Background Subcutaneous (SC) administration of KZR-616 (30 and 45 mg weekly [QW]) was demonstrated as safe and well-tolerated, and successfully achieved target levels of immunoproteasome inhibition in healthy volunteers.1,2

Methods SLE patients in this open-label multicenter dose escalation trial received KZR-616 at doses of 45 mg (Cohort 1), 60 mg (Cohort 2), or 30 mg with escalation to 60 mg (Cohorts 2a and 2b) subcutaneously weekly through Week 13 (W13) with 12 weeks of follow-up.

Results As of 16 January 2020, 33 patients had enrolled and received at least 1 dose of KZR-616. The majority of TEAEs have been mild or moderate with no reported peripheral neuropathy, prolonged GI-related AEs, and no clinically significant laboratory AEs. When compared to baseline, improvement in measures of disease activity were seen at W13 and beyond. A single patient with active class IV/V nephritis who failed prior treatment with tacrolimus was enrolled on prednisone 10 mg, leflunomide 10 mg, and hydroxychloroquine 200 mg/day; nephrotic-range proteinuria (baseline: 3.8±2.2 g/day) decreased to 0.6 g/day 4 weeks after the last dose of KZR-616.

Conclusions Weekly SC administration of KZR-616 at 45 and 60 mg was safe and well-tolerated. Evidence of disease suppression at W13 was observed, and 94% of evaluable patients had improvements on at least 2 measures/assessments of disease activity. In addition, one study participant with active proliferative LN was enrolled with significant reduction in proteinuria. The Phase 2 portion of this study in active proliferative LN is open for enrollment.

REFERENCES
inadequate response to standard of care (SOC) therapy (NCT04058028).

Methods In this adaptive, phase 2, placebo-controlled, dose-ranging study, subjects (N=300, age 18–75 years) will be randomized to receive placebo or 1 of 3 doses of AMG 570 Q2W for 52 weeks, followed by 16 weeks of safety follow-up. The primary objective is to evaluate efficacy of AMG 570 compared with placebo at week 24 using the SLE Responder Index (SRI-4). Key secondary endpoints include SRI-4 at week 52 with oral corticosteroid (OCS) reduction (≥10 mg/day at baseline to ≤7.5 mg/day in weeks 44–52) and SRI-4 and Lupus Low Disease Activity State at week 52. Subjects will undergo 2 screening visits to fulfill criteria for active SLE and demonstrate adherence to prior SLE treatment including OCS, immunosuppressants, and/or immunomodulators. Blood screening tests will confirm detectable serum drug levels of baseline SOC medications. RAR aims to allocate more subjects to more efficacious doses while maintaining the placebo allocation constant; the randomization ratio could be adapted after interim analyses based on clinical efficacy. The trial includes interim analyses for futility using the Bayesian approach.

Results Study ongoing.

Conclusion This study will provide safety and efficacy data for AMG 570 compared with placebo, and its adaptive trial design aims to optimize development of a novel therapy for SLE patients with inadequate response to current SOC.

Acknowledgments Amgen Inc. sponsored this study.

Results In preclinical validation studies with the MRL mouse model, 2 compounds were differentiated by significant efficacy and excellent tolerability. TXR-711 and TXR-712 increased renal function, decreased renal inflammation and decreased inflammation compared to vehicle-treated control mice. In particular, TXR-711 and TXR-712 significantly decreased serum blood urea nitrogen (BUN) levels, decreased proteinuria levels, and significantly improved kidney histology readouts such as glomerulonephritis and tubule basophilia. Additionally, TXR-711 and TXR-712 treatment resulted in significantly decreased inguinal lymph node weight.

Conclusions TXR-711 and TXR-712 were identified as SLE drug discovery leads with novel MOAs for further preclinical development. Ongoing studies with TXR-711 and TXR-712 includes pharmacokinetic, pharmacodynamic, and additional MRL mouse efficacy characterization.

P134 A PRECLINICAL DOUBLE-BLINDED, RANDOMIZED, CONTROLLED, MULTICENTER TRIAL (PRCT) ON JAK1/JAK2 INHIBITION IN LUPUS NEPHRITIS

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Background Most treatments reported to favourably impact on experimental lupus nephritis failed to reproduce these results in multicenter randomized controlled trials (RCT) in patients. Preclinical multicenter RCT (pRCT) may help to close the gap between preclinical and clinical trials. We therefore performed the first pRCT in lupus nephritis. We selected the Jak1/2 inhibitor baricitinib as a therapeutic intervention given that similar Jak/Stat inhibitors have shown protective effects in single center animal studies and baricitinib is currently tested in several clinical trials recruiting patients with systemic lupus (NCT 03843125, 03616964, 03616912).

Methods The effect of baricitinib was tested in a randomized, controlled, blinded pre-set study design at two Spanish (Madrid, Barcelona) and two German (Munich, Freiburg) academic sites. Each site included MRL/lpr mice of their own breeding colonies or from diverse commercial providers and kept at housing conditions as per their local standard operating procedures. Group size calculation was based on the assumption that baricitinib would reduce the primary endpoint, i.e. protein/creatinine ratio, by 20%, with a type I error of 0.05, type II error of 0.2, and a power of 0.8. Eligibility criteria were: female, 13–14 weeks old, had developed signs of systemic lupus erythematosus, had stress scores of less than 2, and had no visible tumor or signs of infection. Block randomization was used to randomly assign mice at a 1:1 ratio to receive either 20 mg/kg baricitinib in 0.5% methylcellulose or vehicle daily by oral gavage for 4 weeks. Medication was provided in a blinded fashion by the coordinating study center. Periodically, each site collected urine and blood samples,