and scored urine proteinuria, skin lesions and lymphadenopathy. At the end of the treatment interval, kidney, lung, spleen, skin, plasma and urine samples were collected and shipped to the coordinating study center for blinded analysis. All histopathological assessments were performed by an independent kidney pathology institute (RWTH Aachen, Germany) in a blinded fashion. The pre-set primary endpoint was urinary protein/creatinine ratio. Secondary endpoint analyses included plasma auto-antibodies levels, kidney histologic scores (activity and chronicity indices). Glomerular filtration rate and flow cytometry of splenocytes was performed on subgroups of mice at single centers.

**Results** A total of 56 mice were used, of which 13 in Madrid, 15 in Barcelona, 14 in Freiburg, and 14 in Munich. Mice were randomly assigned to baricitinib treatment (n=28) or vehicle (n=28). At treatment initiation, the average score of proteinuria (tested by sticks 0–4), skin lesion (0–4), and lymphadenopathy (0–6) for baricitinib group were 1.38 ± 0.99, 0.95 ± 1.28, and 2.10 ± 1.80, respectively; above scores for vehicle group were 1.45 ± 1.10, 0.77 ± 1.02, and 1.81 ± 2.02, respectively. Data analysis is ongoing and will be presented at the conference.

**Conclusions** Preclinical double-blind, randomized, controlled, multicenter trials are a novel tool in preclinical drug testing that might help to predict the outcome of randomized clinical trials.

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**P135 A PHASE I, FIRST-IN-HUMAN STUDY TO ASSESS THE SAFETY, PHARMACOKINETICS AND PHARMACODYNAMICS OF SINGLE AND MULTIPLE ASCENDING DOSES OF M5049, A DUAL ANTAGONIST OF TLR7/8, IN HEALTHY SUBJECTS**

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**Background** Toll-like receptors 7 and 8 (TLR7/8) are widely recognized as an important part of the immune system, activates antigen-presenting cells and is involved in the development of autoimmune disease. TLR7/8 activity in vitro and in vivo in the mouse model of SLE has demonstrated efficacy in mouse SLE models, suggesting potential to inhibit pathological immune complex activities in SLE patients.

**Methods** This was a phase I, randomized, double-blind, placebo-controlled (3:1) study of oral M5049 conducted in healthy participants. M5049 was dosed as single (1, 3, 9, 25, 50, 100 and 200 mg) or placebo, and MAD cohorts received M5049 (9, 25, 200 mg once daily, 25 and 50 mg twice daily) or placebo for 14 days. A sentinel dosing strategy was used in MAD cohorts. The study assessed safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (ex vivo-stimulated cytokine secretion). Food effect was assessed in the 25 mg MAD cohort.

**Results** Preliminary results showed that M5049 was well-tolerated over the dosing interval, with no significant or dose-limiting adverse events observed to date. PK parameters were linear and dose-proportional from 1 to 200 mg, with higher clearance and shorter half-life than predicted based on preclinical studies. Exposure-dependent inhibition of ex vivo-stimulated IL-6 secretion was observed, with maximum inhibition achieved at 200 mg. PK results indicate a slight food effect.

**Conclusions** M5049 was well-tolerated with no safety signals in healthy participants, warranting further investigation as a potential treatment for autoimmune diseases, such as SLE.