EU Clinical Trials Register

Clinical trial results:
A Phase IIb, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Neutralization of the Interferon Gene Signature and the Clinical Efficacy of IFN-Kinoid in Adult Subjects with Systemic Lupus Erythematosus

Summary

EudraCT number	2015-001341-86
Trial protocol	DE BE HR ES BG IT
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	31 October 2019
First version publication date	31 October 2019
Summary attachment (see zip file)	IFN-K-002 CSR synopsis (IFN-K-002_Main study period_CSR Synopsis_2019.06.26.pdf)

Trial information

Trial identification

Sponsor protocol code	IFN-K-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02665364
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Neovacs
Sponsor organisation address	3-5 Impasse Reille, Paris, France, 75014
Public contact	Valérie Salentey, Neovacs S.A., 33 15310 9300, vsalentey@neovacs.com
Scientific contact	Valérie Salentey, Neovacs S.A., 33 15310 9300, vsalentey@neovacs.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	26 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 March 2018
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Objective:
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 modified by mandatory CS tapering.

Protection of trial subjects:

The Phase IIb - IFN-K-002 study was conducted in accordance with the European Union Clinical Trial Directive, and local national laws as applicable, International Conference on Harmonization (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.
An independent data safety monitoring board (iDSMB) consisting of experts in the appropriate disciplines, has been set up to oversee the conduct of the study as well as the safety with specific attention on "Lupus flares" and "Infections". Data review meetings held by iDSMB were planned 6 months after randomization of the first subject and then on a 6-monthly basis unless unscheduled meetings are required to adress particular safety concerns.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 September 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 18
Country: Number of subjects enrolled	Croatia: 2
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Chile: 6
Country: Number of subjects enrolled	Colombia: 18
Country: Number of subjects enrolled	Georgia: 5
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Mexico: 19
Country: Number of subjects enrolled	Moldova, Republic of: 20

Country: Number of subjects enrolled	Peru: 21
Country: Number of subjects enrolled	Philippines: 19
Country: Number of subjects enrolled	Russian Federation: 22
Country: Number of subjects enrolled	Korea, Republic of: 2
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	Thailand: 3
Country: Number of subjects enrolled	Tunisia: 9
Country: Number of subjects enrolled	United States: 6
Worldwide total number of subjects	185
EEA total number of subjects	32

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	185
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 185 subjects positive for IFN gene signature were randomized (1:1) to IFN-K or placebo. One subject was randomized in the IFN-K group and did not receive IFN-K. 184 subjects were treated; 91 subjects received IFN-K; and 93 subjects received Placebo.

Pre-assignment

Screening details:

4-week screening period
A total of 707 subjects were screened, 185 subjects were randomized.

Period 1

Period 1 title	Main study Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The main study was conducted with a double-blind design (subjects and Investigators were blinded).

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received placebo normal saline (0.9% Sodium Chloride) adjuvanted with ISA 51 VG via intramuscular injection. 1 administration of 240 µg at week (W)0, W1, W4 and 1 administration of 120 µg at month 3 (W12) and month 6 (W24) in addition to standard of care treatment.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received placebo normal saline (0.9% Sodium Chloride) adjuvanted with ISA 51 VG via intramuscular injection. 1 administration of 240 µg at W0, W1, W4 and 1 administration of 120 µg at month 3 (W12) and month 6 (W24) in addition to standard of care treatment.

Arm title	IFN-K

Arm description:

Subjects received IFN-K adjuvanted with ISA 51 VG via intramuscular injection. 1 administration of 240 µg at W0, W1, W4 and 1 administration of 120 µg at month 3 (W12) and month 6 (W24) in addition to standard of care treatment.

Arm type	Experimental
Investigational medicinal product name	IFN-alpha Kinoid
Investigational medicinal product code	IFN-K
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received IFN-K adjuvanted with ISA 51 VG via intramuscular injection. 1 administration of 240 µg at W0, W1, W4 and 1 administration of 120 µg at month 3 (W12) and month 6 (W24) in addition to standard of care treatment.

Number of subjects in period 1[1]	Placebo	IFN-K
Started	93	91
Completed	84	85
Not completed	9	6
Adverse event, serious fatal	1	1
Consent withdrawn by subject	8	3
other	-	1
Lost to follow-up	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 185 subjects were randomized. One subject was randomized in IFN-K group and did not receive IFN-K. 184 subjects were treated; 91 subjects received IFN-K and 93 subjects received placebo.

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	

Subjects received placebo normal saline (0.9% Sodium Chloride) adjuvanted with ISA 51 VG via intramuscular injection. 1 administration of 240 µg at week (W)0, W1, W4 and 1 administration of 120 µg at month 3 (W12) and month 6 (W24) in addition to standard of care treatment.

Reporting group title	IFN-K
Reporting group description:	

Subjects received IFN-K adjuvanted with ISA 51 VG via intramuscular injection. 1 administration of 240 µg at W0, W1, W4 and 1 administration of 120 µg at month 3 (W12) and month 6 (W24) in addition to standard of care treatment.

Reporting group values	Placebo	IFN-K	Total
Number of subjects	93	91	184
Age categorical			
The mean (± S.D) age was 39.1 ± 10.7 years			
Units: Subjects			
adultes 18-64 years	93	91	184
Gender categorical			
Most subjects 93.5% were female			
Units: Subjects			
Female	88	84	172
Male	5	7	12

Subject analysis sets

Subject analysis set title	Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received placebo normal saline (0.9% Sodium Chloride) adjuvanted with ISA 51 VG via intramuscular injection. 1 administration of 240 µg at W0, W1, W4 and 1 administration of 120 µg at month 3 (W12) and month 6 (W24) in addition to standard of care treatment.

Subject analysis set title	IFN-K
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received IFN-K adjuvanted with ISA 51 VG via intramuscular injection. 1 administration of 240 µg at W0, W1, W4 and 1 administration of 120 µg at month 3 (W12) and month 6 (W24) in addition to standard of care treatment.

Reporting group values	Placebo	IFN-K	
Number of subjects	93	91	
Age categorical			
The mean (± S.D) age was 39.1 ± 10.7 years			
Units: Subjects			
adultes 18-64 years	93	91	
Gender categorical			
Most subjects 93.5% were female			
Units: Subjects			
Female	88	84	

Male	5	7	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received placebo normal saline (0.9% Sodium Chloride) adjuvanted with ISA 51 VG via intramuscular injection. 1 administration of 240 μg at week (W)0, W1, W4 and 1 administration of 120 μg at month 3 (W12) and month 6 (W24) in addition to standard of care treatment.	
Reporting group title	IFN-K
Reporting group description:	
Subjects received IFN-K adjuvanted with ISA 51 VG via intramuscular injection. 1 administration of 240 μg at W0, W1, W4 and 1 administration of 120 μg at month 3 (W12) and month 6 (W24) in addition to standard of care treatment.	
Subject analysis set title	Placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects received placebo normal saline (0.9% Sodium Chloride) adjuvanted with ISA 51 VG via intramuscular injection. 1 administration of 240 μg at W0, W1, W4 and 1 administration of 120 μg at month 3 (W12) and month 6 (W24) in addition to standard of care treatment.	
Subject analysis set title	IFN-K
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects received IFN-K adjuvanted with ISA 51 VG via intramuscular injection. 1 administration of 240 μg at W0, W1, W4 and 1 administration of 120 μg at month 3 (W12) and month 6 (W24) in addition to standard of care treatment.	

Primary: percent change from baseline in IFN gene signature at W36

End point title	percent change from baseline in IFN gene signature at W36
End point description:	
The biological endpoint aimed at evaluating the neutralization of the IFN gene signature following treatment with IFN-K compared to placebo, as measured by the % change from baseline of the expression of IFN-induced genes.	
End point type	Primary
End point timeframe:	
Baseline and W36	

End point values	Placebo	IFN-K		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	84	87		
Units: percent				
arithmetic mean (standard deviation)	-0.44 (± 27.34)	-31.04 (± 38.96)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
The percent of change from baseline to last available value between W24 and W36 of treatment in the	

expression of IFN-induced genes was analyzed using an analysis of covariance (ANCOVA) model.

Comparison groups	IFN-K v Placebo
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-30.2802
Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.6653
upper limit	-19.8951
Variability estimate	Standard error of the mean
Dispersion value	5.2588

Primary: BICLA Response with superimposed CS Tapering at Week 36

End point title	BICLA Response with superimposed CS Tapering at Week 36

End point description:

BICLA responder was defined as a subject who had the following 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 W36, and
- No BILAG worsening in other body systems: no new BILAG A or ≥ 2 new BILAG B scores at W36, and
- No worsening in SLEDAI-2K total score at W36 compared with baseline, and
- No deterioration in Physician Global Assessment (PGA) (< 10% worsening) on Visual Analog Scale (VAS) 100 mm at W36 compared with baseline, and
- No addition or increased dose level of anti-malarial drugs or immunosuppressive drugs or CS* between W24 and W36 (*≤5 mg prednisolone or equivalent /day at W24 and no increase until W36).

End point type	Primary

End point timeframe:

At Week 36

End point values	Placebo	IFN-K		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	84	85		
Units: number of patients	29	35		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

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.

Comparison groups	Placebo v IFN-K

Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.34
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.716
upper limit	2.657

Secondary: SRI-4 response at Week 36

End point title	SRI-4 response at Week 36

End point description:

SLE Responder Index (SRI); SRI-4 responder was defined as a subject who had the following criteria at week 36:
- reduction ≥4 points in SELENA-SLEDAI at week 36 compared with baseline, and
- no new BILAG A at week 36, and
- no more than 1 new BILAG B at week 36, and
- no deterioration in PGA (<10% worsening) on 100-mm VAS compared with baseline

End point type	Secondary

End point timeframe:

At Week 36

End point values	Placebo	IFN-K		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	83	84		
Units: patient number	54	57		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The SRI-4 response was 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.

Comparison groups	Placebo v IFN-K

Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6243
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.602
upper limit	2.329

Secondary: Composite SRI-4 including CS ≤5mg/day response at Week 36

End point title	Composite SRI-4 including CS ≤5mg/day response at Week 36

End point description:

SRI-4 plus CS ≤ 5mg/day responder was defined as a participant who had the following criteria at week 36:
- reduction ≥4 points in SELENA-SLEDAI at week 36 compared with baseline, and
- no new BILAG A at week 36, and
- no more than 1 new BILAG B at week 36, and
- no deterioration in PGA (<10% worsening) on 100-mm VAS compared with baseline
plus corticosteroids (CS) ≤5mg equivalent prednisolone per day at week 36

End point type	Secondary

End point timeframe:

At Week 36

End point values	Placebo	IFN-K		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	77	79		
Units: number of patients	30	43		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v IFN-K
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0762
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.83

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.938
upper limit	3.574

Secondary: SLEDAI response at Week 36

End point title	SLEDAI response at Week 36

End point description:

SLE Disease Activity Index (SLEDAI)-2K is an activity index that measures disease activity and records feature of active Lupus as present or not present. There are 24 items in a total of 9 organs/systems; total scores range from 0 (non-active disease) – 105 points. Scores were attributed taking into account disease activity over the previous 10 days.
 SLEDAI-2K responder was defined as a participant who had reduction of the SLEDAI-2K score of at least 4 points at week 36 compared to baseline.

End point type	Secondary

End point timeframe:

At Week 36

End point values	Placebo	IFN-K		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	84	85		
Units: number of patients	55	61		

Statistical analyses

No statistical analyses for this end point

Secondary: BILAG global score change from baseline at Week 36

End point title	BILAG global score change from baseline at Week 36

End point description:

British Isles Lupus Assessment Group (BILAG)-2004 index, it categorizes disease activity into 5 different levels from A to E, with Grade A representing very active disease and Grade E indicating no current or previous disease activity. Scoring was based on a total of 101 items, grouped into 9 organ/systems. The BILAG global score change from baseline to Last Available Value (LVA) week 24 and week 36 were presented analyzed.

End point type	Secondary

End point timeframe:

At Week 36

End point values	Placebo	IFN-K		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	84	87		
Units: BILAG score				
arithmetic mean (standard deviation)	-10.76 (± 7.84)	-11.43 (± 8.57)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Baseline to last available value between W24 and W36	
Comparison groups	Placebo v IFN-K
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7946
Method	Wilcoxon (Mann-Whitney)

Secondary: SELENA-SLEDAI - change from baseline to Week 36

End point title	SELENA-SLEDAI - change from baseline to Week 36

End point description:

Safety of Estrogens in Systemic Lupus Erythematosus National Assessment (SELENA)-SLEDAI, is a slightly modified version of the SLEDAI. This is a weighted index in which signs and symptoms, laboratory tests, and Physician's Global Assessment (PGA) for each of nine organ systems are given a weighted score and summed up if present at the time of the visit or in the preceding 10 days. The maximum theoretical score for the SELENA SLEDAI is 105 (all 24 descriptors present simultaneously) with 0 indicating inactive disease.

End point type	Secondary

End point timeframe:

Baseline and Week 36

End point values	Placebo	IFN-K		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	83	84		
Units: SELENA SLEDAI Score				
arithmetic mean (standard deviation)	-5.54 (± 4.44)	-5.48 (± 4.30)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v IFN-K

Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9224
Method	student - pooled

Secondary: SLICC/ACR-DI change from baseline at Week 36

End point title	SLICC/ACR-DI change from baseline at Week 36

End point description:

Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for systemic lupus erythematosus (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.

End point type	Secondary

End point timeframe:

Baseline and Week 36

End point values	Placebo	IFN-K		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	83	82		
Units: SLICC/ACR-DI Score				
arithmetic mean (standard deviation)	-0.17 (± 0.49)	-0.09 (± 0.59)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

SLICC/ACR-DI was analyzed using Student-pooled

Comparison groups	Placebo v IFN-K
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3258
Method	student - pooled

Secondary: CLASI total activity change from baseline at Week 36

End point title	CLASI total activity change from baseline at Week 36

End point description:

Cutaneous Lupus Erythematosus Disease Area and Severity Index (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.

End point type	Secondary

End point timeframe:

Baseline and Week 36

End point values	Placebo	IFN-K		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	84	85		
Units: CLASI Total activity				
arithmetic mean (standard deviation)	-2.85 (± 3.60)	-3.22 (± 5.94)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v IFN-K
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6169
Method	Student - Satterthwaite

Secondary: LLDAS at Week 36

End point title	LLDAS at Week 36

End point description:

Lupus low disease activity state (LLDAS) was conceptually defined as 'a state which, if sustained, is associated with a low likelihood of adverse outcome, considering disease activity and medication safety'. Subsequently defined using consensus methodology, LLDAS is attained if all the following items are met:
- SLEDAI-2K ≤4, with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever) and no hemolytic anemia or gastrointestinal activity
- No new features of lupus disease activity compared with the previous assessment
- SELENA-SLEDAI physician global assessment (PGA, scale 0–3) ≤1
- Current prednisolone (or equivalent) dose ≤7.5 mg daily
- Well tolerated standard maintenance doses of immunosuppressive drugs and approved biological agents, excluding investigational drugs

End point type	Secondary

End point timeframe:

At Week 36

End point values	Placebo	IFN-K		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	84	85		
Units: patient number	25	45		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	IFN-K v Placebo
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0022
Method	Pearson's Chi-squared

Secondary: Neutralizing Anti-IFN-alpha antibodies response at W36

End point title	Neutralizing Anti-IFN-alpha antibodies response at W36

End point description:

Individual serum antibody neutralizing capacity against recombinant IFN-alpha2b was measured by reporter gene assay using Interferon Sensitive Response Element (ISRE) reporter.

End point type	Secondary

End point timeframe:

At week 36

End point values	Placebo	IFN-K		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[1]	79		
Units: number of patients		72		

Notes:

[1] - No Neutralizing Anti-IFN-alpha antibodies were performed on placebo subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Composite SRI-4 including CS ≤7,5mg/day response at Week 36

End point title	Composite SRI-4 including CS ≤7,5mg/day response at Week 36

End point description:

SRI (4) plus CS ≤ 7.5 mg/day responder was defined as a participant who had the following criteria at week 36:
- reduction ≥4 points in SELENA-SLEDAI at week 36 compared with baseline, and
- no new BILAG A at week 36, and

- no more than 1 new BILAG B at week 36, and
- no deterioration in PGA (<10% worsening) on 100-mm VAS compared with baseline
plus CS ≤7.5mg equivalent prednisolone per day at week 36

End point type	Secondary

End point timeframe:

At Week 36

End point values	Placebo	IFN-K		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	77	79		
Units: number of patients	33	46		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v IFN-K
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0796
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.932
upper limit	3.524

Other pre-specified: CS mean daily dose at W36

End point title	CS mean daily dose at W36

End point description:

mean daily dose of corticosteroid (CS) (prednisone equivalent)

End point type	Other pre-specified

End point timeframe:

W36

End point values	Placebo	IFN-K		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	84	85		
Units: mg/day				
arithmetic mean (standard deviation)	7.06 (± 4.69)	5.42 (± 3.28)		

Attachments (see zip file)	Figure - Corticosteroids-IFN-K-002/IFN-K-002 STUDY - CS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v IFN-K
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0097
Method	Student - Satterthwaite

Post-hoc: Composite SRI-4 (CS ≤5mg/day) response excluding IFN-K subjects without positive anti-IFNalpha neutralizing antibodies at Week 36

End point title	Composite SRI-4 (CS ≤5mg/day) response excluding IFN-K subjects without positive anti-IFNalpha neutralizing antibodies at Week 36

End point description:

Subjects who had the following criteria defined as : SRI-4 plus CS ≤5mg/day -excluding IFN-K subjects without positive anti-IFN-alpha neutralizing antibodies

End point type	Post-hoc

End point timeframe:

At week 36

End point values	Placebo	IFN-K		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	77	72		
Units: number of patients	30	40		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v IFN-K

Number of subjects included in analysis	149
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0425
Method	Pearson's Chi-squared

Post-hoc: Composite SRI-4 (CS ≤7.5mg/day) response excluding IFN-K subjects without positive anti-IFNalpha neutralizing antibodies at Week 36

End point title	Composite SRI-4 (CS ≤7.5mg/day) response excluding IFN-K subjects without positive anti-IFNalpha neutralizing antibodies at Week 36

End point description:

participant who had the following criteria defined as : SRI-4 plus CS ≤7.5mg/day -excluding IFN-K Patients without positive anti-IFN-alpha neutralizing antibodies

End point type	Post-hoc

End point timeframe:

At week 36

End point values	Placebo	IFN-K		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	77	72		
Units: number of patients	33	43		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v IFN-K
Number of subjects included in analysis	149
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0396
Method	Pearson's Chi-squared

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) non serious and serious (SAEs) were collected from the start of study medication to Week 36.

Adverse event reporting additional description:

Due to IFN-K mechanism of action, i.e. immunization, and the administration route, i.e. intramuscular (IM), some AEs, local and/or systemic AEs, were expected and solicited within 7 days after study Investigational Medicinal Product (IMP) administration.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received placebo normal saline (0.9% Sodium Chloride) adjuvanted with ISA 51 VG via intramuscular injection. 1 administration of 240 µg at W0, W1, W4 and 1 administration of 120 µg at month 3 (W12) and month 6 (W24) in addition to standard of care treatment.

Reporting group title	IFN-K

Reporting group description:

Subjects received IFN-K adjuvanted with ISA 51 VG via intramuscular injection. 1 administration of 240 µg at W0, W1, W4 and 1 administration of 120 µg at month 3 (W12) and month 6 (W24) in addition to standard of care treatment.

Serious adverse events	Placebo	IFN-K	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 93 (12.90%)	6 / 91 (6.59%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Papillary thyroid cancer			
subjects affected / exposed	2 / 93 (2.15%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system lymphoma			
subjects affected / exposed	1 / 93 (1.08%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Rectal cancer stage II			

subjects affected / exposed	1 / 93 (1.08%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Haemolytic anaemia			
subjects affected / exposed	0 / 93 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 93 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	0 / 93 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Systemic lupus erythematosus			
subjects affected / exposed	3 / 93 (3.23%)	2 / 91 (2.20%)	
occurrences causally related to treatment / all	1 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lupus nephritis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropsychiatric lupus			
subjects affected / exposed	0 / 93 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	1 / 93 (1.08%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Postmenopausal haemorrhage			
subjects affected / exposed	1 / 93 (1.08%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 93 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 93 (1.08%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	1 / 93 (1.08%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 93 (1.08%)	2 / 91 (2.20%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Kaposi's varicelliform eruption			

subjects affected / exposed	0 / 93 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 93 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 93 (1.08%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	IFN-K	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	74 / 93 (79.57%)	78 / 91 (85.71%)	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 93 (2.15%)	10 / 91 (10.99%)	
occurrences (all)	3	19	
General disorders and administration site conditions			
Injection site induration			
subjects affected / exposed	0 / 93 (0.00%)	5 / 91 (5.49%)	
occurrences (all)	0	8	
Pyrexia			
subjects affected / exposed	5 / 93 (5.38%)	2 / 91 (2.20%)	
occurrences (all)	7	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 93 (5.38%)	0 / 91 (0.00%)	
occurrences (all)	6	0	
Immune system disorders			
Systemic lupus erythematosus			

subjects affected / exposed	12 / 93 (12.90%)	10 / 91 (10.99%)
occurrences (all)	19	14

Musculoskeletal and connective tissue disorders		
Arthralgia		
subjects affected / exposed	2 / 93 (2.15%)	7 / 91 (7.69%)
occurrences (all)	3	8
Pain in extremity		
subjects affected / exposed	1 / 93 (1.08%)	6 / 91 (6.59%)
occurrences (all)	1	6
Myalgia		
subjects affected / exposed	7 / 93 (7.53%)	3 / 91 (3.30%)
occurrences (all)	7	8

Infections and infestations		
Upper respiratory tract infection		
subjects affected / exposed	5 / 93 (5.38%)	16 / 91 (17.58%)
occurrences (all)	6	17
Urinary tract infection		
subjects affected / exposed	9 / 93 (9.68%)	11 / 91 (12.09%)
occurrences (all)	10	11
Nasopharyngitis		
subjects affected / exposed	2 / 93 (2.15%)	7 / 91 (7.69%)
occurrences (all)	2	10
Pharyngitis		
subjects affected / exposed	3 / 93 (3.23%)	6 / 91 (6.59%)
occurrences (all)	4	7
Bronchitis		
subjects affected / exposed	4 / 93 (4.30%)	5 / 91 (5.49%)
occurrences (all)	4	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 August 2015	Amendment #1 (dated 11 August 2015): it amended the protocol Version 2.0 into protocol Version 3.0 as per request of the European Health Authorities. This amendment introduced and update of the promary objective to: - 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.
08 December 2015	Amendment #2 (dated 08 December 2015), amending the protocol Version 3.0 into protocol Version 4.0, introduced the following modifications: - Addition of the extended follow-up within the IFN-K-002 protocol rather than in a separate protocol: the protocol Version 4.0 therefore integrated an extended follow up period up to a total duration of 5 years (60 months, i.e. 240 weeks) after the last visit of the main study (Visit 12 at week 36). The visit at week 276 (Month 69), i.e. FU10, was then considered as the last planned visit. - complete extended follow-up only for some subjects receiving the active treatment: due to the double-blind study design, all subjects who had completed the main study (up to Visit 12 at week 36) would enter into the extended follow-up period. When the results would be available, only subjects having received IFN-K and having produced anti-IFN-alpha antibodies (neutralizing) would continue the extended follow up. Subjects would remain into the extended follow-up period until they become negative for anti-IFN-alpha neutralizing antibodies or for up to 5 years (60 months, i.e. 240 weeks) after Visit 12, whichever comes first. - frequency of visits during the extended follow-up: subjects would be followed every 6 months, as in the IFN-K-001 study. - regular analyses: for safety purpose, a descriptive analysis would be performed at regular intervals, according to DSUR timelines.
28 January 2016	Amendment #3 (dated 28 January 2016), amending the protocol Version 4.0 into protocol Version 5.0, introduced the following modifications: - Expansion of geographic areas for the study conduct: worldwide epidemiology studies reported large variations in incidence and prevalence of SLE, reflecting influences of race, ethnicity and socio-economic status; in addition, several studies have demonstrated an overexpression of IFN-alpha inducible genes in SLE subjects and a possible correlation between their expression and the disease activity notably the serological markers. The study being originally planned to be conducted in 3 geographic areas (Europe, Asia-Pacific and Latin-America), the protocol was amended to expand the study to the 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 was taken into account in the randomization (minimization factor) and the sample size calculation was revised to ensure statistical power on the primary endpoints.

11 April 2016	Amendment #4 (dated 11 April 2016), amending the protocol Version 5.0 into protocol Version 6.0, introduced the following modifications: - Complete extended follow-up only for all subjects receiving the active treatment: as requested by Food and Drug Administration (FDA), all subjects having received IFN-K would be followed up for up to 60 months, irrespective of the production of anti-IFN-alpha antibodies at Visit 12 (Week 36) and during the whole extended follow up period. - Modification of inclusion criterion #8: as requested by FDA, the time on treatment and time on stable dose has been increased to 12 weeks prior to study product injection for subjects taking Methotrexate (MTX), Azathioprine (AZA) and Mycophenolate Mofetil (MMF). - Modification of exclusion criterion #11 for US subjects only: as requested by FDA, only subjects with negative screening tests for malignancy according to the American Cancer Society (ACS) guidelines within 12 months before screening Visit could be enrolled; in addition, for subjects with history of treated cancers, only treated basal cell carcinoma was not preventing enrollment. - Modification of an event leading to study product dicontinuation: as requested by FDA, "the occurrence of bronchospasm after administration of study product must be considered as a criterion for study product discontinuation" was revised as "bronchospasm or anaphylactic reaction following the administration of the study product". - Modification is AE reporting: 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.
15 May 2017	Local amendment (amendment #5) for Argentina (dated 15 May 2017), amending the protocol Version 5.0 into protocol Version 6.1: per request of the Argentinian Health Authority, the following modifications have been made: - Modification of exclusion criterion #11 for: "history of malignant cancer, except the following treated cancers: basal cell carcinoma or dermatological squamous cell carcinoma". - Modification of exclusion criterion #23 for: "cytological abnormalities ≥LSIL (low grade squamous intraepithelial lesions) on a cervical swab at Screening or within 3 months prior to the first planned study product administration". - Addition of clarification to inclusion criterion #9. - Addition of clarification to exclusion criterion #1.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported