be observed for at least 1 hour following the administration of study product, with appropriate medical treatment readily available in case of a rare anaphylactic reaction. AEs will be recorded during that period by the Principal Investigator or delegate. A missed or delayed injection of the study product will not lead to patient's withdrawal from the study and will not impact further injections. However, it may impact patient's eligibility in the per protocol analysis.

11.4 Safety Assessments

11.4.1 SLE-specific and General Medical History

A history-directed medical interview and examination of records will be performed during the Screening Visit (Visit 1, Week -4 to 0). Any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study will be recorded in the eCRF. Treatment of any abnormality observed during this examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

Information on alcohol, drug and tobacco use will also be collected.

11.4.2 Physical Examination and Vital Signs

Complete physical examination

A complete physical examination will be performed at each visit.

The complete physical examination comprises measurements of oral body temperature (in ˚C), weight, height (Visit 1 only), and routine medical examination of body systems (cardiovascular [CVS], pulmonary, abdominal systems assessment). Height without shoes will be recorded in centimeters, and body weight without shoes will be recorded in kilograms.

Vital signs

Vital signs will be evaluated during each visit. Vital signs include brachial pulse rate and systolic and diastolic blood pressures. These recordings will be made after at least 3 minutes of rest, measured in the supine position. Recordings will be made prior to and 1 hour post study product administration, when applicable.

11.4.3 Electrocardiogram

Standard 12-lead ECG recordings will be made during the Screening Visit, Visit 2 (Week 0), Visit 6 (Week 12), Visit 9 (Week 24) and Visit 12 (Week 36).

11.4.4 Concomitant Medications/Vaccinations

Any concomitant medication or any vaccination (name, dose, unit, frequency, route of administration, reason for medication, start and end dates) will be recorded at each visit.

At screening, total duration, duration on stable dose, and current dose of CS, HCQ-CQ, MTX, AZA, MMF, Topical agents and NSAIDs will be recorded. Any other pulse CS, potent immunosuppressive drugs such as cyclophosphamide, cyclosporine A, oral tacrolimus, biologics including but not limited to IFN mabs, rituximab and epratuzumab taken in the past, with time since discontinuation will be recorded.

CS Tapering is encouraged along Induction period and is mandatory along maintenance period as described in Table 4. Tapering is also encouraged for MTX, AZA, MMF, topical agents and NSAIDs from maintenance period onwards as described in Table 4.

At each seasonal period, flu vaccination is allowed according to local practice/recommendation in the different geographic area from Visit 5 at any time except within 7 days before and after study product administration to avoid interference in safety assessment. Blood sample is to be performed 28 days +/- 7 days after flu vaccination within planned visits. Name of vaccine, date of vaccination and of blood sample will be recorded in the eCRF.

Study patient and his/her partner have to use effective method of contraception for the duration of the study period (up to week 36) plus 6 months.

11.4.5 Recording of Adverse Events and Serious Adverse Events

At each visit, the Investigator will record any AEs that have occurred since the last visit.

An injection site reaction assessment will be performed 1 hour after each injection. The intensity of local AEs at the injection site (including redness, swelling, induration, itching and pain) and systemic AEs will be assessed by the study site personnel.

Patients will be also provided with a diary card to record the presence or absence and severity of specific local reactions and systemic signs and symptoms on the day of the injection and the six (6) subsequent days, in the evening. The patients will be asked to bring the diary card back at the next visit. The Investigator will then review the diary card with the patient and transcribe it into the eCRF (see Section 12.2).

The patients will be instructed to contact the Investigator immediately if they experience any signs or symptoms that they perceive to be serious. Please refer to Section 12.3 for SAE reporting procedures.

11.5 Laboratory Assessments

11.5.1 Sample Handling and Analysis

Samples will not be labeled with information that directly identifies the patients but will be coded with the identification number of the patient.

Collected samples may be used for purposes related to the quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these current tests, the maintenance or improvement of these current tests, the development of new test methods for the markers described in this protocol, as well as making sure that new tests are comparable to previous methods and work reliably.

It may be that any findings in the present or in other studies necessitate further investigation by Neovacs SA into the efficacy or immune responses of IFN-K and its constituents under study or further research in the study of SLE. Under these circumstances, additional testing could be performed by Neovacs using these samples. No genetic testing will be performed on these samples.

Any sample testing will be done in line with the signed consent of the individual patient for the present study.

11.5.2 Blood Sample Volumes and Handling

Maximum volume of blood collected from each patient during the study (i.e. 10 months) will not exceed 500 mL. Further details on blood treatment procedures are provided in the Laboratory Manual.

11.5.3 Urine Sample Collection and Handling

Urine sample will be collected:

- For female with childbearing potential (pregnancy test).
- For dipstick urinalysis
- For biochemistry analysis

11.5.4 Laboratory Assays

The tests to be conducted throughout the study are described in Table 6. Collection and shipment procedures are described in the Laboratory Manual.

Table 6 Laboratory Assays

Read Out	Analyses	Laboratory
Hematology/Coagulation	Complete blood cell count and differential (RBC, WBC, Lymphocytes, Neutrophils, Platelets); CD19; Total lymphocytes, CD4+, CD8+	Central Safety Laboratory
	Hemoglobin	
	Prothrombin time (PT)	
	Partial Thromboplastin Time (PTT)	
	Fibrinogen	
Biochemistry	Alanine Aminotransferase (ALT)[1]	Central Safety Laboratory
	Aspartate Aminotransferase (AST)[1]	
	Alkaline phosphatase[1]	
	Creatine phosphokinase (CPK)	
	Creatinine[2]	
	Urea	
	Total proteins	
	Albumin	
	Coomb's test (direct)	
	Circulating Anti-Coagulant	
Viral Serology	HBsAg	Central Safety Laboratory
	Antibodies to HCV, HIV, HTLV 1-2	
	IgG to HSV (HSV-1 and HSV-2), VZV, CMV and EBV	
High risk HPV	COBAS HPV test	Central Safety Laboratory
Pregnancy test	Serum β-hCG	Central Safety Laboratory
	Urine β-hCG	Local Laboratory
Urine testing	Dipstick urinalysis (pH, glucose, etc)	Local Laboratory
	Microscopic examination (RBC, WBC, urinary casts)	Central Safety Laboratory
	Albumin, creatinine, protein concentrations	
Binding Antibodies	Anti-IFNα antibodies	Central Specialized Laboratory
	Anti-KLH antibodies	
Neutralizing Antibodies	Anti-IFNα antibodies	Central Specialized Laboratory
Other Antibodies	e.g. IFNβ cross neutralization	Central Specialized Laboratory
Autoantibodies	Antinuclear antibodies (ANA)	Central Safety Laboratory
	Anti-dsDNA antibodies	
	Anti-Sm, anti-RNP antibodies	
	Anti-SSA/Ro antibodies	
	Anti-SSB/La antibodies	
	Anticardiolipin antibodies (IgG, M, A)	
	Anti-β_2-glycoprotein I antibodies	
Inflammatory markers	C3, C4, CH50	Central Safety Laboratory
IFN gene signature [3]	IFNα-inducible genes	Central Specialized Laboratory

* See Laboratory Manual for more details and for exact volumes of blood and types of samples at each visit

[1] Not required for disease-oriented testing at Visit 5, Visit 7, Visit 8, Visit 10 and Visit 11.

[2] Creatinine clearance GFR will be calculated using the Cockcroft-Gault formula: CrCl GFR = (140-age) * (Wt in kg) * (0.85 if female) / (72 * Cr) and MDRD formula: GFR = 170 x [serum creatinine (mg/dl)]-0.999 x [age]-0.176 x [serum urea (mg/dl]-0.17 x [serum albumin (g/dl)]0.318 x [0.762 if female] x [1.180 if African ancestry]

[3] Interferon gene signature: messenger RNA will be extracted from whole blood and the expression of a panel of IFN-inducible genes will be assessed, according to the methodology described previously (Yao *et al*., 2009a; Yao *et al*., 2009b).

11.6 SLE Disease Activity Assessment

The specific research instruments that will be used to assess disease activity and quality of life include:

- Chest X-Ray
  Chest X-Ray will be obtained where allowed by Local Regulation for SLICC/ACR-DI purpose at Visit 2 (X-Ray obtained within previous month is acceptable) and at Visit 12.

- SLEDAI-2K score (Gladman *et al*., 2002) - see Appendix 2
  The SLEDAI scale measures disease activity. The original version was modified (SLEDAI-2K) to better reflect persistent active disease. There are 24 items in a total of 9 organs/systems; total scores range from 0 (non-active disease) – 105 points. Scores are attributed taking into account disease activity over the previous 10 days.

- BILAG-2004 index (Yee *et al*. 2010) - see Appendix 3
  The BILAG 2004 index categorizes disease activity into 5 different levels from A–E, with Grade A representing very active disease and Grade E indicating no current or previous disease activity. Scoring is based on a total of 101 items, grouped into 9 organ/systems. Scores are attributed taking into account the signs/symptoms of SLE occurring over the previous 4 weeks.

- PGA score
  PGA score is captured using 100 mm VAS

- SELENA-SLEDAI flare index (Petri *et al*., 1999; Griffiths, *et al*. 2005) – see Appendix 4

- SLICC/ACR-DI (Gladman *et al*., 1996) – see Appendix 5
  The SLICC/ACR-DI captures permanent changes which have occurred in patients with SLE, regardless of causality. The questionnaire contains 41 items covering 12 different organ systems.

- Count of Tender and Swollen Joints and joint pain VAS – see Appendix 6
  Count of Tender and Swollen Joints will be captured with 28-Tender and Swollen Joint counts and Joint pain is captured using 100 mm VAS

- CLASI (Albrecht *et al*., 2005) – see Appendix 7
  The CLASI was specifically developed to assess the cutaneous manifestations of SLE. It measures both disease activity and permanent damage (e.g. dyspigmentation and scarring) over the entire body surface.

11.7 Quality of Life (QoL) Assessment

- SF-36 (Ware and Sherbourne, 1992) – see Appendix 8

  The SF-36 is a measure of health status and consists of eight scaled scores, which are the weighted sums of the questions in their section.

- FACIT fatigue score – see Appendix 9

  The FACIT Fatigue Scale is a short, 13-item, easy to administer tool that measures an individual's level of fatigue during their usual daily activities over the past week. The level of fatigue is measured on a four point Likert scale (0 = not at all fatigued to 4 = very much fatigued).

12. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study product.

AEs will be recorded and reported from the time a patient gives informed consent to study completion.

12.1 Definitions

12.1.1 Adverse event

International Conference on Harmonization (ICH) E6 Good Clinical Practice (GCP) Guidelines define an AE as any untoward medical occurrence in a patient or patient administered a pharmaceutical product in a clinical investigation regardless of its causal relationship to the study treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of medicinal (investigational) product, whether or not related to the medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews or by a study recipient presenting for medical care.

All AEs must be graded for intensity and relationship to study product.

SLE flare which is a worsening of the pre-existing SLE condition will be reported as AE.

12.1.2 Intensity of event

All AEs shall be graded by the Investigator using the World Health Organization (WHO) Toxicity Scale (Appendix 10). If an event cannot be graded by the WHO scale, the Investigator shall evaluate the severity according to a similar 4-point scale using the following definitions:

- **Mild**: The subject is aware of the event or symptom, but the event or symptom is easily tolerated.
- **Moderate**: The subject experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.
- **Severe**: Significant impairment of functioning: the subject is unable to carry out usual activities.
- **Life threatening**: any AE that places the patient, in the view of the Investigator, at immediate risk of death from the event as it occurred, i.e., it does not include an event that had occurred in a more severe form, might have caused death.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The following **local AEs** at the injection site (pain, redness, swelling, itching and induration) will be graded by study center staff and by the patient on the diary cards according to the intensity scale in Table 7.

Table 7 Intensity Scale for Local Reactions

Local Reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Pain	Does not interfere with activity	Interferes with activity	Prevents daily activity
Redness*	> 0 to < 30 mm	≥ 30 to < 120 mm	≥ 120 mm
Swelling*	> 0 to < 30 mm	≥ 30 to < 120 mm	≥ 120 mm
Itching	Does not interfere with activity	Interferes with activity	Prevents daily activity
Induration	> 0 to < 30 mm	≥ 30 to < 120 mm	≥ 120 mm

*Measure at greatest single diameter

The following **systemic reactions** (fever, headache, fatigue, myalgia and nausea) will be graded by study site staff and by the patient on the diary cards according to the intensity scale in Table 8.

Table 8 Intensity Scale for Systemic Reactions

Systemic Reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Fever (°C)*	37.1 - 38.0	38.1 - 40.0	> 40.0
Headache	Mild	Moderate or severe but transient	Unrelenting and severe
Fatigue	Increased fatigue over baseline, but not altering normal activities	Moderate or causing difficulty performing some activities	Severe or loss of ability to perform some activities
Myalgia	Mild	Decrease in ability to move	Disabled
Nausea	Able to eat reasonable intake	Intake significantly decreased but can eat	No significant intake

*Oral temperature; no recent hot or cold beverages or smoking. [Note: A fever can be considered not product-related if an alternative etiology can be checked and documented by the Investigator.]

Laboratory abnormalities will be graded according to the intensity scale in World Health Organization (WHO) Toxicity Scale (Appendix 10). Study site will also have to assess laboratory abnormalities using the following categories:

- abnormality not clinically significant (NCS)
- abnormality clinically significant, but normal for the study population (CS/N)
- abnormality clinically significant and is an adverse event (CS/AE)

It should be noted that all clinically significant abnormalities, not normal for the study population, count as Adverse Events even if they are not related to the use of study medication. Adverse Event section of eCRF needs to be completed accordingly.

12.1.3 Relationship to study products

The Investigators will decide if AEs are related to the administered products. The assessment of causality will be made using the following definitions:

- **Unrelated**: This category is applicable to AEs which are judged to be clearly and incontrovertibly due to extraneous causes (disease, environment, etc.) and do not meet the criteria for drug relationship listed under Unlikely, Possible or Probable.
- **Unlikely**: In general, this category is applicable to an AE which meets the following criteria (must have the first two):
  1. It does not follow a reasonable temporal sequence from administration of the drug.
  2. It may readily have been produced by the patient's clinical state, environment or toxic factors, or other modes of therapy administered to the patient.
  3. It does not follow a known pattern of response to the suspected drug.
  4. It does not reappear or worsen when the drug is re-administered.
- **Possible**: This category applies to AEs in which the connection with the investigational product administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possible if, or when (must have the first two):
  1. It follows a reasonable temporal sequence from administration of the drug.
  2. It may have been produced by the patient's clinical state, environment or toxic factors, or other modes of therapy administered to the patient.
  3. It follows a known pattern of response to the suspected drug.
- **Probable**: This category applies to AEs which are considered to be related to the investigational product with a high degree of certainty. An AE may be considered probable, if (must have the first three):
  1. It follows a reasonable temporal sequence from administration of the drug.
  2. It cannot be reasonably explained by the known characteristics of the patient's clinical state, environment or toxic factors, or other modes of therapy administered to the patient.
  3. It disappears or decreases on cessation or reduction in dose.
  4. It follows a known pattern of response to the drug.
  5. It reappears on re-challenge.

12.1.4 Serious adverse events

An SAE is defined as an AE that meets one of the following conditions:

- Death.

- Life threatening event (defined as any AE that places the patient, in the view of the Investigator, at immediate risk of death from the event as it occurred, i.e., it does not include an event that had occurred in a more severe form, might have caused death).
- An event requiring inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance.
- Results in a persistent or significant disability/incapacity.
- Congenital anomaly or birth defect in the offspring of a study participant.
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An SAE is not necessarily severe; for example, an overnight hospitalization for a diagnostic procedure must be reported as an SAE even though the occurrence is not medically serious. By the same token, a severe AE is not necessarily serious: nausea of several hours' duration may be rated as severe but may not be considered serious.

12.2 Adverse Event Recording

Each AE experienced by a patient, either spontaneously revealed by the patient or observed by the Investigator, whether believed by the Investigator to be related or unrelated to the study product, must be recorded on the patient's hospital notes and on the appropriate section of the eCRF.

12.2.1 Events occurring within one hour after injection

The presence and intensity of local and systemic AEs occurring within one hour after injection will be recorded by the study staff according to the intensity scale in World Health Organization (WHO) Toxicity Scale (Appendix 10).

12.2.2 Diary cards

After each study product administration, patients will be provided with a diary card. These will include the definitions of mild, moderate and severe AEs, as described in Section 12.1.2, in order to facilitate the assessments by the patients of their own level of functional impairment for each experienced AE.

The diary card will be used to record from Day 1 to Day 7 after each immunization, with Day 1 being the day of study product administration, the presence or absence and intensity of the following solicited AEs:

- Local AEs, at each injection site:
  - Pain, itching with grading of intensity.
  - Swelling, redness, induration with measurement of size (in millimeters).
- Systemic AEs:
  - Temperature (°C).
  - Nausea, fatigue, myalgia, headache, with grading of intensity.

Patients will also have the possibility to record unsolicited adverse events.

Patients will be instructed to bring their diary card with them to the unit when they return for their visits. Following discussion of symptoms with the Investigator, information on local tolerability/AEs will be recorded in the eCRF, as appropriate. Diary cards will be retained with the patient's source notes after completion.

12.3 Adverse Event and Pregnancy Reporting

12.3.1 Adverse event reporting

Any medical condition that is present at the time that the patient gives informed consent should be considered as pre-existing and not reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

All **SAEs** will also be:

- Recorded on the relevant SAE reporting form and followed up through to resolution by an Investigator,
- Then, submitted to the Pharmacovigilance Department of the contracted CRO,
- Then, submitted by the contracted CRO to Neovacs SA.

Contact Details for SAEs can be found in the "Guidelines for completing SAE and pregnancy forms" document.

All SAEs and FUP of SAEs, regardless of relationship, will be reported via fax or via e-mail (NeovacsPV@ubc.com) by the site within 24 hours of the Investigator becoming aware of the event.

Other supporting documentation of the event may be requested and should be provided as soon as possible.

All SAEs will be followed up until satisfactory resolution or until the Investigator deems the event to be chronic or the patient to be stable.

Following notification by the Investigator, Neovacs SA's delegate for Pharmacovigilance will report events that are both serious and unexpected and are associated with study product(s) to the Regulatory Health Authorities within the required timelines: **fatal and life threatening events within 7 calendar days and all other SAEs within 15 calendar days**, or according to local requirements if appropriate.

The classification of expectedness will be based on the material provided in the current version of the IB.

12.3.2 Pregnancy reporting

Any pregnancy that occurs during the study must be recorded on a pregnancy notification form and reported to the contracted CRO with 24 hours of learning of the occurrence (as described in Section 12.3.1). In case of pregnancy, unblinding procedure must be performed. The pregnancy should be followed up to determine its outcome (i.e., healthy birth, spontaneous or voluntary abortion, presence or absence of any birth defects, congenital abnormality, or maternal and/or newborn complications). A pregnancy report should include the Investigator's assessment of any possible relationship between the outcome and the exposure to study products.

12.4 Emergency Medication

The possibility that IFN-K can cause anaphylaxis in humans cannot be excluded. All participating centers should therefore be equipped to manage cardiovascular resuscitation with adequate material ready for use at the time of study product administration and during the 1 hour observation period after each administration.

Please refer to Section 10.2.2 for emergency unblinding and contact details of Neovacs SA's Clinical Safety Physician and Delegate Medical Monitor.

13. STATISTICAL ANALYSES

An electronic data capture (EDC) system will be utilized for this study. The statistical analysis of these data will be performed by an independent CRO. All data will be listed, and summary tables will be provided.

This section describes the statistical analysis as it is foreseen at the time of planning the study. Any major deviations from this plan, the reasons for such deviations, and all alternative or additional statistical analyses that may be performed will be described in the Statistical Analysis Plan (SAP), which will give a detailed technical description of all statistical analyses.

13.1 Determination of Sample Size

The primary objective of this study is to evaluate the neutralization of the IFN gene signature following treatment with IFN-K, as measured by the change from baseline of the expression of IFN-induced genes **and** to evaluate the efficacy of treatment with IFN-K using the British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) response criteria. The following assumptions were made for the sample size calculation:

- The error probability for a 2-sided t-test should not exceed 5%;
- The power should be 80% or higher;
- The change of the expression of IFN-induced genes in patients treated with IFN-K is assumed to be -22.6% (data from study IFN-K-001, Lauwerys *et al*., 2013);
- The change of the expression of IFN-induced genes in patients treated with placebo is assumed to be 10% (data from study IFN-K-001, Lauwerys *et al*., 2013);
- The common standard deviation of the change is 68 (data from study IFN-K-001, Lauwerys *et al*., 2013).

The assumptions for the change in expression of IFN gene signature and the standard deviation are based on the original data of study IFN-K-001 as presented in Lauwerys *et al*., 2013.

With 80 evaluable patients per group i.e. a total of 160 evaluable patients, the study will have a power of 85% to detect a difference of 32.6% in the expression of IFN-induced genes in patients treated with IFN-K compared to patients treated with placebo, assuming that the common standard deviation is 68% and using a two group t-test with a 0.050 two-sided significance level.

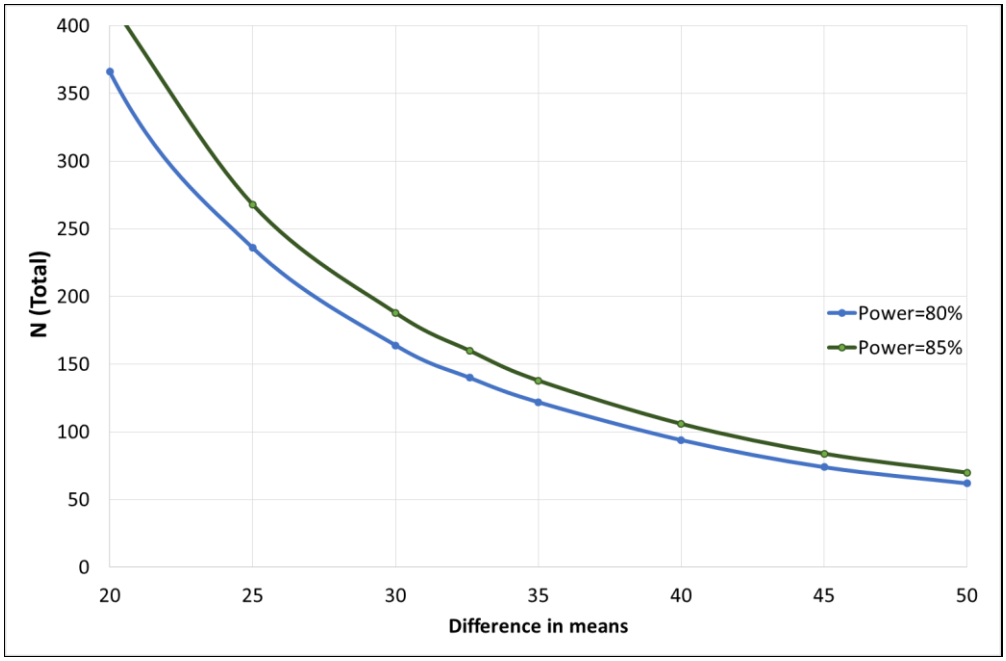
Assuming a rate of 10% drop-out patients, 178 patients should be enrolled in order to have 160 evaluable patients at Week 36 (80 evaluable patients in each treatment arm=90% of the enrolled patients).

Figure 1 shows – as a sensitivity analysis for the sample size calculation - the number of patients requested for analysis for different assumptions for differences in mean values and standard deviation in the sample size calculation. An increase in the difference of mean values of 5% would

decrease the number of required patients by approximately n=40, whereas a decrease in mean differences would increase the required sample size by n=60. A decrease in the standard deviation of 8 - at the reference point of 30% mean difference – would decrease the sample size by approximately n=36, whereas an increase of 8 would increase the required sample size by approximately n=38.

Taking into account, that the number of patients will be considerable higher in this trial than in the study IFN-K-001, there is a high probability of a smaller standard deviation that could compensate for a possible smaller difference in mean changes. Therefore the sample size calculation gives a realistic estimate of the patients required for analysis to show a significant difference between active treatment and placebo.

Figure 1: Sample-size for different values of between group differences (expression of IFN-induced genes)



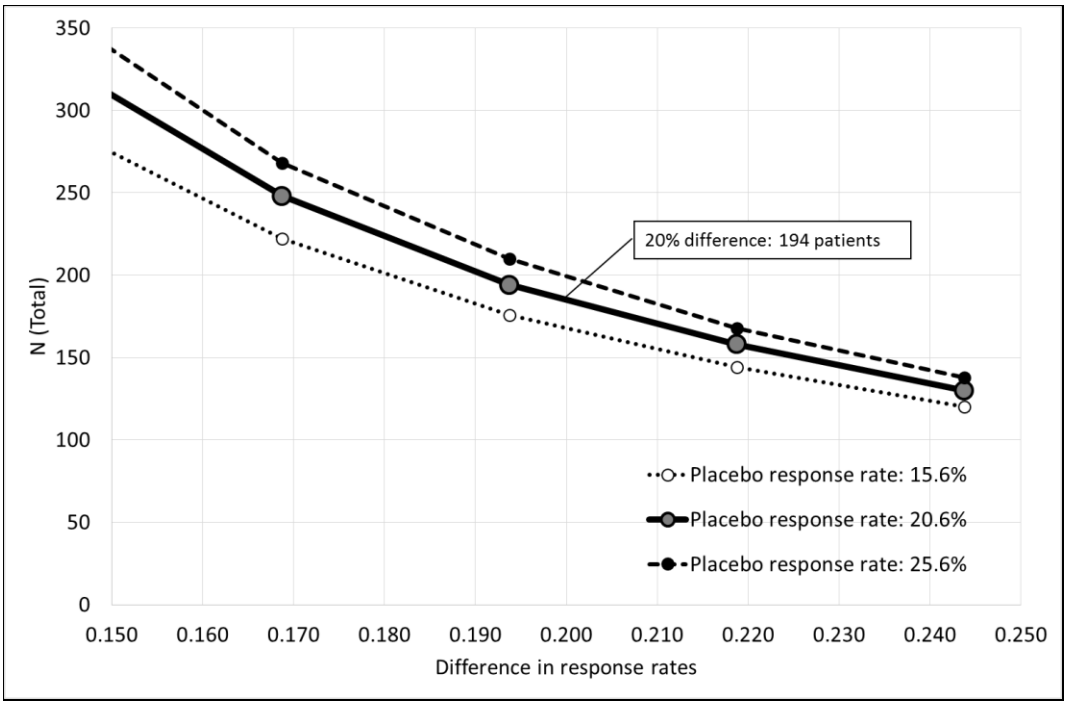
Assuming common SD=68 and a 0.05 two-sided type-one error rate

Assuming a BICLA response of 20.6% in the placebo group and 40.6% in IFN-K treated patients (i.e. an absolute difference of 20%) with 80 evaluable patients per group, there will be a 73% power to detect a difference of 20% in the BICLA response criterion.

The sample size needed to ensure a 80% power to the comparison of BICLA response rates between IFN-K and placebo for different response rates in the placebo arm and varying between

groups differences are presented in Figure 2. 97 evaluable patients per group would be needed for a power of 80% to detect a difference of 20% with a placebo response rate of 20.6%.

Figure 2: Sample-size for different values of between group differences (BICLA Response rate)



Assuming a power of 80% and a 0.05 two-sided type-one error rate

13.2 Primary Efficacy Endpoint

Two co-primary endpoints will be evaluated in the trial:

- Change from baseline in the expression of IFN-induced genes at Week 36.
- Response to treatment with IFN-K as measured by the British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) response criteria at Week 36:
  - All BILAG A scores at baseline improve to B/C/D and all BILAG B scores improve to C/D at Week 36

  and
  - No BILAG worsening in other body systems: no new BILAG A or ≥ 2 new BILAG B scores at Week 36

  and

- No worsening in SLEDAI-2K total score at Week 36 compared with baseline

and

- No deterioration in PGA (< 10% worsening) on VAS 100 mm at Week 36 compared with baseline

and

- No addition or increased dose level of anti-malarial drugs or immunosuppressive drugs or corticosteroids between Week 24 and Week 36

13.3 Secondary Endpoints

13.3.1 Clinical Secondary Endpoints

- Response to treatment with IFN-K, as measured by the SLE Responder Index (SRI)-4 response criteria at Week 36:
  - Reduction ≥ 4 points in SELENA-SLEDAI

  and

  - No new BILAG A

  and

  - No more than 1 new BILAG B

  and

  - No deterioration in PGA (< 10% worsening) on VAS 100 mm compared with baseline

- Response to treatment with IFN-K, as measured by SLEDAI response, defined as a reduction of the SLEDAI-2K score of at least 4 points at Week 36 compared to baseline

- Response to treatment with IFN-K, as measured by BILAG grade changes by body system

- Response to treatment with IFN-K, as measured by Incidence of SLE flare (SELENA SLEDAI flare index. BILAG flares)

- Response to treatment with IFN-K, as measured by SLICC/ACR-DI

- Response to treatment with IFN-K, as measured by Cutaneous LE Disease Area and Severity Index (CLASI)

13.3.2 Immunogenicity Secondary Endpoints

At time points specified on the flow chart (Table 1), Geometric Mean Titers (GMT) and seroconversion rates for:

- Anti-IFNα binding antibody titers

- Anti-IFNα neutralizing antibody titers

- Anti-KLH binding antibody titers

13.4 Safety Endpoints

- Occurrence, intensity and relationship of any solicited local and systemic AEs during a 7-day follow-up period (i.e. day of study product administration and 6 subsequent days) after each IFN-K or placebo dose
- Occurrence, intensity and relationship of unsolicited local and systemic AEs occurring throughout the study period
- Occurrence and relationship of all SAEs occurring throughout the study period
- Occurrence and intensity of solicited local reactions 1 hour post study product administration
- Occurrence and intensity of solicited systemic reactions 1 hour post study product administration
- Hematological and biochemical levels within or outside the normal ranges and percent change from baseline at each visit
- Occurrence, intensity and relationship of any abnormality in physical examination, vital signs, 12-lead ECG, clinical laboratory evaluations
- Rate and severity of viral infections

13.5 Exploratory Endpoints

Evaluation of clinical response by assessing disease activity using: PGA scores, number of SLE flares, Time to first SLE flare in patients, 28-Tender and Swollen Joint Counts (SJC), Joint Pain VAS and the incidence of an increase or addition in lupus therapy (intensification and/or add of drugs).

- Quality of life using:
  - FACIT fatigue score
  - Changes in the SF-36 score: Physical Component Summary (PCS) and Mental Component Summary (MCS) scores
- Evaluation of biological response by assessing:
  - Changes in the levels of auto-antibodies (anti-dsDNA, anti-Smith antigen [anti-Sm], anti-RNP, anti-SSA/Ro, anti-SSB/La, anti-cardiolipin, and anti-β2-glycoprotein I antibodies)

- Changes in levels of biomarkers (C3, C4, CH50)
- Anti-IFNα and anti-KLH antibody isotyping
- Neutralizing Anti-IFNα antibodies towards IFNα subtypes
- IFNβ cross neutralization
- Anti-Hemagglutinin antibody response

13.6 Analysis Populations

Intention-to-treat analysis population

The efficacy analysis population is the intention-to-treat analysis population (ITT). It will include all randomized patients who received at least one dose of study product. This population will be analyzed according to the result of the random treatment assignment.

Per protocol population

The PP population will be a subset of the ITT including all randomized patients who met all inclusion and exclusion criteria, received at least one dose of study product, did not meet any elimination criteria during the study, and complied with the procedures defined in the protocol (*i.e.*, who did not have major protocol deviations that could impact the primary endpoint analysis). This will be the population used in the immunogenicity analysis.

Safety population

The safety population (SP) will include all patients who received at least one dose of study product (placebo or IFN-K). The patients in the SP are analyzed according to the treatment actually received. This will the population used in the safety analysis.

13.7 Statistical Considerations

Statistical analyses will be performed using the SAS® software (SAS Institute, Cary, NC, USA).

Continuous data will be summarized using the number of observations, mean, 95% confidence interval (CI) of the mean (unless specified otherwise), standard deviation, median, minimum, and maximum. Categorical data will be presented with frequencies, percentages, and 95% CIs (unless specified otherwise).

Two-sided 95% CIs for two-sample differences in means/proportions between the treated and control groups and one-sample means/proportions will be calculated using:

- The normal-approximation method for GMT and other continuous endpoints,
- The “score” method without the continuity correction (Newcombe, 1998a) for binary endpoints.

Unless specified otherwise in the SAP, statistical tests will be two-sided at a 5% significance level.

Medications will be coded using the WHO Drug Dictionary. Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

13.8 Handling of Missing Values

Missing values at baseline will not be replaced.

For the primary endpoint – IFN gene signature – the last available value either at Visit 9 or 12 will be used for the inferential analysis.

13.9 Statistical Methods

This section briefly describes the planned primary analysis. The SAP will provide the full details of the analysis.

13.9.1 Demographic, Baseline and Follow-up Characteristics

Demographic, baseline, and follow-up characteristics such as medical history (classified based on MedDRA Dictionary) and concomitant medications (classified based on WHO Drug Dictionary) will be described by treatment group (placebo or IFN-K) in the SP and then in the ITT, if the two analysis sets are different.

13.9.2 Analysis of the Primary Efficacy Endpoint

The first co-primary efficacy endpoint - Percent change from baseline after 36 weeks of treatment in the expression of IFN-induced genes – will be analyzed using an ANCOVA.

The dependent variable will be the percentage change in the expression of IFN-induced genes and the treatment as independent variable. The minimization factors used for randomization - Race, Age range, Presence or absence of renal BILAG at screening, corticosteroid treatment, hydroxychloroquine treatment and MMF treatment at randomization - will be included as covariates.

The second co-primary efficacy endpoint - response to treatment according to BICLA - will be analyzed using a logistic regression using the response rate as dependent variable and treatment as independent variable, while adjusting for the minimization factors used for randomization.

First, the hypothesis with respect to the change from baseline in the expression of IFN-induced genes will be tested at an error probability of 5% for a 2-sided test. If and only if this Null-hypothesis can be rejected, the hypothesis with respect to the response to treatment according to BICLA will be tested also at an error probability of 5% for a 2-sided test.

The study will be considered as positive if a statistically significant better effect of IFN-K compared to placebo is observed on the neutralization of the IFN gene signature (i.e. the first co-primary endpoint) and if at least a trend favoring IFN-K is observed on the BICLA response (i.e. the second co-primary endpoint).

13.9.3 Analysis of the Clinical Secondary Endpoints

- The response to treatment according to response criteria described in section 13.3.1 will be analyzed using a logistic regression using the response rate as dependent variable and treatment as independent variable, while adjusting for the minimization factors used for randomization.

- The SRI-4, 6, 8, 10 response to treatment according to response criteria described in section 13.3.1 will be analyzed using a logistic regression using the response rate as dependent variable and treatment as independent variable, while adjusting for the minimization factors used for randomization.

- Number of patients achieving a SLEDAI response, defined as a reduction of the SLEDAI-2K score of at least 4 points at Week 36 compared to baseline will be analyzed using frequency table methods

- BILAG grade changes by body system will be analyzed using non-parametric Wilcoxon-test

- Number of patients with an SLE flare (SELENA-SLEDAI flare index; BILAG flares) will be analyzed using frequency table methods

- Clinical response by assessing disease activity using: SELENA-SLEDAI, SLICC/ACR-DI, and Cutaneous LE Disease Area and Severity Index (CLASI) will be analyzed using a t-test

13.9.4 Analysis of the Immunogenicity secondary Endpoints

The analysis will be performed using the PP population:

- The number of patients with a positive antibody response over time (seropositivity and seroconversion rates) will be analyzed using frequency table methods. A positive antibody response is defined as an increase of at least 3 folds in anti-huIFNα antibody titers compared to a negative control

- Log-transformed dilution titers for anti-IFNα binding and neutralizing antibodies and anti-KLH binding antibodies expressed as dilution factors at each time point will be analyzed using a repeated measurement model

- Reverse cumulative distribution curves will be generated using anti-IFNα and anti-KLH antibody titers and concentrations

- GMT for anti-IFNα binding and neutralizing antibodies and anti-KLH binding antibodies. Results will be expressed with 95% CI

13.9.5 Analysis of the Safety Endpoints

Safety data will be presented and analyzed using the SP:

- SAEs will be listed and summarized in a table, including a description and severity and duration of each event

- All AEs (including SAEs) will be listed, and their frequency, severity, and duration will be summarized for each treatment arm. Additionally, summary statistics per the number of doses administered will be obtained

- Premature withdrawals from the study will be displayed and summarized by primary reason

- Abnormal physical examination findings will be summarized over time

- Concomitant medications will be presented in summary tables and listings

- An association between the antibody response and the severity and/or frequency and/or duration of symptoms associated with kinoid administration will be investigated.

- The incidence of severe infections based on the total T-lymphocyte count (lymphocytes < 1000 versus lymphocytes > 1000/mm3) at the visit 2 (D0) will be analyzed.

13.9.6 Analysis of the Exploratory Endpoints

- Clinical response by assessing disease activity using: 28-Tender and Swollen Joint Counts and Joint Pain VAS will be analyzed using a t-test

- Number of SLE flares will be analyzed using frequency table methods

- Time to first SLE flare in patients will be analyzed using life-table methods

- Proportion of patients with an increase or addition in lupus therapy will be analyzed using frequency table methods

- Proportion of treatment failure will be analyzed using frequency table methods. Patients will be considered as treatment failure if they receive more than 5 mg prednisone equivalent/day at any time between Week 24 (Visit 9) and Week 36 (Visit 12) or if their CS dose is increased above the Week 24 level or if any increase of immunosuppressive treatment between Week 12 and Week 36 above CS dose at Week 12 is recorded.

- Changes in the SF-36 score: Physical Component Summary (PCS) and Mental Component Summary (MCS) scores using non-parametric Wilcoxon-test; if one is statistically significant then the individual domain scores will also be analyzed. Also clinically meaningful improvements ≥ Minimum Clinically Important Differences (MCID) of 2.5 points for summary and 5.0 points for domain scores will be analyzed

- Quality of life using FACIT fatigue score will be analyzed using a t-test

- Changes in the levels of auto-antibodies (anti-dsDNA, anti-Smith antigen [anti-Sm], anti-RNP, anti-SSA/Ro, anti-SSB/La, anti-cardiolipin, and anti-β2-glycoprotein I antibodies) will be analyzed using a t-test

- Changes in the levels of biomarkers (C3, C4, CH50) will be analyzed versus baseline

- Anti-IFNα and anti-KLH antibody isotyping

- Anti-Hemagglutinin antibody response: seroconversion (four fold increase in antibody titers post-vaccination) and seroprotection (HIA antibody titers ≥1:40 post-vaccination)

- Correlation between immunogenicity responses and clinical or biological parameters will be performed on an exploratory basis

13.9.7 Analysis of the Extended Follow up Period

A follow-up analysis will be performed at year 5 (week 276 - Month 69) when all patients have completed the extended follow up. For safety purpose, a descriptive analysis will be performed at regular intervals, according to Development Safety Update Report (DSUR) timelines.

The SAP will provide the full details of the analysis, notably on the clinical efficacy or response to treatment, safety and immunogenicity.

14. STUDY MANAGEMENT

14.1 Regulatory Guidelines

This study will be conducted in accordance with the European Union Clinical Trial Directive, or local national laws (as applicable), ICH E6 GCP guidelines, and the guidelines of the Declaration of Helsinki, revised form of 64th World Medical Association (WMA) General Assembly, Fortaleza, Brazil , 2013 (see Appendix 11).

14.2 Independent Ethic Committees / Independent Review Board

The composition of the committee will conform to state and local guidelines. The IEC/IRB will approve all aspects of the study, including study protocol, ICF, patient information sheets, and advertising to be used and any modifications made to the protocol or informed consent prior to study initiation. The IEC/IRB's decision concerning conduct of the study will be sent in writing to the Investigator, and a copy will be forwarded to Neovacs SA. The Investigator and Sponsor agree to make any required progress reports to the IEC/IRB, as well as reports of related SAEs, life-threatening AEs, or death.

14.3 Informed Consent

For each patient, written informed consent will be obtained prior to any protocol-related activities. As part of this procedure, the Principal Investigator or one of his associates must explain orally and in writing the nature, duration, and purpose of the study in such a manner that the patient and (if applicable) appointed guardian are aware of the potential risks, inconveniences, or adverse effects that may occur. They should be informed that the patient may withdraw from the study at any time. They will receive all information that is required by local regulations and ICH GCP guidelines.

Two original copies of the ICF will be signed and dated by the patients in the presence of an Investigator or designee (according to the site delegation of duties list). Participants will be given an original copy of the signed "Information for Patients and Consent Form for Study Participation" for their records. The second signed and dated original copy will be held on file by the Investigator.

14.4 Insurance and Indemnity

Neovacs SA has obtained insurance coverage for the conduct of this clinical trial in each country.

Based on the number of study visits and in order to facilitate the follow-up of patients through the study duration, patients will be compensated for local transportation costs only.

14.5 Protocol Adherence - Amendments

The protocol must be read thoroughly and the instructions must be followed exactly.

Any changes in the protocol will require a formal amendment. Such amendments will be agreed upon and approved in writing by the Investigator and Neovacs SA. Substantial amendments have to be submitted to the IEC and Competent Authorities (CA). Changes that are not substantial, which have no significant impact on the medical or scientific validity of the study will be notified to the IEC and the CA, when required.

14.6 Compliance Control and Monitoring

14.6.1 Patient compliance

All study medications will be administered to the patients by suitably trained clinical staff designated and authorized by the Investigator at the study site. Patients will be required to attend the medical facility for the study required visits at the specified times. Patients who are unable to comply may be withdrawn after discussion between the Investigator and the Medical Monitor. Patients are free to withdraw their consent at any time.

14.6.2 Site compliance and monitoring

In agreeing to participate, the Investigator undertakes to strictly comply with the study protocol, GCP, and the national regulations. The Investigator also guarantees the authenticity of the data collected in the context of the study and agrees to the legal provisions for study Sponsor quality control.

In compliance with GCP, the regular onsite verification of the data by the study monitor or other person authorized to conduct study related monitoring will include a review of the data entered into the system for completeness and clarity, and consistency with source documents/medical records available for each patient. Note that a variety of original documents, data, and records will be considered as source documents in this trial. The eCRF itself is not to be used as a source document under any circumstances.

The Investigator undertakes to make him/herself available to the study monitor and provide direct access to source data/documents for study related monitoring, audits, IEC review, and regulatory inspection.

Sites will be monitored by the contracted CRO according to their procedures. The purpose of site monitoring is to verify that:

- The rights and well-being of human patients are protected.
- The reported trial data are accurate, complete and verifiable from source documents.
- The conduct of the trial is in compliance with the currently approved protocol, GCP, and the applicable regulatory requirements.

Monitoring will be performed during the following on-site visits:

- Pre-study visit
- Initiation visit
- Monitoring visits
- Study end visit

Additional contacts between Sponsor/CRO and Investigator may take place by telephone, fax, letter, or email outside of the on-site visits.

14.6.3 Medical monitoring

The Medical Monitor will represent Neovacs SA in the event of questions regarding patient eligibility, evaluation of AEs, and questions relating to the protocol and conduct of the study.

14.7 Data Handling

Computations for the statistical methods will be performed using the computer software package SAS® version 9.1 or higher.

14.7.1 Electronic case report forms

An EDC system will be utilized for this study. The Investigator or a designee will be responsible for recording study data in the eCRF provided by Neovacs SA. It is ultimately the Investigator's responsibility to ensure the accuracy and completeness of the data entered in the eCRFs.

Clinical data (including AEs and concomitant medications) will be entered into an eCRF developed in accordance with Food and Drug Administration 21 Code of Federal Regulations part 11 requirements. The relevant eCRF pages of each study visit must be fully completed and marked as so within 5 days from the date of the visit. Any data change or correction done in the eCRF will be tracked through the audit trail tool of the EDC system.

Data validation will be performed after data entry and verification by computerized logical checks and manual review.

The contracted CRO will carry out the data processing in accordance with their data management procedures. Database lock will occur once quality assurance procedures have been completed.

14.7.2 Coding of adverse events, concomitant medications, and concomitant diseases

After data entry, the AEs and concomitant diseases will be coded according to the MedDRA version available at the start of the study. Concomitant medication will be coded according to WHO Drug Reference List.

14.8 Reporting and Communication of Results

A clinical study report (CSR) will be generated by Neovacs SA or its delegate when all patients will have completed Week 36. An addendum to the CSR will be generated when all patients have completed the 5-year Extended Follow up Period.

14.9 Quality Assurance

The sites will be audited as necessary during the course of the study. The audits will include control of adherence to the protocol, Standard Operating Procedures (SOPs), ICH GCP Guidelines, and national laws. Source data verification versus eCRFs will be used for assessment of complete and reliable documentation as well as the review of the investigator's study documentation.

The Investigator will allow Neovacs SA or their designated representatives to audit, at mutually convenient time(s) during the study, or after the study has been completed, investigator site file, all eCRFs, source and laboratory records of each study participant as well as all corresponding portions of office, clinic and pharmacy as applicable.

Regulatory authorities and representatives of the relevant independent IEC will be permitted to conduct inspections at the site. The Investigator should notify Neovacs SA if the regulatory authority contacts them to schedule an inspection.

14.10 Retention of Records

The investigator is to keep the identification lists of patients for at least 15 years after the completion or premature termination of the study. The medical records of the patients in the trial together with other data are to be kept for as long as the hospital, or institution allows, but for a minimum of 15 years or according to local regulatory requirements.

The sponsor or subsequent owner is required to keep all other documentation for the life of the product studied. The archived data can be kept in electronic form, provided that a back-up copy is kept and that a paper copy can be provided if necessary.

The protocol, ethical and Competent Authorities, together with all other documents concerning the study, including any audit and inspection certificates are all to be kept as part of the trial master reference file. All data about adverse events also needs to be kept in this trial master file.

All data should be available for inspection by the appropriate authorities on demand.

14.11 Patient Data Protection

Patients will be informed that their clinical data is held on file by the site, that this source information may be viewed by staff of the CRO (including, where necessary, staff of the CRO other than the named Investigators), and that data may also be sighted by Neovacs SA's monitor on behalf of Neovacs SA and by external auditors on behalf of either Neovacs SA or regulatory agencies at the CRO site only. They will similarly be informed that information from the study will be prepared and may also be submitted to Competent Authorities and perhaps for publication. However, participants of the study will only be identified in such reports by their study identification number and perhaps their gender and age. The Investigator undertakes to hold all personal information in confidence.

14.12 Confidentiality

The delegated CRO and Neovacs SA will affirm and uphold the principle of the patient's right to protection against invasion of privacy. Throughout this study, all data will only be identified by an identification number and the patient's gender and date of birth if applicable.

All information concerning this study and which was not previously published is considered confidential information. This confidential information shall remain the sole property of Neovacs SA; it shall not be disclosed to others without written consent of Neovacs SA and shall not be used except in the performance of this study.

The information compiled during the conduct of this clinical study is also considered confidential and may only be disclosed and/or used by Neovacs SA as they deem necessary. To allow the use of the information derived from this clinical study and to ensure compliance to current Competent Authorities regulations, the Investigator is obliged to furnish Neovacs SA with the complete test results and all data compiled in this study.

14.13 Publication

Publications arising out of this study are permissible in the view of Neovacs SA and are consistent with the preceding statement regarding confidentiality. Any formal presentation or publication of data collected as a direct or indirect result of this trial will be considered a joint publication by the investigator and the appropriate personnel of Neovacs SA.

The authorship will be discussed at the time of the analysis and will take into account contribution to the study as well as manuscript preparation.

Whatever the results of this study, whether favorable to the tested product or not, in the interest of scientific openness and in order to inform the wider medical and scientific community, Neovacs SA and the investigators are jointly committed to submit an article on the results of the trial for publication. Results of the trial as a whole will be drafted by a writing committee chaired by the study chairman and including Neovacs SA.

Unless otherwise agreed, the results of the complete study are to be published before the publication of results from nested sub-studies. The authors from these sub-studies will be determined by mutual agreement.

For any publication or presentation, a manuscript of the paper, abstract, or other materials must be received by, and approved by the steering committee and Neovacs SA prior to outside submission. A period of 7 working days for materials for presentation and abstracts, and 30 working days for manuscripts will be required for Neovacs SA review.

These requirements acknowledge the Sponsor’s responsibility to evaluate such publications for their accuracy and consonance with the database, to ascertain whether proprietary information (including trade secrets and patient protected materials) is being utilized and inappropriately released, to provide the investigator with information which may not yet have been available, and to provide input from co-authors regarding content and conclusion of the publication or presentation.

14.14 Funding

The costs necessary to perform the study will be agreed with the investigator and/or the management of the study facility, and will be documented in a separate financial agreement that will be signed by the investigator and/or the management of the study facility and Neovacs S.A.

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16. APPENDICES

Appendix 1 1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus

1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus

Criterion	Definition
1. Malar Rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Nonerosive Arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Pleuritis or Pericarditis	1. Pleuritis–convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion 1. OR 2. Pericarditis–documented by electrocardigram or rub or evidence of pericardial effusion
7. Renal Disorder	1. Persistent proteinuria > 0.5 grams per day or > than 3+ if quantitation not performed 1. OR 2. Cellular casts–may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic Disorder	1. Seizures–in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance 1. OR 2. Psychosis–in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic Disorder	1. Hemolytic anemia–with reticulocytosis 1. OR

Criterion	Definition
	2. Leukopenia—< 4,000/mm³ on ≥ 2 occasions 1. OR 3. Lyphopenia—< 1,500/ mm³ on ≥ 2 occasions 1. OR 4. Thrombocytopenia—<100,000/ mm³ in the absence of offending drugs
10. Immunologic Disorder	1. Anti-DNA: antibody to native DNA in abnormal titer 1. OR 2. Anti-Sm: presence of antibody to Sm nuclear antigen 1. OR 3. Positive finding of antiphospholipid antibodies on: 1. 1. an abnormal serum level of IgG or IgM anticardiolipin antibodies, 2. 2. a positive test result for lupus anticoagulant using a standard method, or 3. 3. a false-positive test result for at least 6 months confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11. Positive Antinuclear Antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

Appendix 2 Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K)

Scoring for SLEDAI: items should be recorded if the descriptor is present at the time of the visit or in the preceding 10 days (Gladman *et al*., 2000).

SLEDAI score	Descriptor	Definition
8	Seizure	Recent onset, exclude metabolic, infectious or drug causes
8	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized or catatonic behavior. Exclude uremia and drug causes
8	Organic brain syndrome	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least two of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes
8	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudates or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes
8	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves
8	Lupus headache	Severe, persistent headache; may be migrainous, but must be non-responsive to narcotic analgesia
8	Cerebrovascular accident	New onset cerebrovascular accident(s). Exclude arteriosclerosis
8	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages or biopsy or angiogram proof of vasculitis
4	Arthritis	≥ 2 joints with pain and signs of inflammation (i.e. tenderness, swelling or effusion)
4	Myositis	Proximal muscle aching/weakness, associated with elevated creatinine phosphokinase/aldolase, or EMG changes or a biopsy showing myositis
4	Urinary casts	Heme-granular or RBC casts
4	Hematuria	> 5 RBC/high power field. Exclude stone, infection or other cause
4	Proteinuria	> 0.5 g/24 hour
4	Pyuria	> 5 WBC/high power field. Exclude infection
2	Rash	Inflammatory type rash
2	Alopecia	Abnormal, patchy or diffuse loss of hair
2	Mucosal ulcers	Oral or nasal ulcerations

SLEDAI score	Descriptor	Definition
2	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening
2	Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion or ECG or echocardiogram confirmation
2	Low complement	Decrease in CH50, C3 or C4 below lower limit of normal for testing laboratory
2	Increased DNA binding	Increased DNA binding above normal range for testing laboratory
1	Fever	> 38 °C. Exclude infectious cause
1	Thrombocytopenia	< 100×109 platelets/l, exclude drug causes
1	Leucopenia	$< 3\times10^9$ WBC/l, exclude drug causes
Total score		

CH50: total hemolytic compliment (classical pathway functional activity); DNA: deoxyribonucleic acid; ECG: electrocardiogram; EMG: electromyogram; RBC: red blood cell; SLE: systemic lupus erythematosus; WBC: white blood cell.

Appendix 3 Updated British Isles Lupus Assessment Group (BILAG) Index

- **Only record manifestations/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**

Record: **ND** Not Done
0 Not present
1 Improving
2 Same
3 Worse
4 New
Yes/No OR Value (where indicated)
***Y/N Confirm this is due to SLE activity (Yes/No)**

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 ( )

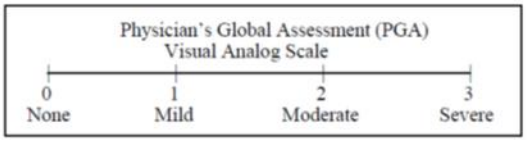
RENAL
78. Systolic blood pressure (mm Hg) value ( ) Y/N*
79. Diastolic blood pressure (mm Hg) value ( ) Y/N*
80. Accelerated hypertension Yes/No ( )
81. Urine dipstick protein (+=1, ++=2, +++=3) ( ) Y/N*
82. Urine albumin-creatinine ratio mg/mmol ( ) Y/N*
83. Urine protein-creatinine ratio mg/mmol (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

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

Revision: 1/Sep/2009

Reprinted from Yee *et al*., 2010

Appendix 4 SELENA-SLEDAI Flare Index



SELENA-SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) INSTRUMENT SCORE

Check box: if descriptor is present at the time of visit or in the preceding 10 days.

Wt	Check if Present	Descriptor	Definition
8	☐	Seizure	Recent onset (last 10 days). Exclude metabolic, infectious or drug cause, or seizure due to past irreversible CNS damage.
8	☐	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations; incoherence; marked loose associations; impoverished thought content; marked illogical thinking; bizarre, disorganized or catatonic behavior. Exclude uremia and drug causes.
8	☐	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 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes.
8	☐	Visual disturbance	Retinal and eye changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, optic neuritis, scleritis or episcleritis. Exclude hypertension, infection or drug causes.
8	☐	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves. Include vertigo due to lupus.
8	☐	Lupus headache	Severe persistent headache: may be migrainous, but must be nonresponsive to narcotic analgesia.
8	☐	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis or hypertensive causes.
8	☐	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	☐	Arthritis	More than 2 joints with pain and signs of inflammation (i.e., tenderness, swelling or effusion).
4	☐	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	☐	Urinary casts	Heme-granular or red blood cell casts.
4	☐	Hematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause.
4	☐	Proteinuria	New onset or recent increase of more than 0.5 gm/24 hours.
4	☐	Pyuria	>5 white blood cells/high power field. Exclude infection.
2	☐	Rash	Ongoing inflammatory lupus rash.
2	☐	Alopecia	Ongoing abnormal, patchy or diffuse loss of hair due to active lupus.
2	☐	Mucosal ulcers	Ongoing oral or nasal ulcerations due to active lupus.
2	☐	Pleurisy	Classic and severe pleuritic chest pain or pleural rub or effusion or new pleural thickening due to lupus.
2	☐	Pericarditis	Classic and severe pericardial pain or rub or effusion, or electrocardiogram confirmation.
2	☐	Low complement	Decrease in CH50, C3 or C4 below the lower limit of normal for testing laboratory.
2	☐	Increased DNA binding	>25% binding by Farr assay or above normal range for testing laboratory.
1	☐	Fever	>38°C. Exclude infectious cause.
1	☐	Thrombocytopenia	<100,000 platelets/mm^3.
1	☐	Leukopenia	<3,000 white blood cells/mm^3. Exclude drug causes.

_____ **TOTAL SCORE** (Sum of weights next to descriptors marked present)

Mild or Moderate Flare ☐

- ☐ Change in SELENA-SLEDAI instrument score of 3 points or more (but not to more than 12)
- ☐ New/worse:
  - Discoid, photosensitive, profundus, cutaneous vasculitis, bullous lupus
  - Nasopharyngeal ulcers
  - Pleuritis
  - Pericarditis
  - Arthritis
  - Fever (SLE)
- ☐ Increase in prednisone, but not to >0.5 mg/kg/day
- ☐ Added NSAID or hydroxychloroquine for SLE activity
- ☐ ≥1.0 increase in PGA score, but not to more than 2.5

Severe Flare ☐

- ☐ Change in SELENA-SLEDAI instrument score to greater than 12
- ☐ New/worse:
  - CNS-SLE
  - Vasculitis
  - Nephritis
  - Myositis
  - Plt <60,000
  - Hemolytic anemia: Hb <70 g/L or decrease in Hb >30 g/L

  Requiring: double prednisone, or prednisone increase to >0.5 mg/kg/day, or hospitalization
- ☐ Increase in prednisone to >0.5 mg/kg/day
- ☐ New cyclophosphamide, azathioprine, methotrexate for SLE activity
- ☐ Hospitalization for SLE activity
- ☐ Increase in Physician's Global Assessment score to >2.5

Reprinted from Petri *et al*., 2005

Appendix 5 Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index for Systemic Lupus Erythematosus

Table 1. Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus*

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 *or*	1
End-stage renal disease (regardless of dialysis or transplantation)	3
Pulmonary	
Pulmonary hypertension (right ventricular prominence, or loud P2)	1
Pulmonary fibrosis (physical and radiograph)	1
Shrinking lung (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.

Reprinted from Gladman *et al.*, 1996

Appendix 6 Tender Joint Count (TJC), Swollen Joint Count (SJC) and Joint Pain Visual Analog Scale (VAS)

TJC 28 and SJC 28 should be assessed using the same 28-joint counts (shoulders, elbows, wrists, MCP joints, proximal interphalangeal joints and knees)

Joint pain is captured using 100 mm VAS

Appendix 7 Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)

Select the score in each anatomical location that describes the most severely affected cutaneous lupus-associated lesion

Extent

	activity		damage		
Anatomical Location	Erythema	Scale/ Hypertrophy	Dyspigmentation	Scarring/ Atrophy/ Panniculitis	Anatomical Location
	0-absent 1-pink; faint erythema 2- red; 3-dark red; purple/violaceous/ crusted/ hemorrhagic	0-absent; 1-scale 2-verrucous/ hypertrophic	0-absent, 1-dyspigmentaton	0 … absent 1 … scarring 2 … severely atrophic scarring or panniculitis	
Scalp				See below	Scalp
Ears					Ears
Nose (incl. malar area)					Nose (incl. malar area)
Rest of the face					Rest of the face
V-area neck (frontal)					V-area neck (frontal)
Post. Neck &/or shoulders					Post. Neck &/or shoulders
Chest					Chest
Abdomen					Abdomen
Back, buttocks					Back, buttocks
Arms					Arms
Hands					Hands
Legs					Legs
Feet					Feet

Mucous membrane

Mucous membrane lesions (examine if patient confirms involvement)	
0-absent; 1-lesion or ulceration	

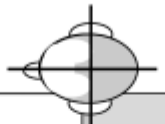
Dyspigmentation

Report duration of dyspigmentation after active lesions have resolved (verbal report by patient … tick appropriate box)

☐ Dyspigmentation usually lasts less than 12 months (dyspigmentation score above remains)

☐ Dyspigmentation usually lasts at least 12 months (dyspigmentation score is doubled)

Alopecia



Recent Hair loss (within the last 30 days/as reported by patient)	
1-Yes 0-No	

NB: if scarring and non-scarring aspects seem to coexist in one lesion, please score both

Divide the scalp into four quadrants as shown. The dividing line between right and left is the midline. The dividing line between frontal and occipital is the line connecting the highest points of the ear lobe. A quadrant is considered affected if there is a lesion within the quadrant.

Alopecia (clinically not obviously scarred)		Scarring of the scalp (judged clinically)	
0-absent 1-diffuse; non-inflammatory 2-focal or patchy in one quadrant; 3-focal or patchy in more than one quadrant		0- absent 3- in one quadrant 4- two quadrants 5- three quadrants 6- affects the whole skull	

Total Activity Score (For the activity score please add up the scores of the left side i.e. for Erythema, Scale/Hypertrophy, Mucous membrane involvement and Alopecia)		Total Damage Score (For the damage score, please add up the scores of the right side, i.e. for Dyspigmentation, Scarring/Atrophy/Panniculitis and Scarring of the Scalp)	

Appendix 8 SF-36 Health Survey

Scoring Outcome study: 36-Item Short Form Survey Instrument RAND 36-Item Health Survey 2.0 Questionnaire Items (http://www.rand.org).

Your Health and Well-Being

This questionnaire 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	<u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b	<u>Moderate activities</u>, such as moving a table, using a vacuum cleaner, bowling, or doing tai chi	☐ 1	☐ 2	☐ 3
c	Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d	Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e	Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking <u>more than a kilometre</u>	☐ 1	☐ 2	☐ 3
h	Walking <u>several hundred metres</u>	☐ 1	☐ 2	☐ 3
i	Walking <u>one hundred metres</u>	☐ 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 physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, 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 sad and low in mood 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 with 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 9 Functional Assessment of Chronic Illness Therapy (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 past 7 days.**

		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 starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing 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

Appendix 10 MODIFIED WHO TOXICITY SCALE

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
Hemoglobin (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/100mL)	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
Hematologic – 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 hours	2-5 x in 24 hours	6 - 10 x in 24 hours	> 10 x in 24 hours or requiring IV support
Diarrhea	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 diarrhea, or need for parenteral support
Stomatitis	none	painless ulcers, erythema, or mild soreness	painful erythema, edema, or ulcers but can eat	painful erythema, edema, or ulcers and cannot eat	requires parenteral or enteral support

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Esophagitis/ Obstruction	none	painless ulcers erythema, mild soreness or dysphagia	painful erythema, edema, 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
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
Alkaline 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
Hematuria	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	- -

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hemorrhagic 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					
Dyspnea	none or no change	asymptomatic, with abnormality in PFTs	dyspnea on significant exertion	dyspnea at normal level of activity	dyspnea 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
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	- -

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Pulmonary edema	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 product fever < 38°C	urticaria, product 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 ischemia	none	non-specific T wave flattening	asymptomatic ST and T wave changes for ischemia	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 > 20 mm 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

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hypotension	none or no change	changes not requiring therapy (including transient orthostatic hypotension)	requires fluid replacement or other therapy but not hospitalization	requires therapy and hospitalization; resolves within 48 hrs of stopping the agent	requires therapy and hospitalization for > 48 hrs the agent
Phlebitis/thrombosis embolism	- -	- -	superficial phlebitis(not local)	deep vein thrombosis	major event (cerebral/hepatic/ pulmonary/other infarction) or pulmonary embolism
Edema	none	1+ or dependent in evening only	2+ or dependent throughout day	3+	4+, generalized anasarca
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 tremor, 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

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
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
Behavioral change	none	change, not disruptive to patients or family	disruptive to patients 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
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 hours	> 40.0°C (104.0°F) for > 24 hours 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	- -	- -

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
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					
Hyperglycemia	< 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
Hypoglycemia	> 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
Hypercalcemia	< 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
Hypocalcemia	> 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
Hypomagnesia	> 1.4 mmol/l	1.4 - 1.2	1.1 - 0.9	0.8 - 0.6	≤ 0.5
Hyponatremia	WNL or > 135	131 - 135	126 - 130	121 - 125	≤ 120
Hypokalemia	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
ENDOCRINE					
Impotence/libido	normal	decrease in normal function	- -	absence of function	- -
Sterility	- -	- -	yes	- -	- -
Amenorrhea	no	yes	- -	- -	- -
Gynecomastia	normal	mild	pronounced or painful	- -	- -
Hot flushes	none	mild or < 1/day	moderate and ≥ 1/day	frequent and interferes with	- -

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
				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 11 WORLD MEDICAL ASSOCIATION (WMA) DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Patients

Adopted by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician

or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.
    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that

renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

- Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
- Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Appendix 12 Guidelines for Early Detection of Cancer – American Cancer Society – last revised 20-Oct-2015

The American Cancer Society recommends these cancer screening guidelines for most adults. Screening tests are used to find cancer before a person has any symptoms.

Visit our website, www.cancer.org, or call our toll-free number, 1-800-227-2345, to get more details on our cancer screening guidelines or to learn more about what you can do to help reduce your risk of getting cancer.

• Breast cancer

- **Women ages 40 to 44** should have the choice to start annual breast cancer screening with mammograms (x-rays of the breast) if they wish to do so.
- **Women age 45 to 54** should get mammograms every year.
- **Women 55 and older** should switch to mammograms every 2 years, or can continue yearly screening.
- Screening should continue as long as a woman is in good health and is expected to live 10 more years or longer.
- **All women** should be familiar with the known benefits, limitations, and potential harms linked to breast cancer screening. They also should know how their breasts normally look and feel and report any breast changes to a health care provider right away.

Some women – because of their family history, a genetic tendency, or certain other factors – should be screened with MRIs along with mammograms. (The number of women who fall into this category is very small.) Talk with a health care provider about your risk for breast cancer and the best screening plan for you.

• Colon and rectal cancer and polyps

Starting at age 50, both men and women should follow one of these testing plans:

– Tests that find polyps and cancer

- Flexible sigmoidoscopy every 5 years*, or
- Colonoscopy every 10 years, or
- Double-contrast barium enema every 5 years*, or
- CT colonography (virtual colonoscopy) every 5 years*

– Tests that mostly find cancer

- Yearly guaiac-based fecal occult blood test (gFOBT)**, or
- Yearly fecal immunochemical test (FIT)**, or
- Stool DNA test (sDNA) every 3 years*

* If the test is positive, a colonoscopy should be done.

** The multiple stool take-home test should be used. One test done in the office is not enough. A colonoscopy should be done if the test is positive.

The tests that can find both early cancer and polyps should be your first choice if these tests are available and you're willing to have one of them. Talk to a health care provider about which test is best for you.

If you are at high risk of colon cancer based on family history or other factors, you may need to be screened using a different schedule. Talk with a health care provider about your history and the testing plan that's best for you.

- ## Cervical cancer

- **Cervical cancer testing should start at age 21.** Women under age 21 should not be tested.
- **Women between the ages of 21 and 29** should have a Pap test done every 3 years. HPV testing should not be used in this age group unless it's needed after an abnormal Pap test result.
- **Women between the ages of 30 and 65** should have a Pap test plus an HPV test (called "co-testing") done every 5 years. This is the preferred approach, but it's OK to have a Pap test alone every 3 years.
- **Women over age 65** who have had regular cervical cancer testing in the past 10 years with normal results should not be tested for cervical cancer. Once testing is stopped, it should not be started again. Women with a history of a serious cervical pre-cancer should continue to be tested for at least 20 years after that diagnosis, even if testing goes past age 65.
- **A woman who has had her uterus and cervix removed (a total hysterectomy)** for reasons not related to cervical cancer and who has no history of cervical cancer or serious pre-cancer should not be tested.
- **All women who have been vaccinated against HPV** should still follow the screening recommendations for their age groups.

Some women – because of their health history (HIV infection, organ transplant, DES exposure, etc.) – may need a different screening schedule for cervical cancer. Talk to a health care provider about your history.

- ## Endometrial (uterine) cancer

The American Cancer Society recommends that at the time of menopause, all women should be told about the risks and symptoms of endometrial cancer. Women should report any unexpected vaginal bleeding or spotting to their doctors.

Some women – because of their history – may need to consider having a yearly endometrial biopsy. Please talk with a health care provider about your history.

- ## Lung cancer

The American Cancer Society does not recommend tests to check for lung cancer in people who are at average risk. But, we do have screening guidelines for those who are at high risk of lung cancer due to cigarette smoking. Screening might be right for you if you are all of the following:

- 55 to 74 years of age
- In good health
- Have at least a 30 pack-year smoking history AND are either still smoking or have quit within the last 15 years (A pack-year is the number of cigarette packs smoked each day multiplied by the number of years a person has smoked. Someone who smoked a pack of cigarettes per day for 30 years has a 30 pack-year smoking history, as does someone who smoked 2 packs a day for 15 years.)

Screening is done with an annual low-dose CT scan (LDCT) of the chest. If you fit the list above, talk to a health care provider if you want to start screening.

- **Prostate cancer**

The American Cancer Society recommends that men make an informed decision with a health care provider about whether to be tested for prostate cancer. Research has not yet proven that the potential benefits of testing outweigh the harms of testing and treatment. We believe that men should not be tested without first learning about what we know and don't know about the risks and possible benefits of testing and treatment.

Starting at age 50, men should talk to a health care provider about the pros and cons of testing so they can decide if testing is the right choice for them.

If you are African American or have a father or brother who had prostate cancer before age 65, you should have this talk with a health care provider starting at age 45.

If you decide to be tested, you should get a PSA blood test with or without a rectal exam. How often you're tested will depend on your PSA level.

- **Cancer-related check-ups**

For people aged 20 or older who get periodic health exams, a cancer-related check-up should include health counseling and, depending on a person's age and gender, exams for cancers of the thyroid, oral cavity, skin, lymph nodes, testes, and ovaries, as well as for some other diseases besides cancer.

- **Take control of your health, and help reduce your cancer risk.**

- Stay away from all forms of tobacco.
- Get to and stay at a healthy weight.
- Get moving with regular physical activity.
- Eat healthy with plenty of fruits and vegetables.
- Limit how much alcohol you drink (if you drink at all).
- Protect your skin.
- Know yourself, your family history, and your risks.
- Get regular check-ups and cancer screening tests.

For more on what you can do to help reduce your cancer risk and other questions about cancer, please visit us online at www.cancer.org, or call us anytime, day or night, at 1-800-227-2345.