

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.

P133 COMPUTATIONAL DISCOVERY AND PRECLINICAL VALIDATION OF THERAPEUTIC LEADS WITH NOVEL MOAS FOR SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Isaac Hakim, Sana Mujahid, Aaron C Daugherty, Timothy S Heuer. *twXAR Inc, Mountain View, CA, USA*

10.1136/lupus-2020-eurolupus.177

Background Lupus is a heterogeneous, systemic disease that affects millions of patients globally with a high unmet medical need. We present results from our powerful and efficient computational drug discovery platform that identifies hits with first-in-class mechanisms of action that can advance rapidly and successfully through preclinical validation studies. The twoXAR discovery platform uses an artificial-intelligence framework to integrate diverse patient-derived biomedical data sets to build holistic and unbiased models of human disease biology. The utilization of diverse, proprietary algorithms and deep learning principles provides a highly sensitive platform to elucidate complex disease-specific associations between biology and biomedical data that are integrated with a library of existing drug molecules. This enables the identification of novel, high-value drug discovery hits with known pharmacological properties. The twoXAR platform also preserves interpretable data-driven links to disease biology to facilitate efficient validation and optimization studies.

Methods Using clinical SLE patient data, we employed the twoXAR platform to build an *in-silico* SLE disease model. Nine molecules with novel mechanisms of action (not previously tested as candidate clinical therapies for lupus) were identified as drug discovery hits and then characterized in preclinical efficacy studies using the MRL mouse model of lupus.

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

¹Yutian Lei, ²Bettina Sehnert, ²Reinhard E Voll, ³Conxita Jacobs-Cachá, ³Maria Jose Soler, ⁴Maria D Sanchez-Niño, ⁴Alberto Ortiz, ⁵Roman D Bülow, ⁵Peter Boor, ¹Hans-Joachim Anders. ¹Division of Nephrology, Dept. of Medicine IV, University Hospital, LMU Munich, Munich; ²Dept. of Rheumatology and Clinical Immunology, Medical Center-University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany; ³Nephrology Dept., Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Nephrology Research Group, Vall d'Hebron Research Institute (VHIR) and REDINREN Barcelona; ⁴IIS-Fundación Jiménez Díaz, School of Medicine, Universidad Autónoma de Madrid, Fundación Renal Iñigo Álvarez de Toledo-IRSIN and REDINREN, Madrid, Spain; ⁵Institute of Pathology and Dept. of Nephrology, RWTH University of Aachen, Aachen, Germany

10.1136/lupus-2020-eurolupus.178

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,