POSTER
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FUNCTIONALLY SELECTIVE IMMUNOMODULATOR SHOWS ROBUST EFFICACY IN SPONTANEOUS LUPUS MOUSE MODEL

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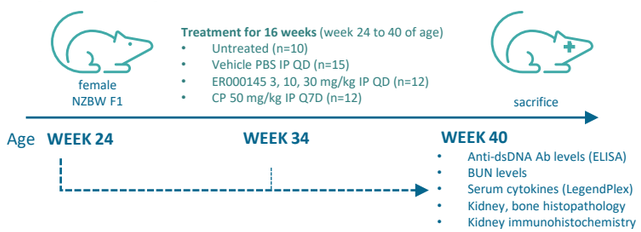
BACKGROUND

- Systemic lupus erythematosus (SLE) is a complex, heterogeneous autoimmune disease[1]. There is still a high unmet need to improve current treatment options. Type 1 interferon (IFN) has recently been validated as clinical target for SLE.
- ER000145 is a functionally selective immunomodulator derived from IT1t, a CXCR4 antagonist with immunomodulating properties[2]. ER000145 has low/no CXCR4 antagonism and increased immunomodulating activity as demonstrated by the inhibition of type 1 IFN and other key inflammatory cytokines secreted by Toll-like receptor 7/8-stimulated immune cells *in vitro*[3]. Furthermore, strong *in vivo* efficacy was shown in the murine pristane-induced lupus[3] and collagen-induced arthritis model[4].
- *In vivo* efficacy of ER000145 was evaluated in (NZB x NZW) F1 mice. This spontaneous lupus mouse model is sharing several pathophysiological features of human SLE, with clear nephropathy development starting around 22 weeks of age.

METHODS

- As of 24 weeks of age, female (NZB x NZW) F1 mice received once daily intraperitoneal (IP) administrations of ER000145 (ER145) at either 3, 10 or 30 mg/kg (mpk) for 16 weeks. Cyclophosphamide (CP) was administered as positive control once a week at 50 mg/kg IP. Body weight was recorded twice per week and assessment of bone marrow cellularity was performed on hematoxylin and eosin (H&E) stained femur sections. Proteinuria was measured weekly up to the age of 40 weeks, at which point nephropathy development was assessed by measuring the levels of blood urea nitrogen (BUN). At 24, 34 and 40 weeks of age, anti-dsDNA antibody (Ab) titers were evaluated by ELISA. After 16 weeks of treatment, mice were sacrificed and serum cytokine levels were determined using ELISA. Histopathological grading of nephropathy was performed on H&E and Periodic Acid-Schiff (PAS) sections. Multiplex immunohistochemistry staining was performed on kidney cores from vehicle- and ER000145-treated (30 mg/kg) mice to get further insights on the phenotype of immune infiltrates and their localization in anatomical area.

Figure 1. Study design



CONCLUSIONS

- ER000145 showed robust and dose-dependent efficacy upon once daily IP treatment for 16 weeks in (NZB x NZW) F1 lupus-prone mice. No signs of immunosuppression were detected.
- Based on these promising efficacy data obtained *in vivo* with ER000145, orally available functionally selective immunomodulators are currently being developed as a potentially novel and innovative treatment option for SLE.

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REFERENCES [1]Kaul et al. Nat Rev Dis Primers. 2016;2:16039; 2010;330(6007):1066-71; [2]Smith et al. Sci Adv. 2019;5(7):eaav9019; [3]Van der Aa et al., Arthr Rheum. 2022;74(suppl 9); [4]Asnagli et al., Ann Rheum Dis. 2023;82:829-830.

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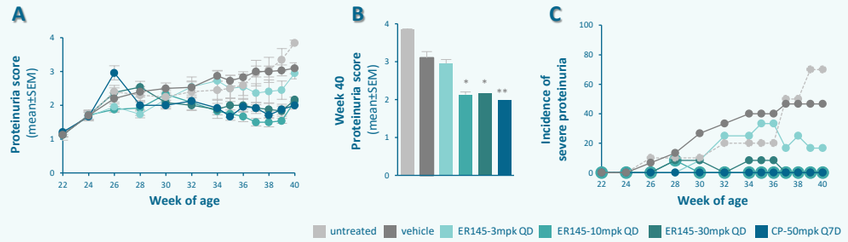
RESULTS

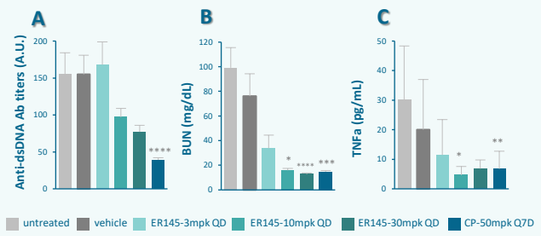
- ER000145 significantly decreases **proteinuria levels** in a dose-dependent manner (*Figures 2A and B*). This is also reflected by lower incidence of severe proteinuria (score 4) in ER000145-treated compared to vehicle-treated mice (*Figure 2C*).

Figure 2. Proteinuria scores over time



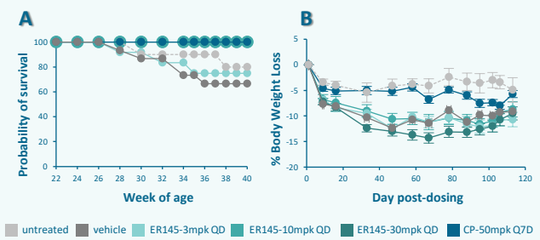
- At 40 weeks of age, ER000145 treatment showed reduced **anti-dsDNA Ab titers** in a dose-dependent manner (*Figure 3A*), and significantly lower **BUN** levels were obtained as of a daily dose of 10 mg/kg (*Figure 3B*), suggesting an impact on kidney disease. Serum cytokine levels were reduced as well, as shown for Tumor Necrosis Factor alpha (**TNFa;** *Figure 3C*).

Figure 3. Anti-dsDNA Ab titers, kidney function marker BUN and systemic TNFa levels at week 40



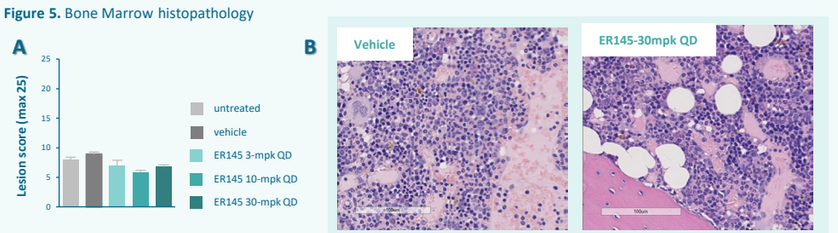
- ER000145 treatment reduces **disease-related mortality** at daily doses as of 10 mg/kg ER000145 (*Figure 4A*) and is not associated with compound-related **body weight loss** (*Figure 4B*).

Figure 4. Survival rate and body weight loss over time



- Daily treatment for 16 weeks with ER000145 did not show any significant alterations in **bone marrow pathology** compared to vehicle control (*Figure 5A*). At the high dose of 30 mg/kg ER000145, no deletion of specific lineages in the myelogram, nor reactive changes secondary to that like cell atypia were observed. Consequently, there was no morphological evidence of overt immune suppression (*Figure 5B*).

Figure 5. Bone Marrow histopathology



- ER000145 treatment significantly decreases in a dose-depending manner kidney pathology as measured by total **glomerular and tubular histological scores** (*Figures 6A and 6B*). The typical aberrant remodeling of both glomeruli (with inhibition of glomerular crescent formation and mesangial hypercellularity) and renal tubules (with inhibition of protein cast formation and suppression of tubular dilation) is significantly reduced after ER000145 administration. Furthermore, the normal glomerular and epithelial tubule structures are conserved (*Figure 7*).

Figure 6. Kidney histopathology: individual total scores (A) and mean subscores (B)

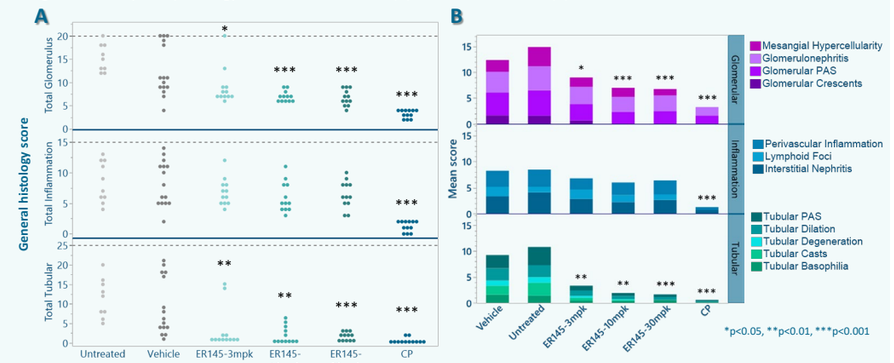
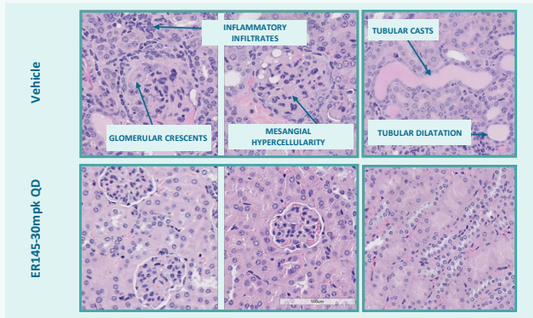


Figure 7. Representative images of glomerular (left and middle) and tubular (right) kidney histology



- ER000145 treatment is associated with a significant overall decrease in **myeloid cells and helper T cells** in kidney cores analyzed compared to vehicle treatment, combined with an **attenuated B cell (progenitor) drive** to glomerular and cortical compartments (*Figure 8*).

Figure 8. Multiplex immunohistochemistry staining of kidney cores