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

Clinical Study Report Synopsis

Name of test drug/ investigational product:	IFNα-Kinoid emulsified with ISA 51 VG adjuvant
Sponsor:	Neovacs S.A., 3-5 Impasse Reille, 75014 Paris, France Neovacs Inc., 50 Milk Street, Boston MA 02109, USA
Study Code:	IFN-K-002
EudraCT number:	2015-001341-86
IND number:	016840
Abbreviated title:	Phase IIb study of IFN-K in Systemic Lupus Erythematosus
Development phase:	IIb
Study initiation date (Informed Consent Form signature of first subject):	23 September 2015
Study completion date (last subject having completed the main study, i.e. Visit 12):	15 March 2018
Coordinating Investigator:	Pr Frédéric Houssiau Université Catholique de Louvain (UCL) at Brussels, Belgium
Sponsor's responsible medical officer:	Thérèse Croughs, MD Neovacs S.A., 3-5 Impasse Reille, 75014 Paris, France
Sponsor signatory:	Thérèse Croughs, MD Neovacs S.A., 3-5 Impasse Reille, 75014 Paris, France
Sponsor contact persons for questions arising during review of the study report:	Thérèse Croughs, MD Neovacs S.A., 3-5 Impasse Reille, 75014 Paris, France
Date of the report:	26 June 2019
Version number:	1

Versions history	Date	Description
Not applicable		

This study was performed under the provisions of the Declaration of Helsinki, in compliance with Good Clinical Practice (GCP), and all local regulatory requirements.

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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

Abbreviated Title: Phase IIb study of IFN-K in Systemic Lupus Erythematosus

Study code: IFN-K-002

EudraCT number: 2015-001341-86

IND number: 016840

Coordinating Investigator: Pr Frédéric Houssiau, Cliniques Universitaires Saint-Luc (UCL), Service de Rhumatologie, Avenue Hippocrate 10, Brussels, Belgium (Phone: +32 (0)2 764 29 92; Fax: +32 (0)2 764 53 94; Email: frederic.houssiau@uclouvain.be).

Study centers: The study was performed as a multicenter study: 122 investigational centers in 22 countries across Eurasia, the Americas and North Africa were initiated and received Independent Ethics Committee approval, and patients were screened / randomized in 106 centers in 21 countries.

Publication (reference): None

Studied period (years): 23 September 2015 (first screening Visit and first ICF signed) - 15 March 2018 (last Visit 12)	**Phase of development**: IIb

Objectives:

Primary objective: 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 is to 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:

1. To evaluate the efficacy of treatment with IFN-K using:
    a. the systematic lupus erythematosus (SLE) responder index [(SRI)-4 and above]
    b. the SLE Disease Activity Index-2000 (SLEDAI-2K)
    c. the Safety of Estrogen in Lupus Erythematosus National Assessment-SLEDAI (SELENA-SLEDAI) flare index
    d. the BILAG-2004 index
    e. the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for SLE (SLICC/ACR-DI)
    f. the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) in patients with cutaneous lesions at baseline
    g. the Lupus Low Disease Activity State (LLDAS)
2. To evaluate the immune response induced by IFN-K:
    a. anti-IFNα antibody response
    b. anti-IFNα antibody neutralizing capacities
    c. anti-keyhole limpet hemocyanin (KLH) antibody response
3. To assess the safety of IFN-K emulsified with ISA 51 VG.

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Exploratory objectives:

1. To assess disease activity using:
    a. the physician global assessment (PGA) score
    b. the 28-tender and swollen joint counts
    c. a joint pain visual analog scale (VAS)
    d. the flare description
    e. the changes in lupus therapy
2. To assess quality of life using:
    a. the short form-36 (SF-36) survey score
    b. the functional assessment of chronic illness therapy (FACIT) fatigue score
3. To assess biological parameters:
    a. levels of lupus-related serum auto-antibodies and biomarkers
    b. neutralizing anti-IFNα antibodies towards IFNα subtypes
    c. anti-IFNα and anti-KLH antibody isotyping
    d. IFNβ cross-neutralization
    e. antibody response to influenza vaccination
4. To assess correlations between immune responses, IFN gene signature and clinical responses.

Methodology: This was a Phase IIb, randomized, double-blind, placebo-controlled, multicenter study assessing intramuscular administration of IFN-K against an adjuvanted placebo. Study patients were enrolled into one of two treatment groups and allocated in 1:1 randomization ratio to receive the study product: IFN-K or placebo.

The study consisted in a main study followed by an extended follow-up period.

Number of analyzed patients:

185 patients (92 patients in the IFN-K group and 93 patients in the placebo group) were included and randomized

Diagnosis and main criteria for inclusion:

Inclusion criteria: A patient meeting all the following inclusion criteria at Screening was eligible for participation in this study:

1. Had a diagnosis of SLE according to American College of Rheumatology (ACR) criteria (4 of 11 ACR criteria)
2. Had SLEDAI-2K ≥6
3. Had at least 1 BILAG A and/or at least 2 BILAG B
4. Had a positive IFN gene signature by reverse transcription quantitative polymerase chain reaction (RT-qPCR) as assessed on a limited number of genes
5. Had anti-nuclear antibodies (ANA) ≥1:160 and/or anti-dsDNA antibodies ≥7.0 IU/mL
6. Was a male or female, aged between 18 and 65 years, inclusive, at the time of the screening Visit
7. Agreed to receive influenza vaccination during each influenza season of the study period
8. Was receiving at least one of the following treatments:
    - CS at a dose of ≤20 mg of prednisone equivalent/day
    - Antimalarial drugs (hydroxychloroquine [HCQ] or chloroquine [CQ]); the patient had to 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 had to 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 had to 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 had to 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

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9. Study patient and his/her partner had to use effective method of contraception for the duration of the study including the extended follow-up period

   Note: If of childbearing potential, effective contraception methods included:

   - Female sterilization (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 have been 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 were considered post-menopausal and not of childbearing potential if they had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 weeks before Screening. In the case of oophorectomy alone, she was considered not of childbearing potential only when the reproductive status of the woman had been confirmed by follow-up hormone level assessment.

10. Was 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. Had provided written informed consent

Exclusion criteria: A patient meeting any of the following exclusion criteria at study entry was not eligible for participation in this study:

1. Had active, severe lupus nephritis as defined either by the immediate need for cyclophosphamide treatment or by renal BILAG A
2. Had active, severe, neuropsychiatric SLE, defined as neuropsychiatric BILAG A
3. During the 4 months prior to the first planned study product administration, had been treated with CS at a dose of >20 mg of prednisone equivalent/day for >7 consecutive days
4. Was receiving or had received pulse dose CS (≥250 mg prednisone equivalent/day) within 3 months prior to the first planned administration of the study product
5. Had 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. Had received abatacept, sifalimumab, rontalizumab, anifrolumab, belimumab, tumor necrosis factor (TNF) antagonists or another registered or investigational biological therapy within 6 months prior to the first planned administration of the study product
7. Had received anti-B cell therapy (e.g. rituximab, epratuzumab) within 12 months prior to the first planned administration of the study product
8. Had significant electrocardiogram (ECG) abnormalities that were clinically relevant and precluded study eligibility in the Investigator's opinion
9. Had inflammatory joint or skin disease other than SLE that might have interfered with study assessments
10. Had any laboratory abnormality other than SLE-related that was clinically relevant and precluded study entry in the Investigator's opinion
11. Had 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: Had 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 (ACS) guidelines, documented within the 12 months prior screening Visit, could be enrolled.

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12. Had frequent recurrences of oral or genital herpes simplex lesions (≥6 occurrences during the 12 months prior to first study product administration)
13. Had had an episode of shingles during the 12 months prior to the first planned administration of the study product
14. Had no immunoglobulin (Ig) G against herpes simplex virus (HSV-1 and HSV-2), varicella zoster virus (VZV), cytomegalovirus (CMV) or Epstein-Barr virus (EBV)
15. Was positive for human T-lymphotropic virus (HTLV) 1-2 antibodies, human immunodeficiency virus (HIV) antibodies, hepatitis C virus (HCV) antibodies, or hepatitis B surface antigen (HBsAg)
16. Was at high risk of significant infection and/or had any signs or symptoms of infection at entry or had received intravenous antibiotics within 2 months prior to the first planned administration of the study product
17. Had 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. Had used any investigational or non-registered product within 30 days or 5 half-lives, whichever was longer, or any investigational or non-registered vaccine within 30 days prior to the first planned administration of the study product
19. Had a history of chronic alcohol and/or drug abuse within 6 months prior to the first planned administration of the study product
20. Was breastfeeding, pregnant, or planning to become pregnant during the study period
21. Had known hypersensitivity to any component of the study product
22. Was high risk human papilloma virus (HPV) positive by RT-qPCR on a cervical swab at Screening or within 3 months prior to the first planned study product administration
23. Had 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

Duration of treatment: The main study comprised a total of 12 visits occurring over a period of 40 weeks. It was divided into four periods: a 4-week screening period, a 12-week induction period, a 12-week maintenance period and a 12-week follow-up period.

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

Study products, doses and mode of administration, batch numbers:

The active treatment was a solution of IFN-K emulsified with ISA 51 VG adjuvant. The placebo was a sterile sodium chloride solution (0.9% NaCl) to be emulsified with ISA 51 VG as adjuvant.

Five doses of study product were administered during the main study:

- dose 1 on week 0 (Visit 2) during the induction period: 240 mcg (two syringes)
- dose 2 on week 1 (Visit 3) during the induction period: 240 mcg (two syringes)
- dose 3 on week 4 (Visit 4) during the induction period: 240 mcg (two syringes)
- dose 4 on week 12 (Visit 6) during the maintenance period: 120 mcg (one syringe) [first booster dose]
- dose 5 on week 24 (Visit 9) during the maintenance period: 120 mcg (one syringe) [second booster dose]

The study product was administered by intramuscular route in various body muscles (deltoid, buttock or thigh muscles); the injection site had to be rotated to minimize the injection site reactions.

IFN-K batch numbers:

- IFN-α 2b Kinoid Batch number: DPKINM3
- Montanide ISA 51VG Batch numbers: 2406436 / U 44110 and 2488775

Placebo batch numbers:

- Sodium chloride 0.9% Batch number: 5A037
- Montanide ISA 51VG Batch numbers: 2406436 / U 44110 and 2488775

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Criteria for evaluation:

Efficacy:

- IFN gene signature
- SLE disease activity assessment:
  - composite BICLA response criteria at week 36
  - SRI-4 response criteria at week 36
  - composite SRI-4 response criteria, including CS tapering at week 36
  - SLEDAI-2K
  - BILAG-2004 index
  - PGA score
  - SELENA-SLEDAI flare index
  - SLICC/ACR-DI
  - count of 28-tender and swollen joints and joint pain VAS
  - CLASI
  - LLDAS

Quality of Life:

- SF-36
-FACIT fatigue score

Safety:

- SLE-specific and general medical history
- physical examination and vital signs
- ECG
- concomitant medications/vaccinations
- recording of adverse events (AEs) and serious adverse events (SAEs)
- recording of solicited injection site reactions and solicited systemic AEs

Laboratory assessments:

- blood analysis
- urine analysis
- Anti-IFNα binding and neutralizing antibodies
- Anti-KLH binding antibodies
- Autoantibodies (Antinuclear antibodies (ANA), Anti-dsDNA antibodies, Anti-Sm, anti-RNP antibodies, Anti-SSA/Ro antibodies, Anti-SSB/La antibodies, Anticardiolipin antibodies (IgG, M, A), Anti-β2-glycoprotein I antibodies)
- Inflammatory markers: C3, C4, CH50
- Anti-IFNα and anti-KLH antibody isotyping
- Neutralizing Anti-IFNα antibodies towards IFNα subtypes
- IFNβ and IFNω cross neutralization
- Anti-Hemagglutinin antibody response following influenza vaccination

Statistical methods:

General considerations: The following descriptive statistics were presented:

- for quantitative variables: number of available values, number of missing values, mean, standard deviation (S.D), median, Q1 (first quartiles), Q3 (third quartiles), minimum, maximum values. When relevant, confidence intervals (CIs) were calculated for the mean (Student CI) or the median.

- for qualitative variables: number of available values, number of missing values, number and percentage of observations in each category of the variable. Except if otherwise specified, percentages were calculated using the number of available values as denominator. When relevant, CIs of proportions were calculated using the Wald method or Clopper-Pearson if Wald was not applicable.

Two-sided 95% CIs for two-sample differences in means/proportions between the IFN-K and placebo groups and one-sample means/proportions were calculated using:

- the normal-approximation method for geometric mean titers and other continuous endpoints

- the "score" method without the continuity correction for binary endpoints

Unless specified otherwise in the statistical analysis plan, statistical tests were two-sided at a 5% significance level

Primary efficacy analysis (full analysis set [FAS]):

- *first primary co-endpoint*: descriptive statistics for IFN gene signature at each visit and % of change from baseline by treatment group were presented. The percent of change from baseline after 36 weeks of treatment in the expression of IFN-induced genes was analyzed using an analysis of covariance (ANCOVA) model. The dependent variable was the percentage of change from baseline in the expression of IFN-induced genes with the treatment as independent variable. The minimization factors used for randomization were included as covariates.

supplementary analysis: The primary efficacy analysis was repeated on the per protocol (PP) population. It was also repeated on the FAS population excluding patients with unblinding issue, and then repeated on the FAS for patients treated with IFN-K with (positive/negative) status of IFNα neutralizing antibodies at week 36 as dependent variable.

sensitivity analysis: The time variation in IFN gene signature was modelled using a mixed model for repeated measures (MMRM) with random intercept, with raw values at each time point (after the first dose) as dependent variable, and minimization factors used for randomization age group, presence or absence of renal involvement according to BILAG at Screening, CS treatment, HCQ treatment and MMF treatment at randomization, treatment and time as explanatory variables. The treatment by time interaction was also included in the models. The model was adjusted on baseline IFN gene signature.

- *second primary co-endpoint*: descriptive statistics for the response to treatment according to BICLA at week 36 were presented by treatment group. The response to treatment according to BICLA was analyzed using a logistic regression with the response rate as dependent variable and treatment as independent variable, while adjusting for the minimization factors used for randomization.

Secondary efficacy analyses:

- *SRI response* (FAS and PP population): the SRI-4, -6, -8, -10 responses were described at week 36. The SRI-4 response was analyzed using a logistic regression. The SRI-6, -8, -10 responses to treatment at week 36 were analyzed using a logistic regression. All analyses performed on SRI-4 were also conducted on the composite SRI-4 (both with tapering CS $\leq$5 mg and $\leq$7.5 mg) on the FAS only.

- *SLEDAI response* (FAS): the number of patients achieving a SLEDAI response was analyzed using frequency table methods. The SLEDAI-2K score at each visit and change from baseline by treatment group was also presented.

- *BILAG (FAS)*: shift tables between baseline and the last value available [LVA] (last value available between week 36 and week 24) were presented for each body system. Descriptive statistics for the BILAG global score at each visit and change from baseline to LVA were presented. The difference between treatment groups for the change from baseline to LVA were analyzed using the non-parametric Wilcoxon-test.

- *SELENA-SLEDAI flare index* (FAS): the numbers of patients with a mild or moderate, or severe SLE flare and corresponding number of SLE flare were presented. The total score at each visit and change from baseline by treatment group were presented. The change at week 36 was analyzed using a t-test.

- *SLICC/ACR-DI* (FAS): the total score at each visit and change from baseline by treatment group were presented. The change at week 36 was analyzed using a t-test.

- *CLASI* (FAS): the total activity score and total damage score at each visit and change from baseline by treatment group were presented. The changes at week 36 were analyzed using a t-test.

- *lupus low disease activity state (LLDAS) (FAS)*: the number of patients achieving a LLDAS at week 36 was presented by treatment group.

Immunogenicity analyses (PP population):

- *anti-IFNα binding antibody titers* (on all patients): the number of patients with a positive antibody response over time was analyzed using frequency table methods (seropositivity if titer $\geq$400 dil^{-1}). Descriptive analyses were done on Log-transformed dilution titers for anti-IFNα binding antibodies expressed as dilution factors at each time point. Reverse cumulative distribution curves were generated using anti-IFNα antibody titers. Geometric mean titers (GMT) for anti-IFNα binding antibodies were presented; results were expressed with 95% CI.

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- *anti-IFNα antibody neutralizing capacity (NC50)* (patients treated with IFN-K): the number of patients with a positive antibody response over time was analyzed using frequency table methods (seropositivity if titer ≥200 dil^{-1}). Descriptive analysis was done on Log-transformed NC50 for anti-IFNα neutralizing antibodies expressed as dilution factors at each time point. Reverse cumulative distribution curves were generated using NC50. GMT for anti-IFNα neutralizing antibodies were presented; results were expressed with 95% CI.

- a*nti-KLH binding antibody titers* (all patients): the number of patients with a positive antibody response over time was analyzed using frequency table methods (seropositivity if titer ≥400 dil^{-1}). Descriptive analysis was done on Log-transformed dilution titers for anti-KLH binding antibodies expressed as dilution factors at each time point. Reverse cumulative distribution curves were generated using anti-KLH antibody titers. GMT for anti-KLH binding antibodies were presented. Results were expressed with 95% CI.

Exploratory analyses:

- *PGA* (FAS): PGA score at each visit and change from baseline by treatment group was presented.

- *SLE flares* (FAS): the time to first SLE flare was analyzed using a cox regression model. This first model was adjusted on treatment group. The second model was performed only on patients treated with IFN-K and was adjusted on the presence/absence of neutralizing antibodies.

- *28-tender and swollen joint counts and joint pain VAS* (FAS): results at each visit and change from baseline were presented. The changes at week 36 were analyzed using a t-test.

- *treatment failure* (FAS): the proportion of treatment failure was analyzed using frequency table methods. Patients were considered as treatment failure if they had received 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 was increased above the week 24 level recorded.

- *SF-36* (FAS): physical component summary (PCS) and mental component summary (MCS) scores at each visit and change from baseline were presented. The changes at week 36 was analyzed using a non-parametric Wilcoxon rank sum test. If one was statistically significant, then the individual domain scores was also described. In addition, number of patients with clinically meaningful improvements ≥minimum clinically important difference (MCID) of 2.5 points for summary and 5.0 points for domain scores between baseline and week 36 were presented.

- *FACIT* (FAS): total scores at each visit and change from baseline by treatment group were presented. The change at week 36 was analyzed using a t-test.

- *autoantibodies* (FAS and PP population): levels of auto-antibodies at each visit and change from baseline by treatment group were presented. For anti-dsDNA, the changes at week 36 were analyzed using a t-test.

- *biomarkers* (PP population): biomarkers at each planned visit and change from baseline by treatment group were presented. For C3 complement, the change at week 36 was analyzed using a t-test.

- *anti-IFNα and anti-KLH antibody isotyping* (FAS): a descriptive analysis was performed.

- *anti-hemagglutinin antibody response following influenza vaccination* (FAS, only on patients vaccinated with seasonal flu and with an available sample at baseline and post-baseline): seroconversion and seroprotection were presented by treatment group for each visit. In addition, results by visit were presented according to status of anti-IFNα neutralizing antibodies at the corresponding visit.

- *neutralizing anti-IFNα antibodies towards IFNα subtypes* (FAS): a descriptive analysis was performed.

- *other data* (FAS): IFNβ and IFNω cross-neutralization data were provided.

- *correlation* (PP population): correlation between immunogenicity responses and clinical parameters, between immunogenicity responses and biological parameters were qualitatively and quantitatively described.

- *Corticosteroids use* (FAS): intake between visits 6 and 12, variations in mean and median dose over time, frequency of taper below 5 and 7.5 mg at weeks 24 and 36

Safety analyses (SAF):

Safety variables were tabulated and presented for extent of exposure and compliance; AEs; laboratory safety variables; physical examination results; vital signs; ECG; concomitant medications.

SUMMARY - CONCLUSIONS

Data and results from the main phase, up to 36 weeks i.e. Visit 12 (no extended follow-up phase), are presented in the body of this clinical study report.

EFFICACY RESULTS:

The first co-primary endpoint (biological response, assessed with the interferon gene signature) analyzed on the FAS shows a clear decrease from baseline to week 36 of 31.0% in the IFN-K treated patients compared to a near absence of change (-0.4%) in the patients treated with placebo. The between group absolute difference in percent-change from baseline is 30.3% (95% CI [19.9; 40.7]) and is highly statistically significant ($p<0.0001$).

On the second co-primary endpoint (clinical response assessed with the BICLA) analyzed on the FAS at week 36: a numerically larger absolute difference in response rates of 6.7%, favoring IFN-K (41.2% versus 34.5% in the placebo group) is observed, corresponding to an odds ratio of 1.38 (95% CI: [0.72, 2.66]) favoring IFN-K, but non-significantly different from 1 ($p=0.34$).

The sensitivity and supplementary analyses of the two co-primary endpoints provide results highly consistent with the primary efficacy analyses in terms of magnitude of effects and statistical significance, attesting the robustness of the primary analysis findings.

The magnitude of the effect observed on the interferon gene signature (absolute difference of 30.3%) is consistent with the hypothesized effect of 32.6% used for the sample-size computation. The observed BICLA response rates are consistent with the protocol hypotheses for IFN-K (41.2% observed, 40.6% expected) but much higher than expected for the placebo group (34.5% observed when only 20.6% was expected).

The observed difference in BICLA response rates is only 6.7%, one-third lower than the 10% difference defining a marginal effect, due to a higher than expected placebo response rate. Consequently, and according to the rules stated in the protocol, the study must be considered as having failed achieving its primary objective. Nevertheless, a statistically significant effect is observed on the biological response, assessed with the interferon gene signature, and of the magnitude hypothesized in the protocol, when a non-significant trend favoring IFN-K is observed on the clinical response assessed by the BICLA.

The results on secondary or exploratory efficacy endpoints evaluating the clinical effect show a trend toward improvement over the study in both groups, with, for some endpoints (composite SRI-4 with reduction of CS $\leq$5 mg, composite SRI-4 with reduction of CS $\leq$7.5 mg, severe flares according to SELENA-SLEDAI flare index, SLICC/ACR-DI, 28-swollen joints count, joint pain VAS) a numerically more favorable result in the IFN-K group when compared to the placebo group, but the differences were not statistically significant. Treatment failure is slightly more frequent in the placebo group (43.5% of the patients) than in the IFN-K group (37.9%).

Achievement of LLDAS at week 36 is more frequent by 23.1% in the IFN-K group (52.9% versus 29.8% in the placebo group) and this difference is statistically significant ($p=0.002$). The observed difference in clinical response, in addition to being statistically significant, is higher than the threshold of 15% pre-chosen to define an important effect for the BICLA response.

The mean daily dose of corticosteroids at the end of the main study is significantly smaller (5.4 g/day) in the IFN-K group than in the placebo group (7.1 mg/day, $p=0.01$). More patients in the IFN-K group achieved CS tapering to doses equal or below 7.5 mg/day (84% versus 67% in the placebo arm, $p=0.013$) and to doses equal or below 5 mg/day (75% versus 59%, $p=0.032$).

Immunogenicity analyses showed the development of a strong immunogenic response in the IFN-K group with a consistent pattern for anti IFNα binding antibodies, anti IFNα neutralizing antibodies and anti KLH binding antibodies that all increased in the IFN-K treated patients from absent in nearly all patients at baseline to highly positive in mostly all patients for binding antibodies and in more than 90% for neutralizing antibodies, when they remained negative in nearly all patients in the placebo group.

In patients treated with IFN-K, there was a strong relationship between presence of neutralizing anti IFNα antibodies and response on gene signature ($p=0.0011$) when no significant relationship was found with response to BICLA ($p=0.36$) despite an observed odds-ratio numerically favoring IFN-K. Exploratory analyses also revealed a significant relationship between presence of neutralizing anti-IFNα antibodies and time to first flare (HR 6.4, $p<0.0001$).

SAFETY RESULTS:

Most treated patients received the 5 planned administrations, i.e. 89.0% (81/91) patients in the IFN K group and 86.0% (80/93) patients in the placebo group.

Adverse events: Overall, slightly more patients in the IFN-K group (75/91, 82.4%) than in the placebo group (71/93, 76.3%) reported at least one TEAE, and more TEAEs were reported in the IFN-K group (371 versus 277 in the placebo group). A similar trend was observed for TEAEs related to the study treatment, with 95 events in 37 patients (40.7%) in the IFN-K group versus 54 events in 23 patients (24.7%) in the placebo group. TEAEs of at least severe intensity were reported by similar numbers of patients but were more numerous in the IFN-K group (27 events in 10 (11.0%) patients, versus 11 events in 10 patients (10.8%) in the placebo group). Four patients in each group discontinued the study treatment permanently due to TEAEs.

With regards to serious AEs, a similar number of TESAEs were reported in both groups, but more patients presented at least one TESAE in the placebo group (15 events in 12 patients, 12.9% versus 13 events in 6 subjects (6.6%) in the IFN-K

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group. Seven (7) TESAEs in 2 patients (2.2%) in the IFN-K group were considered as related to the study treatment, versus 2 events in 2 patients (2.2%) in the placebo group. Two deaths, one in each group occurred during the main study.

Solicited local reactions (SLR): A high proportion of patients, similar in both groups (80, 87.9% in the IFN-K group and 80, 86.0% in the placebo group) reported at least one solicited local reaction. The number of SLRs was roughly twice greater in the IFN-K group (1200 versus 570 in the placebo group). Pain was the most frequent SLR (86.8% of the patients in the IFN-K group and 78.5% in the placebo group), followed by pruritus (45.1% and 33.3%), Swelling (33.0% versus 5.4%), erythema (31.9% versus 12.9%) and induration (30.8% versus 6.5%). Severe SLRs were rare (4.9% of all SLRs in the IFN-K group and 4.2% in the placebo group).

Solicited systemic reactions (SSRs): The numbers of SSRs were roughly similar between the two groups: 1092 SSR in 75 patients (82.4%) in the IFN-K group and 967 SSR in 76 patients (81.7%) in the placebo group. Fatigue was the most frequent SSR (69.2% of the patients in the IFN-K group and 65.6% in the placebo group), followed by headache (IFN-K: 63.7%, placebo: 66.7%) and myalgia (IFN-K: 60.4%, placebo: 60.2%), nausea (IFN-K: 36.3%, placebo: 33.3%) and pyrexia (IFN-K: 33.0%, placebo: 24.7%). SSRs of severe intensity were rare (6.0% of all SSRs in the IFN-K group, 4.9% in the placebo group).

Adverse events: Infectious events were slightly most frequent in the IFN-K group (overall: 94 events in 52 patients, 57.1% versus 63 events in 40 patients, 43.0% in the placebo group). Upper respiratory tract infections (IFN-K: 17 events in 17.6% of the patients, placebo: 6 events in 5.4% of the patients), Urinary tract infections (IFN-K: 11 events in 12.1% of the patients, placebo: 10 events in 9.7% of the patients), Nasopharyngitis (IFN-K: 10 events in 7.7% of the patients, placebo: 2 events in 2.2% of the patients, Pharyngitis (IFN-K: 7 events in 6.6% of the patients, placebo: 4 events in 3.2% of the patients) and Bronchitis (IFN-K: 5 events in 5.5% of the patients, placebo: 4 events in 4.3% of the patients) were the most frequent infectious events.

General disorder and administration site conditions were also more frequent in the IFN-K group (51 events in 26.4% of the patients, versus 26 events in 14.0% of the patients in the placebo group). The two most frequent events (fatigue and pyrexia), did not show any imbalance in disfavor of IFN-K, pyrexia being even more frequent in the placebo group. Injection site pain and injection site induration were only reported in the IFN-K group (8 events each in 4.4% and 5.5% of the patients respectively).

Among the other most frequent reported PTs, Systemic lupus erythematosus was fairly balanced between the two groups (14 cases in 11.0% of the patients for IFN-K and 19 cases in 12.9% of the patients in the placebo group), Myalgia occurred in twice more patients in the placebo group (7.5% versus 3.3%), but the total number of events were similar (8 in the IFN-K group and 7 in the placebo group), Arthralgia was more frequent in the IFN-K group (8 events in 7.7% of the patients versus 3 events in 2.2%). Headache was also more frequent in the IFN-K group (19 cases in 11.0% of the patients versus 3 cases in 2.2% in the placebo group). Taken together, AEs corresponding to SLE flares were slightly more frequent in the placebo group, reported in 12 patients (13.2%, 19 events) in the IFN-K group and 20 patients (21.5%, 28 events) in the placebo group.

Most of the TEAEs were considered as unrelated to the study treatment. 58 TEAEs in 25 patients (27.5%) in the IFN K group and 43 TEAEs in 20 patients (21.5%) in the placebo group were possibly related and 37 TEAEs in 20 patients (22.0%) in the IFN K group and 11 TEAEs in 6 patients (6.5%) in the placebo group were probably related to the study product. The most frequently possibly or probably related TEAEs were: injection site pain (8 events in 4 patients in the IFN-K group, none in the placebo group), injection site induration pain (8 events in 5 patients in the IFN-K group, none in the placebo group) and nasopharyngitis (5 events in 3 patients in the IFN-K group, none in the placebo group).

Twenty-five (25) TEAEs in 10 patients (11.0%) in the IFN K group and 9 TEAEs in 8 patients (8.6%) in the placebo group were of severe intensity, and 3 TEAEs, 2 in 2 patients (2.2%) in the placebo group and 2 in 1 patient (1.1%) in the IFN-K group were life threatening.

Serious events: A total of 28 TESAEs was reported: 13 TESAEs in 6 patients (6.6%) in the IFN K group and 15 TESAEs in 12 patients (12.9%) in the placebo group.

There were two deaths, one in each group (pneumonia and disease progression in the IFN-K group and CNS lymphoma in the placebo group). Four TESAEs, two in the placebo group (Lymphoma Intracranial diffusion, with fatal outcome and Papillary Cancer of the Thyroid) and two (in the same patient) in the IFN-K arm (SLE flare and neuropsychiatric SLE) were life threatening. Seven TESAEs in 2 patients in the IFN-K group and four TESAEs in 4 patients in the placebo arm were of severe intensity. Seven (7) TEASAEs in 2 patients in the IFN-K group and 2 TESAEs in 2 patients in the placebo group were considered related to the study treatment. One TESAE in 1 patient in the IFN K and 3 TESAEs in 3 patients in the placebo group led to the permanent discontinuation of study treatment.

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No safety signal was identified from laboratory investigations results, clinical examinations, vital signs measurements and ECGs.

CONCLUSION:

This study has achieved its co-primary biological objective but not the co-primary clinical objective. The study allowed to demonstrate the immune response induced by IFN-K (91.1% of patients developed anti-IFNα antibodies), the biological effect of IFN-K treatment on interferon gene signature ($p<0.0001$) and provided a body of evidence in favor of a clinical effect of treatment with IFN-K. Particularly, achievement of LLDAS at week 36 was significantly ($p=0.002$) more frequent by 23.1% in the IFN-K group (52.9% versus 29.8% in the placebo group) this difference of 23.1% is above the threshold of 15% chosen to define a clinically important difference for BICLA response. This study showed also a significant corticosteroid sparing effect of IFN-K from week 28 onwards and up to week 36 ($p=0.0097$).

Further clinical studies should be conducted to obtain a definitive demonstration of clinical efficacy. The results of the current study speak in favor of the use of LLDAS as one of the endpoints of interest to assess clinical efficacy.

With regards to safety, despite a slightly higher incidence and a larger number of adverse events with IFN-K compared to placebo, no specific safety signal could be identified that precludes continuing the clinical development of IFN-K.

Date of the report: 26 June 2019