CLINICAL SCIENCE

IFN-α kinoid in systemic lupus erythematosus: results from a phase IIb, randomised, placebo-controlled study

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ABSTRACT

Objective To evaluate the efficacy and safety of the immunotherapeutic vaccine interferon-α kinoid (IFN-K) in a 36-week (W) phase IIb, randomised, double-blind, placebo (PBO)-controlled trial in adults with active systemic lupus erythematosus (SLE) despite standard of care.

Methods Patients with SLE (185) with moderate to severe disease activity and positive interferon (IFN) gene signature were randomised to receive IFN-K or PBO intramuscular injections (days 0, 7 and 28 and W12 and W24). Coprimary endpoints at W36 were neutralisation of IFN gene signature and the BILAG-Based Composite Lupus Assessment (BICLA) modified by mandatory corticosteroid (CS) tapering.

Results IFN-K induced neutralising anti-IFN-α2b serum antibodies in 91% of treated patients and reduced the IFN gene signature ($p<0.0001$). Modified BICLA responses at W36 did not statistically differ between IFN-K (41%) and PBO (34%). Trends on Systemic Lupus Erythematosus Responder Index-4, including steroid tapering at W36, favoured the IFN-K and became significant ($p<0.05$) in analyses restricted to patients who developed neutralising anti-IFN-α2b antibodies. Attainment of lupus low disease activity state (LLDAS) at W36 discriminated the two groups in favour of IFN-K (53% vs 30%, $p=0.0022$). A significant CS sparing effect of IFN-K was observed from W28 onwards, with a 24% prednisone daily dose reduction at W36 in IFN-K compared with PBO ($p=0.0097$). The safety profile of IFN-K was acceptable.

Conclusions IFN-K induced neutralising anti-IFN-α2b antibodies and significantly reduced the IFN gene signature with an acceptable safety profile. Although the clinical coprimary endpoint was not met, relevant secondary endpoints were achieved in the IFN-K group, including attainment of LLDAS and steroid tapering.

Trial registration number NCT02665364.

Key messages

What is already known about this subject?

- Type I interferons (IFNs) play a pathogenic role in systemic lupus erythematosus (SLE).
- Interferon-α kinoid (IFN-K), an immunotherapeutic agent, elicits the production of anti-IFN-α antibodies.

What does this study add?

- IFN-K induced a strong polyclonal immunogenic response directed against IFN-α in nearly all patients and significantly reduced the IFN gene signature in the IFN-K group compared with placebo (PBO).
- The safety profile was acceptable.

How might this impact on clinical practice orfuture developments?

- In a 36-week phase IIb trial performed in patients suffering from active SLE, treatment with IFN-K did not increase the percentage of BILAG-Based Composite Lupus Assessment responders (clinical coprimary endpoint) but allowed more steroid reduction. Lupus low disease activity state was achieved in more patients on IFN-K compared with PBO.

INTRODUCTION

The pivotal role of type I interferons (IFNs) in pathogenesis of systemic lupus erythematosus (SLE) has been the focus of extensive research spanning two decades.[1–3] Despite promising preclinical evidence, results of clinical trials of several type I IFN blockers in SLE have been mixed.[4–7] Rontalizumab, a monoclonal antibody against IFN-α, did not meet its primary endpoint (Systemic Lupus Erythematosus Responder Index-4 (SRI-4)) in a phase II trial, although exploratory analyses indicated clinical benefit and steroid-sparing effects in the subset of patients with a lower IFN gene signature at baseline, reflecting IFN-regulated gene expression.[5] Sifalimumab, a fully human monoclonal antibody against most IFN-α subtypes, achieved its primary endpoint (SRI-4) in a phase IIb study, but differences were only modest.[6] Anifrolumab, a monoclonal antibody against the type I IFN receptor that inhibits signalling of all type I IFNs, was superior to placebo (PBO) across multiple endpoints in a phase IIb trial.[7] One of the two phase III trials (TULIP-1), using SRI-4 as primary outcome measure, did not confirm these results,[8] while the other (TULIP-2)[9] achieved an alternative primary endpoint, the BILAG-Based Composite Lupus Assessment (BICLA). Baricitinib

inhibits Janus kinase 1/2 affecting multiple cytokines but also downstream signalling through type I IFNs, and was found to be superior to PBO for SLE arthritis and rash in a recent phase II trial.[10]

The interferon-α kinoid (IFN-K) is an immunotherapeutic vaccine composed of inactivated recombinant human IFN-α2b coupled to a T-helper carrier protein (keyhole limpet haemocyanin), aimed at inducing antibodies against IFN-α by active immunisation. When injected intramuscularly in human IFN-α transgenic mice, IFN-K yielded a strong polyclonal response, targeting multiple epitopes, enabling to recognise not only IFN-α2b but also the 12 other human IFN-α subtypes.[11] Accordingly, IFN-K was shown to slow disease progression in a mouse model of SLE.[12] In a phase I/IIa dose-escalation PBO-controlled study in patients with active SLE, IFN-K was well tolerated, induced high titres of neutralising anti-IFN-α antibodies, especially in patients with a type I IFN signature, and significantly reduced expression of IFN-induced genes.[13] Follow-up analyses on a subgroup of IFN-K-treated patients confirmed the link between persistence of anti-IFN-α antibodies and down-regulation of the IFN signature and revealed an inhibitory effect of IFN blockade on B cell-associated transcripts.[14]

Here, we present and discuss the results of a 36-week (W) phase IIb, randomised, double-blind, PBO-controlled, multicenter study, designed to assess efficacy and safety of IFN-K in patients with active SLE despite standard of care.

PATIENTS AND METHODS

Study design

This study was a W36 randomised, double-blind, PBO-controlled (1:1), multinational (22 countries), phase IIb trial evaluating the neutralisation of the IFN gene signature and the clinical efficacy of IFN-K in adults with SLE. The protocol was approved by an independent institutional review board at each participating site, and all patients signed informed consent before any study-related procedures. An independent data safety monitoring board, consisting of experts in the appropriate disciplines, oversaw patient's safety every 6 months and ad hoc in case of emerging safety concerns. An adjudication committee of independent experts confirmed the accuracy and consistency of the British Isles Lupus Assessment Group (BILAG)−2004 Index.[15]

Inclusion/exclusion criteria

All of the following inclusion criteria were required: age 18–65 years; SLE of ≥4/11 by 1997 American College of Rheumatology criteria,[16] Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K)≥6[17]; ≥1 BILAG A and/or ≥2 BILAG B scores; positive IFN gene signature antinuclear antibody titre of ≥1:160 and/or positivity of antidouble-stranded deoxyribonucleic acid (dsDNA) antibodies; treatment with at least one of the following: corticosteroids (CSs) at ≤20 mg of prednisone equivalent/day, hydroxychloroquine (HCQ) or chloroquine on stable dose for at least 4W prior to the first planned study drug administration, mycophenolate mofetil (MMF)/mycophenolic acid (≤2 g/day), methotrexate (≤20 mg/week) and azathioprine (≤2.5 mg/kg/day), all on stable dose for at least 12W prior to the first study drug administration. The following exclusion criteria were applied: active severe lupus nephritis (renal BILAG A or immediate need for cyclophosphamide), active severe neuropsychiatric lupus, treatment with >20 mg of prednisone equivalent/day for >7 consecutive days within 4 months prior to the first study drug administration, pulse CS (≥250 mg prednisone/day) within 3 months prior to the first study drug administration, treatment with cyclophosphamide, cyclosporine A, tacrolimus, abatacept, sifalimumab, rontalizumab, anifrolumab, belimumab, tumour necrosis factor antagonists, anti-B cell therapy or any other registered investigational biological therapy or live vaccine, and use of investigational non-registered product or investigational non-registered vaccine within 3–12 months (according to drug) prior to the first study drug administration. Additional exclusion criteria included ≥6 occurrences of oral/genital herpes simplex virus (HSV) infections or any episode of shingles within 12 months prior to the first study drug administration, absence of IgG anti-HSV 1/2, antivaricella zoster virus (VZV), anticytomegalovirus (CMV) and anti-Epstein-Barr virus (EBV) serum antibodies at screening, presence of anti-HTLV1/2, anti-HIV, antihepatitis C virus (HCV) serum antibodies or hepatitis B surface antigen at screening, anticipated high risk of significant infection by physician's opinion, current signs or symptoms of infection, treatment with intravenous antibiotics within 2 months prior to the first planned study drug administration, high-risk human papilloma virus (HPV) positivity on a cervical swab by real-ime quantitative polymerase chain reaction (RT-qPCR) and cytological abnormalities of ≥high-grade superficial intraepithelial lesion. Fibromyalgia was not an exclusion criterion but was reported at study entry in only five patients (three and two patients in the IFN-K and PBO groups, respectively).

Treatment

After a 4W screening period, patients with SLE were randomised to the IFN-K or PBO group using a minimisation algorithm by age, ethnicity, presence of renal involvement and treatment with CS and/or HCQ and/or MMF. They received five intramuscular injections of IFN-K or an equivalent volume of 0.9% NaCl, both emulsified with an oil-based adjuvant (Montanide, ISA 51VG, Seppic, France): 240 µg at days (D) 0, 7 and 28 and 120 µg at W12 and W24. CS administration was strictly controlled, with a maximum dose of 20 mg equivalent prednisone/day at D0, a recommended taper to 10 mg/day by W12 and a mandatory target of ≤5 mg/day by W24 without further increase until W36. Patients not fulfilling the CS tapering rule between W24 and W36 remained in the study but were considered treatment failures.

Efficacy and safety evaluations

Coprimary efficacy measures at W36 compared with baseline were (1) neutralisation of IFN gene signature, measured by change in the expression of IFN-induced genes, and (2) clinical response measured by the BICLA[18] with superimposed CS tapering (≤5 mg prednisone equivalent/day at W24 with no increase until W36, modified BICLA). Secondary efficacy measures at W36 were SRI-4,[19] SRI-4 with CS tapering (≤5 or ≤7.5 mg/day), SLEDAI-2K, Safety of Oestrogen in Lupus Erythematosus National Assessment (SELENA)–Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) flare index, BILAG-2004 Index, Systemic Lupus International Collaborating Clinics/ACR Damage Index for SLE,[20] Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)[21] in patients with cutaneous lesions at baseline, lupus low disease activity state (LLDAS)[22] and health-related quality of life assessed by SF36.[23] Safety was evaluated by the incidence, nature, severity and drug relatedness of adverse events (AEs).

IFN gene signature

At screening, from blood samples, IFN gene signature was tested using RT-qPCR, on a selection of 10 IFN-inducible genes

(*IFIT3*, *MX1*, *ISG15*, *IFIT1*, *IFI6*, *OAS2*, *HERC5*, *LY6E*, *IFI27* and *SIGLEC1*) known to strongly correlate with the IFN signature based on the 21-probe set described by Yao *et al*.[24] Positive signature was defined by a fold change of ≥3 compared with healthy donor blood samples. At randomisation (D0) and W12, W24 and W36, the IFN gene signature, including the 21 IFN-regulated genes, was evaluated by Affymetrix.[24] RNA was extracted, quality assessed, labelled, hybridised to GeneChip human genome U133 Plus 2.0 arrays, washed, stained and scanned using GeneChip Scanner 3000 7G. Affymetrix CEL files were uploaded to Affymetrix Expression Console software V.1.4.1. Analysis and Robust multichip Analysis normalisation of raw data were performed per batch, and raw dataset was normalised at once. Data are accessible on request.

Serum anti-IFN-α antibodies and anti-IFN-α neutralising capacity

Serum anti-IFN-α2b antibody titres were measured by ELISA as described elsewhere,[11–14] every 4W from D0 onwards. Serum antibody neutralising capacity against recombinant IFN-α2b and 12 other IFN-α subtypes was measured by reporter gene assay using interferon-sensitive response element reporter, HEK293 cells containing the firefly luciferase gene. Neutralising capacity corresponds to the first dilution factor of sera resulting in 50% neutralisation of IFN-induced luminescence (30 U/mL). Results were expressed as the highest dilution of the serum in which antibodies could be detected. The lowest dilution tested (and the limit for positivity) was 1/400 and 1/200 for binding and neutralising antibodies, respectively.

Statistical analyses

Efficacy and safety analyses were performed on patients who received at least one dose of the study drug. The study was considered positive if there was superiority of IFN-K in neutralising the IFN gene signature and a ≥10% difference favouring the IFN-K on the modified BICLA response. A sample size of 160 evaluable patients (80 patients per group) would provide a 85% power at detecting a 32.6% difference of IFN-K over PBO in IFN-induced gene expression, using a two-group t-test at a 0.05 two-sided significance level, assuming a common SD of 68%. Assuming a 40.6% BICLA response on IFN-K and a 20.6% response on PBO, that sample size would also provide a 73% power at detecting a 20% BICLA response difference between groups. The biological coprimary endpoint was analysed using a covariance model, with percentage change from baseline in the expression of IFN-induced genes as dependent variable and treatment assignment as independent variable. Minimisation factors used for randomisation were included as covariates. Modified BICLA and SRI-4 were analysed by logistic regression, with response as dependent variable and treatment assignment as independent variable, adjusting for minimisation factors. SLEDAI response (≥4-point reduction in SLEDAI-2K) at W36 versus baseline was compared between groups by frequency table methods. LLDAS at W36 in each group was assessed by Pearson χ^2 test. Anti-IFN-α antibody titres and their neutralising capacity over time were analysed using frequency table methods. Statistical analyses were performed by SAS® software V.9.4.

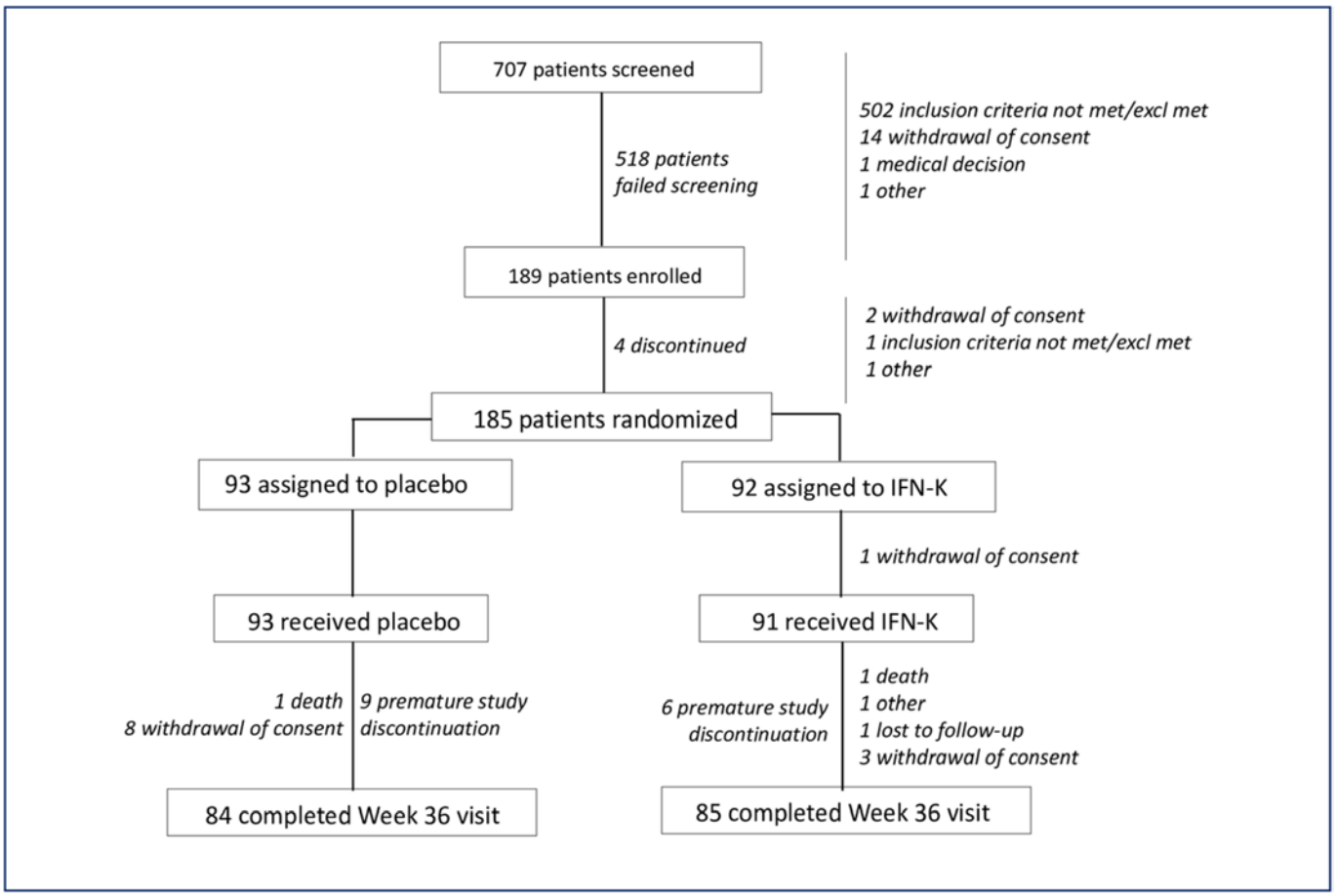

Figure 1 Patients' disposition. Screen failures are detailed in online supplementary material 1. IFN, interferon.

Table 1 Demographics and baseline characteristics

	IFN-K (n=91)	PBO (n=93)
Age (years)	39.53±10.30	38.75±11.16
Gender		
Male, n (%)	7 (7.7)	5 (5.4)
Female, n (%)	84 (92.3)	88 (94.6)
Ethnicity		
Black, n (%)	1 (1.1)	1 (1.1)
Asian, n (%)	16 (17.6)	10 (10.8)
Caucasian/Hispanic, n (%)	64 (70.3)	66 (71.0)
Other, n (%)	10 (11.0)	16 (17.2)
Time since diagnosis (years)	6.7±6.4	7.1±6.6
IFN gene signature (score) at baseline	4.5±1.0	4.5±1.3
SLEDAI-2K Global Score	10.3±3.7	11.3±4.0
BILAG-2004 Index		
BILAG-2004 Index Global Score	18.2±8.2	18.5±5.9
Mucocutaneous BILAG A, n (%)	14 (15.4)	12 (12.9)
Mucocutaneous BILAG B, n (%)	67 (73.6)	66 (71.0)
Musculoskeletal BILAG A, n (%)	17 (18.7)	20 (21.5)
Musculoskeletal BILAG B, n (%)	56 (61.5)	59 (63.4)
Physician's global assessment (mm)	56.3±17.7	53.1±18.1
CLASI Total Activity Score	5.4±6.3	5.3±4.6
Joint pain VAS (mm)	44.8±23.3	46.5±21.9
28-Tender joints count, n	7.3±6.4	7.9±6.5
28-Swollen joints count, n	4.8±4.7	4.6±3.6
FACIT Fatigue Score	32.7±10.0	32.5±10.8
Complement C3 (mg/L)	872±271	909±297
Complement C4 (mg/L)	135±70	151±90
Anti-dsDNA (Phadia, U/mL)	456±2367	101±264
Concomitant medications at scrrening		
Corticosteroids, n (%)	82 (90.1)	84 (90.3)
Mean daily prednisone dose (mg)	8.9	9.3
Hydroxychloroquine, n (%)	60 (65.9)	69 (74.2)
Mycophenolate mofetil, n (%)	9 (9.9)	7 (7.5)
Methotrexate, n (%)	11 (12.1)	14 (15.1)
Azathioprine, n (%)	15 (16.5)	16 (17.2)

Unless stated otherwise, data are means ± SD. No statistical differences were observed between the two treatment groups.
BILAG, British Isles Lupus Assessment Group; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; FACIT, Functional Assessment of Chronic Illness Therapy; IFN, interferon; IFN-K, interferon-α kinoid; PBO, placebo; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index-2000; VAS, Visual Analogue Scale.

RESULTS

Study population

As depicted in figure 1, 185 patients with active SLE with a positive IFN gene signature were randomised, with 93 assigned to PBO and 92 to IFN-K. Reasons for screen failures are detailed in online supplementary material 1. As expected, one-third of patients were excluded because of the absence of IFN signature. Absence of serum IgG antibodies against HSV, VZV, CMV or EBV and/or detection by RT-qPCR of high-risk HPV on a cervical swab also contributed to the high rate of screen failure. Patient demographic and baseline clinical characteristics are described in table 1. The mean age was 39 years. Majority of the patients were female (94%) and Caucasian (71%). Most individuals suffered from mucocutaneous and musculoskeletal disease (BILAG A or B) despite standard of care, including CS, HCQ and/or other immunosuppressants in 90%, 70% and 39% of them, respectively.

Immunogenicity

In the IFN-K group, 98% of the patients developed anti-IFN-α2b-binding antibodies with a titre ≥1/400 at W36. Among them, 50% patients had a serum titre above 1/25 600, 28% above 1/51 200 and 10% above 1/102 400. Neutralising anti-IFN-α2b antibodies were detected in 71% of patients (serum titre ≥1/200) as early as W12, and these were detected in 91% of IFN-K-treated patients at W36 (figure 2A), with 50% displaying a titre above 1/12 800, 30% above 1/25 600, 14% above 1/51 200 and 5% above 1/102 400. The IFN-K also induced polyclonal antibodies able to neutralise other IFN-α subtypes in 30%–97% of treated patients (figure 2B). Taken together, more than half of the patients treated with IFN-K raised a neutralising response against 9–12 IFN-α subtypes. No cross neutralisation against IFN-β was observed, and only some weak cross reactivity was detected against IFN-ω in five patients at W36, with one patient titre at 1/100, two patients at 1/200 and two patients at 1/800.

Efficacy

Treatment with IFN-K induced a statistically significant 31% mean reduction from baseline in the expression of type I IFN gene score at W36 (figure 3A), which was not observed in PBO-treated patients (p<0.0001). Of note, 20/87 patients did experience an increase of IFN gene signature (mean +23%), which is likely related to a lower immune response against IFN-α. Patients with anti-IFN-α2b neutralising antibody titres between 1/100 and 1/1600 had indeed a lower decrease in their signature (mean −8.23%) compared with patients with titres of >1/1600 (mean −42.4%). While the biological coprimary endpoint was met, the modified BICLA response difference in favour of IFN-K over PBO was only of 6.7% (figure 3B).

SRI-4 response at W36 also did not differ between treatment groups. Nevertheless, when CS restrictions were added, a trend favouring the IFN-K was observed (figure 4A). Combined with a requirement for CS tapering to ≤5 or ≤7.5 mg of prednisone equivalent/day (by W24, with no increase to W36), SRI-4 at W36 yielded a 15.4% (p=0.076) and a 15.3% (p=*0.079*) difference of IFN-K over PBO, respectively. This became significant in exploratory analyses restricted to patients with neutralising anti-IFN-α2b antibodies, with a 16.6% (p=0.042) and 16.8% difference (p=0.0396) respectively (figure 4A). At W36, 52.9% of patients assigned to IFN-K achieved LLDAS, which was reached in only 29.8% of PBO-treated patients. This 23% difference was highly significant (p=0.0022). Consistent with differences in composite endpoints when a CS target was included, the mean daily prednisone dose was significantly lower in IFN-K-treated patients from W28 onwards, with a 24% dose reduction from baseline at W36 (*p*=0.009) (figure 4B).

Evolution over time of SLEDAI-2K, BILAG-2004 Global Index, BILAG-2004 musculoskeletal and mucocutaneous domains, Physician Global Assessment (PGA), CLASI, tender joint count, swollen joint count, Complement C3 and C4, and anti-dsDNA are detailed in online supplementary materials 2 and 3. A trend favouring the IFN-K over PBO was observed in change in PGA (baseline to W36, p=0.0537). None of these measures, however, discriminated the two treatment groups. Mild and moderate disease flares, defined per SELENA–SLEDAI flare index, were observed in 9% and 12% of the IFN-K and PBO-treated patients, while severe disease flares were observed in 3% and 6% of IFN-K and PBO patients, respectively (data not shown). Achievement of clinical meaningful improvement in quality of life by 36-Item Short-Form Health Survey (SF-36) questionnaire (≥2.5 change from baseline in physical or mental

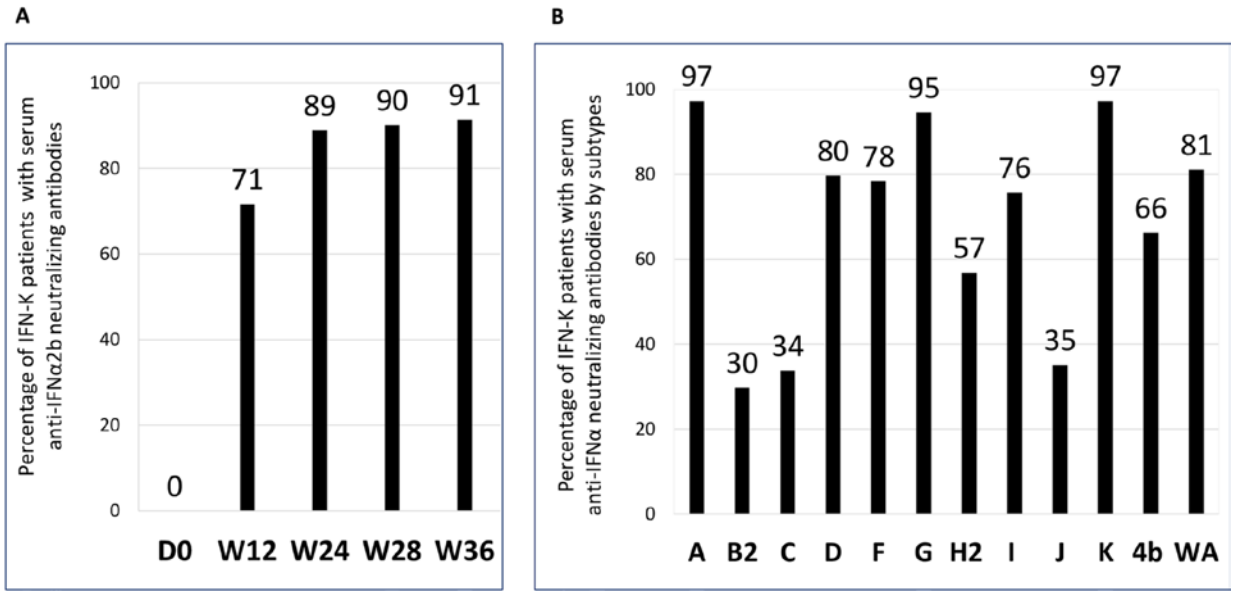

Figure 2 Induction of serum anti-IFN-α neutralising antibodies in IFN-K-treated patients. Percentages of IFN-K-treated patients with serum neutralising antibodies against IFN-α2b (A) and 12 other IFN-α subtypes (B) are indicated on top of each column. Kinetics is shown in (A), while W36 data are shown in (B). Serum titres (dilutions) of ≥1/400 (for binding antibodies) and ≥1/200 (for neutralising capacity) were considered positive. IFN, interferon; IFN-K, interferon-α kinoid.

component summaries or ≥5 for each subdomain) did not differ between groups (online supplementary material 4), except for a trend (p=0.068) favouring IFN-K in the energy/fatigue domain.

Safety and tolerability

Adverse events (AE), treatment-emergent adverse events (TEAEs), severe TEAEs, TEAEs leading to permanent study drug discontinuation and related serious adverse events (SAEs) were equally distributed between the two groups, as indicated in table 2. Related AEs were more frequent with IFN-K (40.7%) than with PBO (24.7%). SAEs were more frequent with PBO (12.9%) than with IFN-K (6.6%). Treatment-emergent serious adverse event (TESAE) leading to permanent study drug discontinuation or of severe intensity were more frequent in PBO (3.2% and 6.5%) than IFN-K (1.1% and 3.3%), respectively. Two patients died, one from pneumonia and lupus disease progression (IFN-K group) and one from central nervous system lymphoma (PBO group). Four cases of cancer were observed in the PBO group and none in the IFN-K group. Shingles were observed in two patients on IFN-K and one on PBO. One patient on IFN-K experienced a severe episode of rash referred to as a

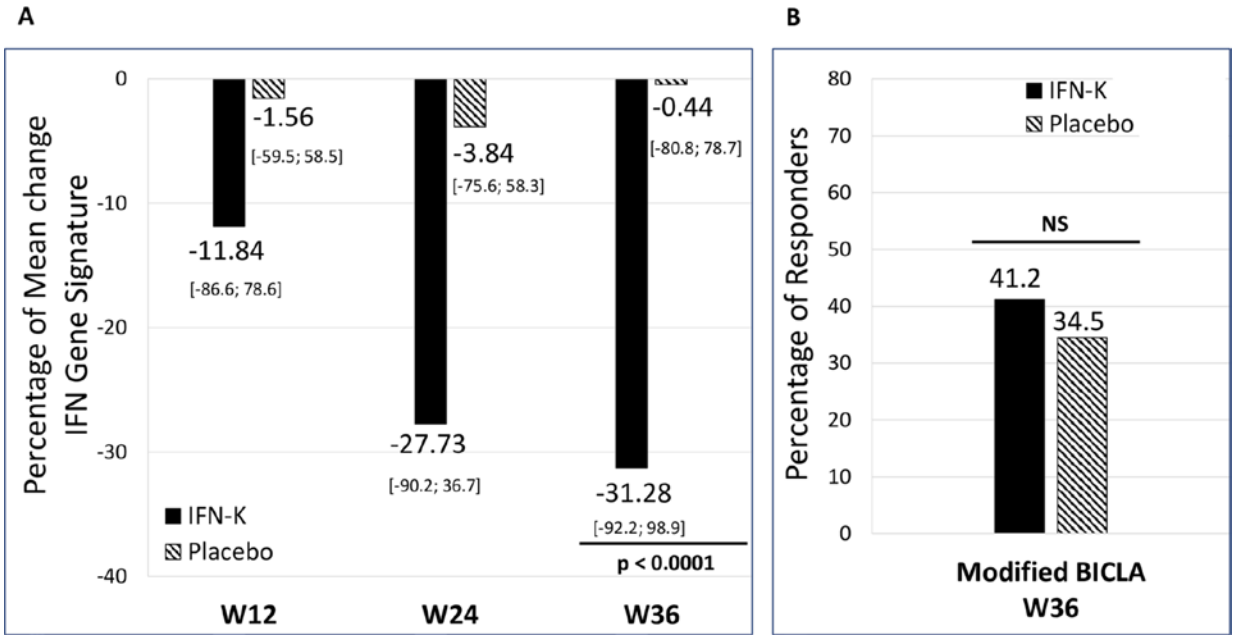

Figure 3 Coprimary endpoints at W36. Mean (min and max) percentages of change from baseline expression of IFN-induced genes (biological coprimary endpoint), evaluated by Affymetrix at W12, W24 and W36, in patients treated with IFN-K (closed columns) and placebo (hatched columns) are shown in (A). P<0.0001 by ANCOVA model (primary readout). Percentages of modified BICLA responders at W36 (clinical coprimary endpoint) are illustrated in (B). As explained in the Patients and methods section, BICLA was modified by the addition of a corticosteroid tapering rule, namely, a ≤5 mg/day prednisone target dose at W24, without further increase until W36. BICLA, BILAG-Based Composite Lupus Assessment; IFN, interferon; IFN-K, interferon-α kinoid.

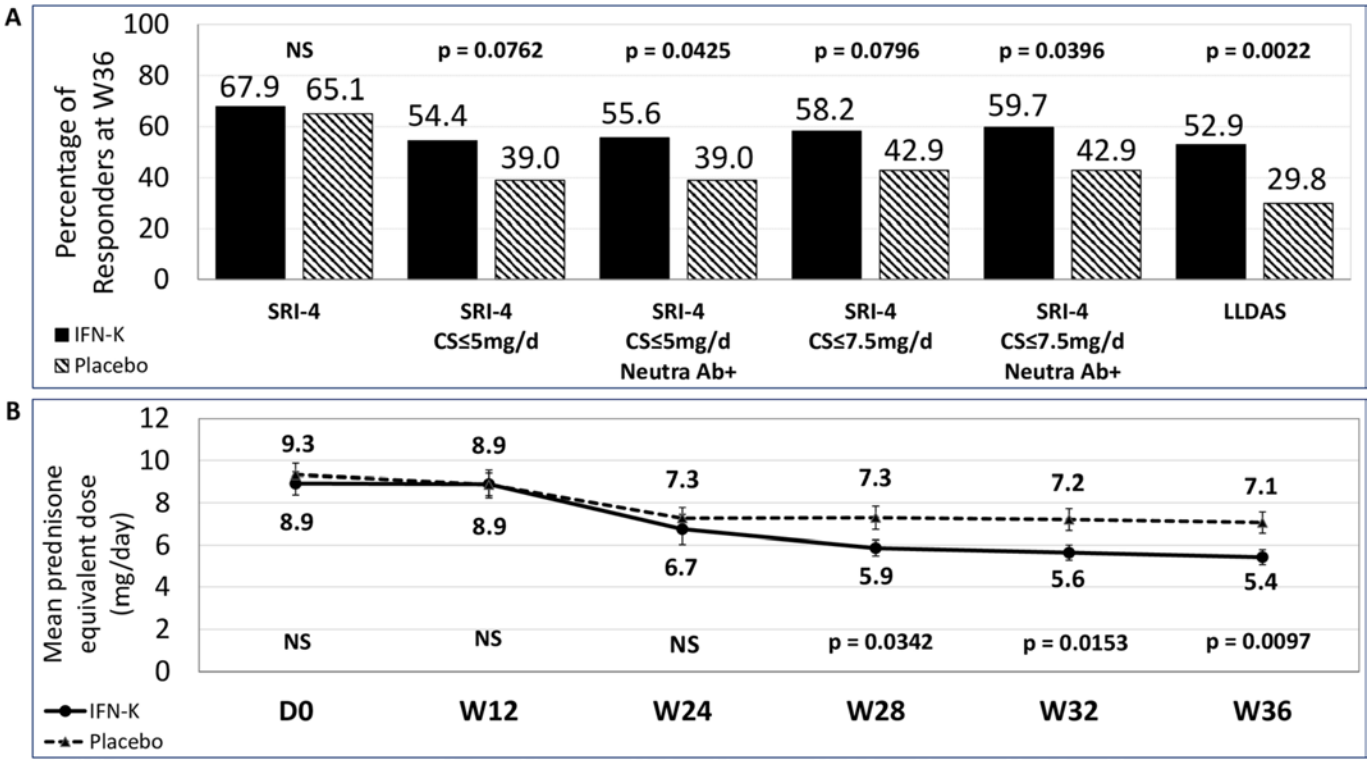

Figure 4 Main secondary endpoints and exploratory analyses at W36. Percentages of SRI-4 and LLDAS responders at W36 in IFN-K-treated patients (closed columns) and those in PBO-treated patients (hatched columns) are shown in (A). As indicated, a trend in favour of IFN-K was observed when a CS target was added to the SRI-4 endpoint (logistic regression model Wald χ^2), which became significant in exploratory analyses when the five patients who did not raise serum neutralising anti-IFN-α2b antibodies were excluded from the analyses (Pearson χ^2). Mean daily prednisone equivalent doses over time in IFN-K-treated patients (continuous line) and PBO-treated patients (dotted line) are shown in (B). They statistically differ from W28 onwards: p=0.0342, 0.0153 and 0.0097 at W28, W32 and W36 respectively (Student-Satterthwaite). CS, corticosteroid; IFN, interferon; IFN-K, interferon-α kinoid; LLDAS, lupus low disease activity state; NS, PBO, placebo;SRI, Systemic Lupus Erythematosus Responder Index.

Kaposi varicelliform eruption, with full recovery except for cutaneous scars. Among TEAEs reported with >5% frequency in the IFN-K group, upper respiratory tract infections and arthralgia were three times more common in the IFN-K group, and nasopharyngitis was twice more common. Injection site induration was observed in 5.5% of IFN-K-treated patients.

DISCUSSION

In this phase IIb trial, the IFN-K induced neutralising anti-IFN-α serum antibodies and significantly down-regulated the IFN gene signature, achieving the biological coprimary endpoint. The clinical coprimary endpoint, that is, the modified BICLA response at W36, was not met. Nonetheless, secondary composite endpoints that incorporated a CS tapering rule favored the IFN-K group. This was observed for SRI-4 with CS tapering to ≤5 or ≤7.5 mg prednisone equivalent/day (by W24 with no increase to W36) and became significant in the subgroup with neutralising antibodies to IFN-K. Similarly, attainment of LLDAS, which also includes a requirement for CS tapering to ≤7.5 mg/day, was significantly in favour of the IFN-K at W36. This is important since LLDAS has been associated with reduced organ damage accrual,[22 25 26] improved quality of life[27] and reduced healthcare costs in SLE.[28]

A statistically significant and clinically relevant CS sparing effect was observed in the IFN-K-group from W28 onwards. Overall, the facilitation of CS tapering by the IFN-K treatment, while maintaining clinical efficacy, was a striking observation in this trial. Damage accrual in SLE has been linked to cumulative CS exposure,[29] and reducing the CS burden remains a major objective of patients themselves due to its adverse effects on their body image and self-esteem. CS taper has been therefore included in treat-to-target recommendations advocated by an international task force,[30] as well as the 2019 update of the EULAR recommendations for management of SLE.[31] While the underlying mechanisms pertaining to its CS sparing effect can only be speculated, it is plausible that, by blocking IFN-α and subsequently decreasing the expression of proteins involved in autoimmunity, IFN-K down-regulates disease activity, thereby allowing lowering of CS, the more so in the setting of a clinical trial where CS tapering is mandatory. In other words, the effects of IFN-K are unmasked by imposing CS reduction. Another hypothesis is that type I IFNs exert yet unknown inhibitory effects on CS-induced pathways. IFN-α inhibition by the IFN-K immunisation may therefore lead to enhanced CS efficacy, thereby allowing CS dose reduction. Evidence supporting this possibility includes the observation that Toll-like receptor (TLR)-induced activation of type I IFN pathways may be intrinsically CS-insensitive. It was indeed shown that IFN-induced genes are not suppressed by CS other than intravenous pulse doses because of TLR-activated NFκB being CS-resistant.[32] This hypothesis requires further experimental evaluation.

Previous studies of other type I IFN targeting therapies did not reveal overt and unexpected toxicities. Similarly, the safety profile of the IFN-K was quite acceptable in this study, with even less SAEs compared with PBO. Of note, HSV-seronegative, VZV-seronegative, CMV-seronegative and EBV-seronegative (IgG) patients were excluded from this trial as a cautionary measure against primary infections when all subsets of IFN-α could have

Table 2 AEs

	IFN-K (n=91)	PBO (n=93)
Any AE	78 (85.7%) (392)	74 (79.6%) (302)
Any TEAE	75 (82.4%) (371)	71 (76.3%) (277)
TEAE leading to study treatment permanent discontinuation	4 (4.4%) (4)	4 (4.3%) (4)
TEAE of intensity severe or more	10 (11.0%) (27)	10 (10.8%) (11)
Related TEAE	37 (40.7%) (95)	23 (24.7%) (54)
Any SAE	6 (6.6%) (13)	12 (12.9%) (15)
Any TESAE	6 (6.6%) (13)	12 (12.9%)(15)
TESAE leading to study treatment permanent discontinuation	1 (1.1%) (1)	3 (3.2%) (3)
TESAE of intensity severe or more	3 (3.3%) (9)	6 (6.5%) (6)
Related TESAE	2 (2.2%) (7)	2 (2.2%) (2)
Death	1 (1.1%) (2)	1 (1.1%) (1)
Adverse events of interest		
Herpes zoster	2 (2.2%) (2)	1 (1.1%) (1)
Severe Infection	2 (2.2%) (2)	0 (0.0%) (0)
Malignancy	0 (0.0%) (0)	4 (4.3%) (4)*
Most common adverse events (>5% in the IFN-K group) by PT		
Upper respiratory tract infection	16 (17.6%)(17)	5 (5.4%)(6)
Urinary tract infection	11 (12.1%)(11)	9 (9.7%)(10)
Nasopharyngitis	7 (7.7%)(10)	2 (2.2%)(2)
Pharyngitis	6 (6.6%)(7)	3 (3.2%)(4)
Bronchitis	5 (5.5%)(5)	4 (4.3%)(4)
Injection site induration	5 (5.5%)(8)	0 (0.0%)(0)
Arthralgia	7 (7.7%)(8)	2 (2.2%)(3)
Pain in extremity	6 (6.6%)(6)	1 (1.1%)(1)
Headache	10 (11.0%)(19)	2 (2.2%)(3)

Data are numbers (and percentage) of patients. Data in brackets () are numbers of events. More than 1 event can be reported per patient. No statistical differences were observed between the two groups.
AEs were considered as treatment emergent if date of event was at or after the date of the first study drug administration.
*Two papillary thyroid cancers, one central nervous system lymphoma, one rectal cancer.
AE, adverse event; IFN-K, interferon-α kinoid; PBO, placebo; PT, preferred term; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse events.

been blocked. Bearing this limitation, the viral infection profile of the IFN-K was reassuring with no increased risk of viral infections compared with PBO. The ongoing follow-up study on patients who received IFN-K will inform us on the long-term safety and efficacy, as well as the kinetics of the IFN-K-induced anti-IFN-α response that is expected to variably wane over time.

The concept of blocking IFN-α by IFN-K is consistent with the paradigm of personalised medicine since we were able to demonstrate that patients with the strongest type I IFN signature at baseline mounted the strongest anti-IFN-α response.[13] Yet, this should not disguise the following limitations. First, only two-thirds of patients with SLE display a type I IFN signature, making them eligible for IFN-K therapy. Second, IFN-K does not block other IFN subtypes like IFN-ω and IFN-β or type-specific like type II (IFN-γ) or type III (IFN-λ), which may explain the level of the effect observed in this trial compared with other IFNs targeted therapies. Third, the kinetics of the persistence of blocking IFN-α antibodies clearly needs to be addressed, as well as the duration of the inhibition of the IFN signature. Finally, the lack of improvement of patient-reported outcomes, shared by other anti-IFN drugs, is puzzling and disappointing.

In summary, based on preclinical data obtained in murine lupus models, on translational research performed in patients with lupus and on clinical trials, type I IFNs and related pathways remain key targets for the treatment of active SLE. Indeed, of all molecules tested so far, rontalizumab,[5] sifalimumab,[6] anifrolumab[7] and baricitinib[10] have demonstrated some efficacy over PBO on one or more outcome measures (primary and/or secondary endpoints, total and/or subset population). Yet, as of today, none of these compounds have yielded positive results in more than one phase III studies, which is required for approval by medical drug agencies. It has been increasingly acknowledged that these failures may be more related to the choice of the outcome measures than to actual inefficacy of the molecules. The IFN-K study reported here further fuels this hypothesis, since the drug did not meet its primary endpoint despite a significant steroid-sparing effect and attainment of LLDAS, indicating that the IFN-K deserves further evaluation in phase III studies.

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