Title:

IFNα-kinoid in systemic lupus erythematosus (SLE): results from a phase 2b, randomized, placebo-controlled study

F. A. Houssiau[1], A. Thanou[2], M. Mazur[3], E. Ramiterre[4], D. A. Gomez Mora[5], M. Misterska-Skora[6], R. A. Perich Campos[7], S. Smakotina[8], S. Cerpa Cruz[9], B. Louzir[10], and study group, T. Croughs[11], M Tee[12].

Background: The immunotherapeutic vaccine Interferon-α-kinoid (IFN-K) consists of a heterocomplex of inactivated recombinant human IFN-α2b coupled to a T-helper carrier protein, Keyhole Limpet Haemocyanin. A phase I/IIa was published. Here, we report the results of a 36-week (w) phase 2b, randomized, double-blind, placebo-controlled (PBO), multi-center study assessing the efficacy and safety of IFN-K in patients with active SLE on standard of care therapy.

Methods: SLE patients (≥4 ACR criteria) with moderate to severe disease activity (SLEDAI 2K ≥6 and ≥1 BILAG A and/or ≥2 BILAG B scores); positive IFN gene signature; and ANA and/or anti-dsDNA, were randomized (1:1) to 5 IM injections of IFN-K or PBO at days 0, 7, 28, and months 3 and 6. Co-primary objectives at w36 were neutralization of IFN gene signature and BICLA response modified by mandatory corticosteroid (CS) tapering (≤5 mg/d prednisolone equivalent) by w24 with no increase to w36. Secondary objectives at w36 were SRI(4) and SRI(4) with CS tapering (≤5 mg or ≤7.5 mg/d prednisolone equivalent) by w36, Lupus Low Disease Activity State (LLDAS), safety and immunogenicity.

Results:

Among 185 patients randomized, 91 and 93 were respectively treated with IFN-K and PBO, and 85 (92.4%) and 84 (90.3%) completed the study. Seventy-two of 79 (91.1%) IFN-K treated patients (Per Protocol Set) developed anti-IFNα neutralizing antibodies (Abs). Primary and secondary outcome measures at w36 are detailed in the Table:

	IFN-K	Placebo	p value
IFN gene signature reduction	**-31.3%**	**-0.4%**	**<0.0001**
Modified BICLA	**35 (41.2%)**	**29 (34.5%)**	**NS**
SRI(4)	**57 (67.9%)**	**54 (65.1%)**	**NS**
SRI(4) with CS ≤5mg/d	**43 (54.4%)**	**30 (39%)**	**0.07**
SRI(4) with CS ≤5mg/d (IFN-K subgroup with neutralizing Abs)	**40 (55.6%)**	**30 (39.0%**	**0.0425**
SRI(4) with CS ≤7.5mg/d	**46 (58.2%)**	**33 (42.9%)**	**0.07**
SRI(4) with CS ≤7.5mg/d (IFN-K subgroup with neutralizing Abs)	**43(59.7%)**	**33 (42.9%)**	**0.0396**
LLDAS	**45 (52.9%)**	**25 (29.8%)**	**0.002**
Mean CS dose *	**5.4 mg/d**	**7.1 mg/d**	**0.0097**
The mean daily CS dose was lower in the IFN-K group from w28 onwards.			

IFN-K was well tolerated, with similar rates of treatment-emergent adverse events (TEAEs 82.4% vs 76.3%) and TEAEs leading to study drug discontinuation (4.4% vs. 4.3%) in the IFN-K and PBO groups, respectively. Serious adverse events (SAEs) were more common on PBO vs IFN-K (12.9% vs 6.6%). Cancer (n=4) and lupus nephritis (n=2) were reported in the PBO group and there was one severe infection in the IFN-K group. One death occurred in each group.

Conclusions:

IFN-K induced neutralizing anti-IFNα Abs in 91.1% of treated patients and significantly reduced the IFN gene signature. Modified BICLA at w36 did not differ between IFN-K and PBO. Trends on SRI (4) with steroid tapering at w36 favored IFN-K, and became significant when patients exhibiting neutralizing Abs were included in the exploratory analysis. Furthermore achieving a Lupus Low Disease Activity State discriminated the two groups at w36, in favor of IFN-K. A significant CS sparing effect of IFN-K was observed from w28 onwards. The safety profile of IFN-K was acceptable. Results merit further evaluation in a phase 3 study.