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TREATMENT OF SLE WITH THE IMMUNOPROTEASOME INHIBITOR KZR-616: RESULTS FROM THE FIRST 4 COHORTS OF THE MISSION STUDY, AN OPEN-LABEL PHASE 1B DOSE ESCALATION TRIAL

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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 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

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BELIMUMAB IN THE TREATMENT OF 38 PORTUGUESE SLE PATIENTS: A REAL-LIFE MULTICENTRIC STUDY

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

Abstract P131 Table 1 Evolution of SLEDAI, anti-dsDNA antibodies and C3 levels at 6, 12 and 24 months of belimumab and its significance compared to baseline values.

	Baseline	6 months	12 months	24 months
SLEDAI - mean±SD	8.2±3.9	3.8±2.2 (p<0.001)	4.1±3.2 (p<0.001)	3.1±1.6 (p=0.002)
Anti-dsDNA antibodies (UI/mL) - mean±SD	231.6 ±238.3	155.3±198.7 (p=0.025)	157.9±341.1 (p=0.031)	107.4±132.2 (p=0.003)
C3 (mg/dL) - mean±SD	82.6±28.8	89.6±27.1 (p=0.223)	94.6±25.8 (p=0.018)	100.9±36.9 (p=0.139)

Methods Multicentric cohort study of SLE patients, fulfilling the 2012 SLICC classification criteria, treated with belimumab in rheumatology departments and registered in the Portuguese registry *Reuma.pt*.

Results Thirty-eight patients were included: 37 (97.4%) female, aged 46.2±13.9 years, mean disease duration of 11.9±8.6 years. The reasons for prescribing belimumab were: multiorgan involvement in 20 (52.6%), haematologic disorders in 9 (23.7%), cutaneous manifestations in 5 (13.0%), arthritis in 3 (7.9%), necrotizing vasculitis in 1 (2.6%). Belimumab was administered intravenously for a mean of 22.3±20.3 months.

SRI response was achieved in 14/27 (51.9%), 12/20 (60%) and 11/12 (91.7%) at 6, 12 and 24 months of belimumab treatment, respectively. Mean SLEDAI significantly decreased from 8.2±3.9 at baseline to 3.8±2.2, 4.1±3.2 and 3.1±1.6 at 6, 12 and 24 months, respectively.

Anti-dsDNA antibodies significantly decreased at 6, 12 and 24 months and C3 increased at 12 months of belimumab (table 1). We found a significant reduction in mean daily prednisolone dosage (p<0.001) from baseline (10.8±5.1 mg) to the last evaluation under belimumab (5.5±3.0 mg).

Eleven (28.9%) patients discontinued belimumab: loss of effectiveness in 4, lost to follow-up in 4, adverse events in 3 (urinary tract infections, acute myocardial infarction, breast cancer). Three presented infections related to belimumab.

Conclusions We confirmed belimumab effectiveness and safety in real-life active SLE patients.

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DESIGN OF AN ADAPTIVE, PHASE 2, PLACEBO-CONTROLLED, DOSE-RANGING STUDY TO ASSESS THE EFFICACY AND SAFETY OF AMG 570 IN SUBJECTS WITH ACTIVE SLE AND INADEQUATE RESPONSE TO STANDARD OF CARE THERAPY

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Background/Purpose Current SLE treatment options have limited efficacy and potential toxicities that impede an individual's ability to remain on therapy. AMG 570 is a bispecific antibody inhibiting both ICOSL and BAFF that engages ICOSL on antigen-presenting cells (dendritic cells and B cells) and reduces circulating naïve B cells in healthy subjects. This phase 2 study will employ SLE drug screening and response-adaptive randomization (RAR) to optimize dose selection of AMG 570 in subjects with active SLE and

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.

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,