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 were 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 at baseline (3.85 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 nephritis (LN) was enrolled with significant reduction in proteinuria. The Phase 2 portion of this study in active proliferative LN is open for enrollment.

REFERENCES

BELIMUMAB IN THE TREATMENT OF 38 PORTUGUESE SLE PATIENTS: A REAL-LIFE MULTICENTRIC STUDY
Bruno Fernandes, Miguel Bernardes, Sofia Barreia, João Euriro Fonseca, Margarida Cunha, Maria José Santos, Nuno Gonçalves, Ana Lúcia Fernandes, Joana Rodrigues, Tomás Fontes, Lúcia Costa. Rheumatology Dept., Centro Hospitalar Universitário São João, Porto; Rheumatology Dept., Hospital do Divino Espírito Santo, Ponta Delgada, Portugal

Background Belimumab, an anti-BLyS monoclonal antibody, is the first biologic available for SLE treatment. We studied its effectiveness and safety in clinical practice.
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.

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

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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.