

PO.6.135 ENPATORAN: PRECLINICAL EVIDENCE SUPPORTING GLUCOCORTICOID DOSE REDUCTION AND PHASE II STUDY DESIGN IN PATIENTS WITH SLE AND/OR CLE (WILLOW)

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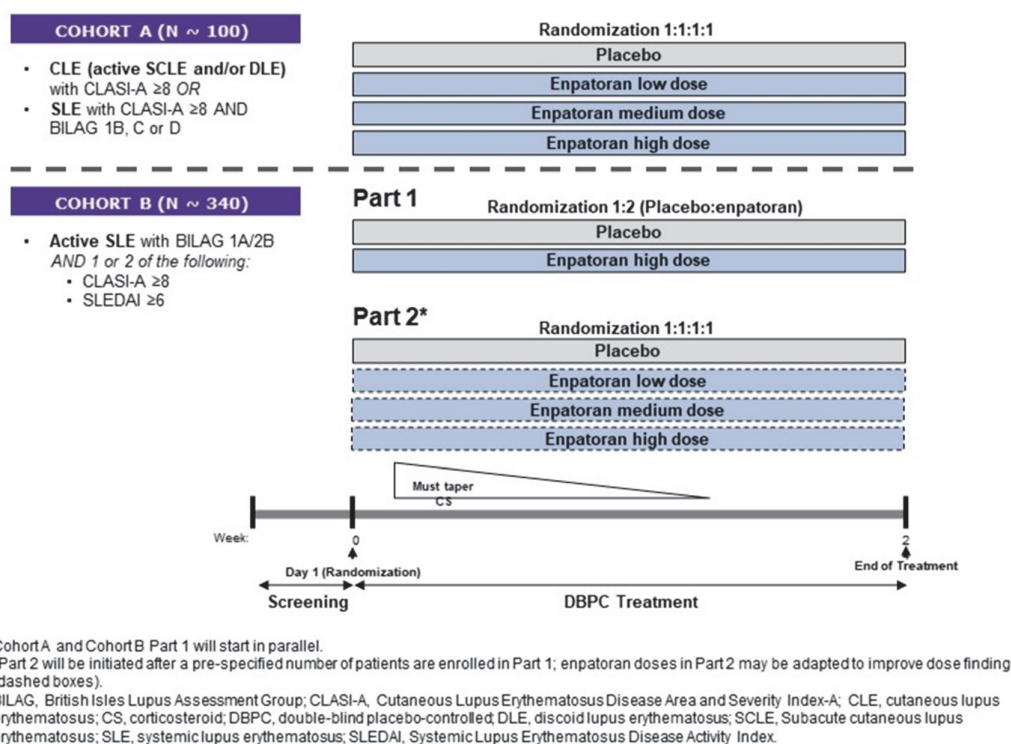
Purpose Enpatoran is a potent selective dual inhibitor of toll-like receptor (TLR) 7 and TLR8. Previous studies have shown aberrant activation of TLR7/8 may be involved in systemic lupus erythematosus (SLE) pathogenesis and glucocorticoid resistance. To assess whether enpatoran could be used in SLE management 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 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.



Abstract PO.6.135 Figure 1 WILLOW study design