Systemic lupus erythematosus (SLE) is the prototypical multisystem autoimmune disease with diverse clinical features in persons with disease. SLE is also unified by characteristic autoimmunity directed against nucleic acid or nucleoprotein complexes. SLE is both more prevalent and typically exhibits a more severe clinical course in persons with African-American ancestry than in persons with European ancestry. The reasons for this discrepancy remain incompletely understood. GWAS studies of SLE in cohorts of individuals with Amerindian, East Asian and European ancestry have identified > 180 risk loci for SLE across the genome. These loci act in several pathways: clearance of autoantigens, innate immune response to nucleic acids, and lymphocyte activation. Despite these advances in understanding the genetic basis of SLE, a genome-wide association scan (GWAS) of SLE in a cohort of individuals with African-American ancestry has not yet been reported. Here, we report preliminary results of GWAS in 1494 SLE cases and 6076 matched controls with African-American ancestry. Illumina Infinium Omni 1, Omni 1S, Omni 2.5 and OmniExpress platforms were used for genotyping. Genotypes were imputed using the TOPMed reference panel at NHLBI. By defining the contribution common genetic variants to disease risk across the genome, our study represents a step towards understanding the genetic basis of SLE and the increased prevalence and severity of SLE in African ancestry populations. To fully define the relative contribution of environment and genetics to the discrepant SLE severity and prevalence observed in African-American populations, future studies will be necessary. These studies should focus both on comprehensive understanding of the environmental influences and comprehensive assessment of genome- wide genetic variation (i.e. whole-genome sequencing) that impact SLE risk and disease severity.

Our results confirm genome-wide significant (P < 5E-8) association with loci ascertained in other populations (*STAT4-STAT1*, *TNIP1*, *MIR146A*, *HLA-C4A-C4B*, *IRF5*, *BLK*, *PLAT-IKBKB*, *RELA-RNASEH2C-OVOL1*, *ITGAM,* and *IRF8*) and identify several novel genome-wide significant risk loci that are newly described in our study (*ENSA*, *IKBKB/Chr8: Centromere* and *PCMTD1-ST18*). Further, we compared associated variants in our study with those from three large SLE GWAS studies in cohorts of individuals with European, East Asian and Amerindian ancestry. This comparison of SLE risk loci revealed pervasive sharing of SLE genetic risk across ancestral groups. For 70% of the risk loci, the lead marker exhibited nominal association (P < 0.05) with SLE in our GWAS of SLE in African- American persons. Importantly, the association of all such variants cohered with the reported direction in other ancestries.

Overall, our findings are consistent with a polygenic contribution to SLE in African-American individuals that is largely shared across populations. We also find association with a rare variant (MAF < 1%) of large effect (OR = 3.91) near a locus previously identified via ImmunoChip (Illumina), *PLAT-IKBKB*. The lead variant at this locus is non-polymorphic in populations with ancestry outside of Africa. This association explains the increased risk of SLE in ~4% of cases in our cohort. On the one hand, our GWAS of SLE in persons African-American ancestry provides insights that reinforce the conclusions concerning the known risk loci from other ancestries. On the other hand, this mechanism uniquely raises SLE risk in a small proportion of African ancestry individuals with SLE. Together our findings reveal both uniformity and diversity of genetic risk factors impacting SLE development across populations.

For Poster Presentation

1501 ENPATORAN: PRECLINICAL EVIDENCE SUPPORTING GLUCOCORTICOID DOSE REDUCTION AND PHASE II STUDY DESIGN IN PATIENTS WITH SLE AND/OR CLE (WILLOW)

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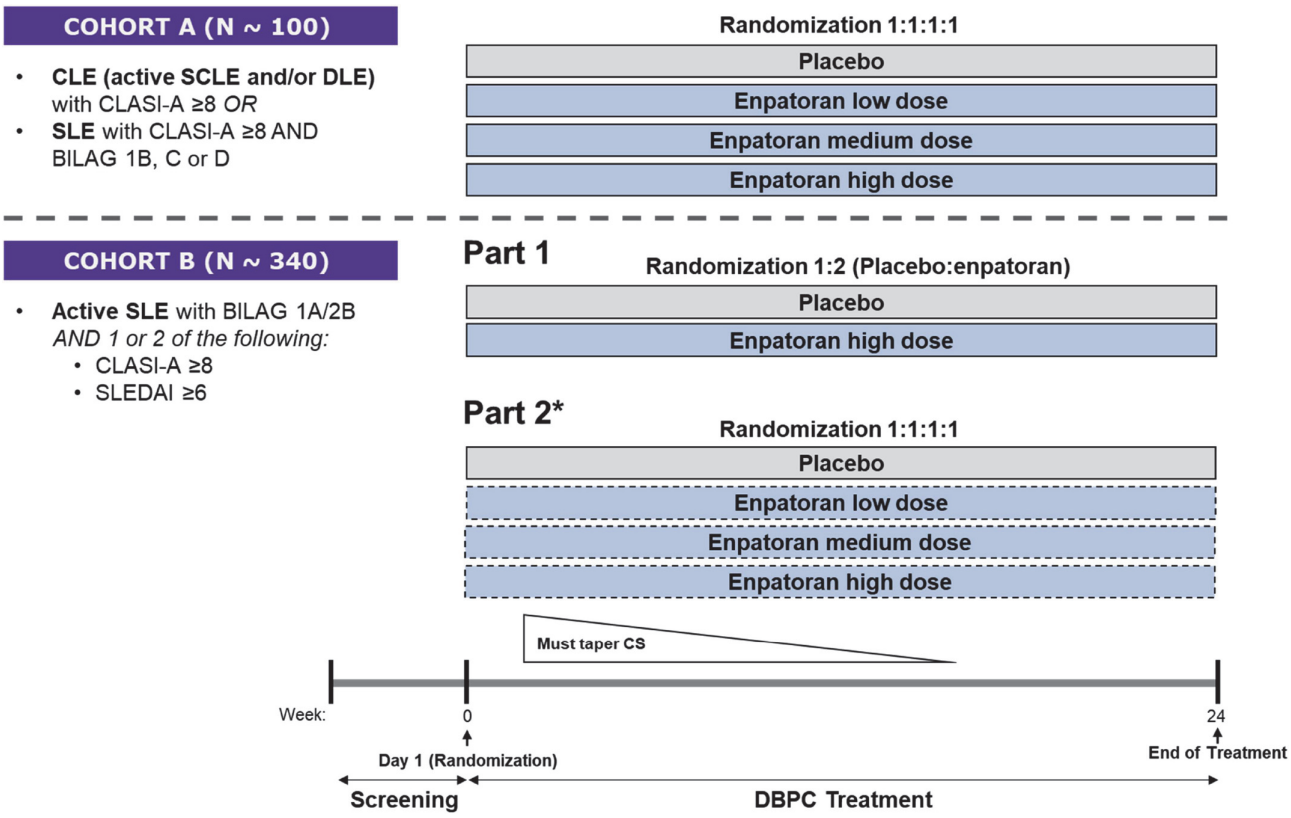
Purpose Enpatoran is a potent selective dual inhibitor of toll-like receptor (TLR) 7 and TLR8. Previous studies have shown aberrant activation of TLR7/8 may be involved in systemic lupus erythematosus (SLE) pathogenesis and glucocorticoid resistance. To assess whether enpatoran could be used in SLE management to avoid the detrimental effects of long-term corticosteroid use, we evaluated its glucocorticoid-sparing effect and designed a basket trial to assess its efficacy and safety in patients with SLE and/or cutaneous lupus erythematosus (CLE).

Methods Cytokine concentrations and gene expression changes were measured in stimulated human peripheral blood mononuclear cells (PBMCs) from healthy donors after treatment with dexamethasone, TLR7/8 inhibitor, or both. A Phase II basket design, proof-of-concept, dose-finding study in patients with SLE and/or CLE (WILLOW) was designed.

Results In healthy donor PBMCs, synergy was observed between TLR7/8 inhibitor and dexamethasone. Combination treatment inhibited cytokine release (interleukin-6) with greater potency than either treatment alone and reduced the expression of nuclear factor-kappa B and interferon-regulated genes. WILLOW is a Phase II, basket proof-of-concept, dose-finding, randomized, double-blind, placebo-controlled 24-week study with two cohorts (NCT05162586, figure 1). The primary objectives of WILLOW are to evaluate the dose–response relationship of enpatoran in reducing disease activity based on Cutaneous Lupus Erythematosus Disease Area and Severity Index-A (CLASI-A) or BILAG- Based Composite Lupus Assessment (BICLA) response rate. The secondary objectives are to investigate effects on both BICLA response and clinically meaningful corticosteroid reduction and evaluate disease control (including clinically meaningful corticosteroid reduction) in patients with predominantly active CLE or SLE. Cohort A will enroll patients with CLE (active subacute CLE and/or discoid LE) or SLE with predominantly active lupus rash. Cohort B, in two parts, will enroll SLE patients with moderate-to-severe systemic disease activity. Part 1 will assess clinical signal



Abstract 1501 Figure 1 WILLOW study design. Cohort A and Cohort B Part 1 will start in parallel. *Part 2 will be initiated after a pre-specified number of patients are enrolled in Part 1; enpatoran doses in Part 2 may be adapted to improve dose finding (dashed boxes).
BILAG, British Isles Lupus Assessment Group; CLASI-A, Cutaneous Lupus Erythematosus Disease Area and Severity Index-A; CLE, cutaneous lupus erythematosus; CS, corticosteroid; DBPC, double-blind placebo-controlled; DLE, discoid lupus erythematosus; SCLE, Subacute cutaneous lupus erythematosus; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

and Part 2 may be adapted to improve dose finding. Glucocorticoid-sparing will be evaluated by mandatory tapering to a prednisone-equivalent dose of ≤5 mg/day.
Conclusions Enpatoran is a novel TLR7/8 inhibitor and may enable glucocorticoid dose reduction in patients with SLE and CLE. The WILLOW study incorporates multiple novel elements including a basket design and evaluation of glucocorticoid-sparing.

1601 NO INCREASED RISK OF ARRHYTHMIA AMONG PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS OR RHEUMATOID ARTHRITIS USING HYDROXYCHLOROQUINE

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Background Hydroxychloroquine (HCQ) is a cornerstone medication for the treatment and management of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and other autoimmune rheumatic diseases. Previous studies have found an association between HCQ use and risk of arrhythmias, however the evidence is limited by small sample sizes and selected populations; additionally, findings have been contradictory. We assessed the risk of arrhythmias among new users of HCQ in newly diagnosed SLE and RA patients.
Methods We used administrative health databases from the entire province of British Columbia, Canada covering January 1997 to March 2015 to identify all patients who met the following criteria: 1) incident SLE or RA; 2) no arrhythmic events or use of anti-arrhythmic medications; and 3) no HCQ use prior to the disease index date. Eligible individuals were separated into HCQ initiator and HCQ non-initiator groups, matched 1:1 by propensity scores using baseline confounders of demographics including presence of SLE or RA disease and duration of disease prior to the index date, comorbidities, other medications, and healthcare utilization. Matching was done within the same calendar year to account for a potential secular trend in HCQ use and risk of arrhythmia. The outcomes assessed were any new arrhythmias, atrial fibrillation, abnormal electrocardiogram including prolonged QT syndrome and conduction disorder, and other unspecified arrhythmias during follow-up. Cox proportional hazard models with death as a competing event were used to assess the association of HCQ initiation and the outcomes.
Results We identified 11,518 HCQ initiators (863 SLE and 10,655 RA patients, mean ± SD age 55.9 ± 15.1 years, 76.1% female) and 11,518 HCQ non-initiators (879 SLE and 10,639 RA patients, mean ± SD age 56.0 ± 16.2 years, 76.4% female) after 1:1 propensity score matching. Over the mean follow-up of eight years, there were 1,610 and 1,646 incident arrhythmias in the HCQ initiator and non-initiator groups, respectively. The crude incidence rates of arrhythmia