Enpatoran: preclinical evidence supporting glucocorticoid dose reduction and Phase II study design in patients with SLE and/or CLE (WILLOW)

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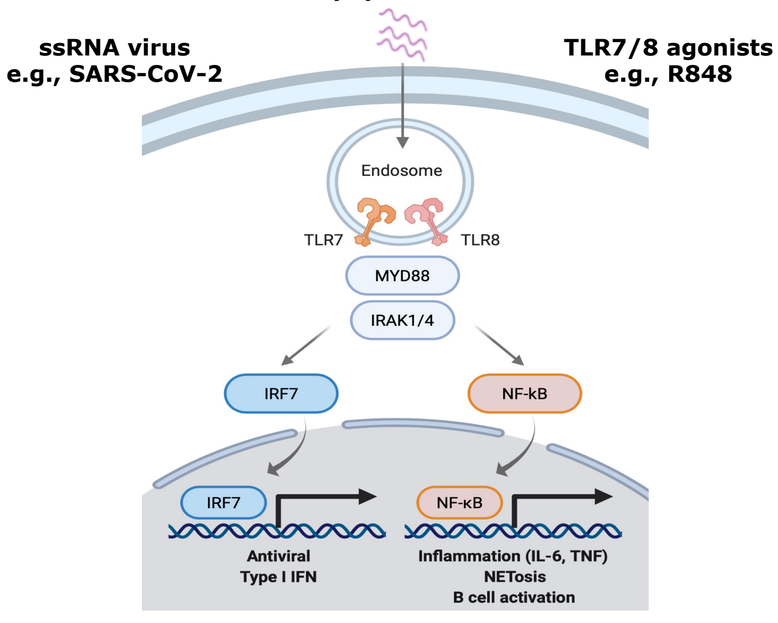
CONCLUSIONS

In preclinical experiments, we found that TLR7/8i and glucocorticoids can synergistically reduce human immune cell activation *in vitro*

WILLOW, a Phase II basket trial in SLE and CLE, will clinically determine if TLR7/8i enpatoran has a glucocorticoid-sparing effect

INTRODUCTION

- TLR7/8 are activated by **internalized ssRNA** from pathogens or endogenous ssRNA that is normally restricted within cells **(Figure 1)**[1]
- **Aberrant TLR7/8 activation** is thought to be involved in SLE and CLE pathogenesis and glucocorticoid resistance[2]



- **TLR7/8i may increase glucocorticoid potency** by inhibiting IRF- and NF-κB-mediated cytokine release (IFN-I and IL-6/TNFα)[2]

ENPATORAN

- **Novel, selective TLR7/8 inhibitor** for autoimmune diseases including SLE and CLE[3]
- **Well tolerated** by healthy participants and patients hospitalized with COVID-19 pneumonia in clinical studies, with no dose-dependent effects on adverse events[4,5]

OBJECTIVE

To evaluate the glucocorticoid-sparing effect of enpatoran

METHODS

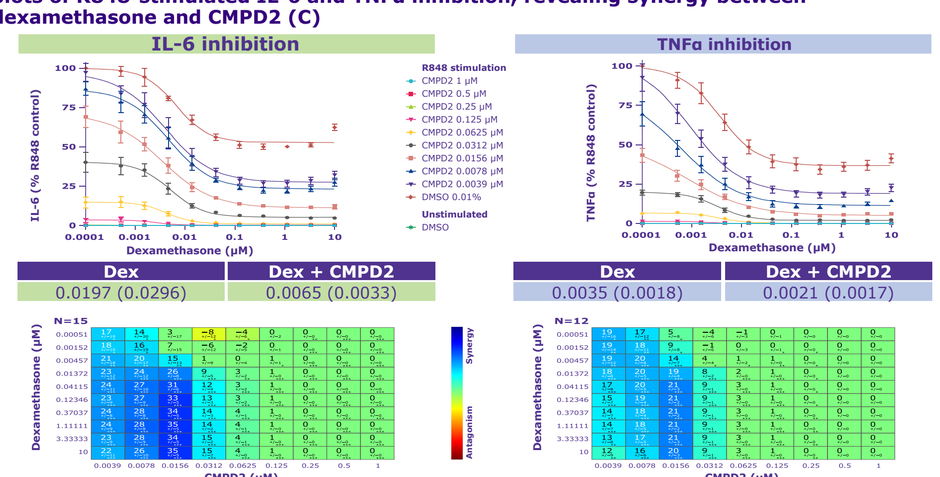
- **PBMCs from healthy donors** were stimulated with the TLR7/8 agonist R848 (3–5 μM) and treated with dexamethasone, TLR7/8i (CMPD2)[3], or both
  - **Cytokine (IL-6, TNFα) concentrations** were measured using an AlphaLISA immunoassay
  - NanoString **gene expression analysis** was performed
  - Effects on **immune cells** were evaluated by flow cytometry

RESULTS

Cytokines

- Dexamethasone partially inhibited cytokine production in R848-stimulated PBMCs, suggesting that **TLR7/8 activated cells are resistant** to dexamethosone (**Figure 2A;** DMSO 0.01%)
- TLR7/8i increased steroid potency on inhibition of R848-induced IL-6 and TNFα production (**Figure 2A and B**); TRL7/8i and dexamethasone demonstrated **synergistic potential** in PBMCs (**Figure 2C**)

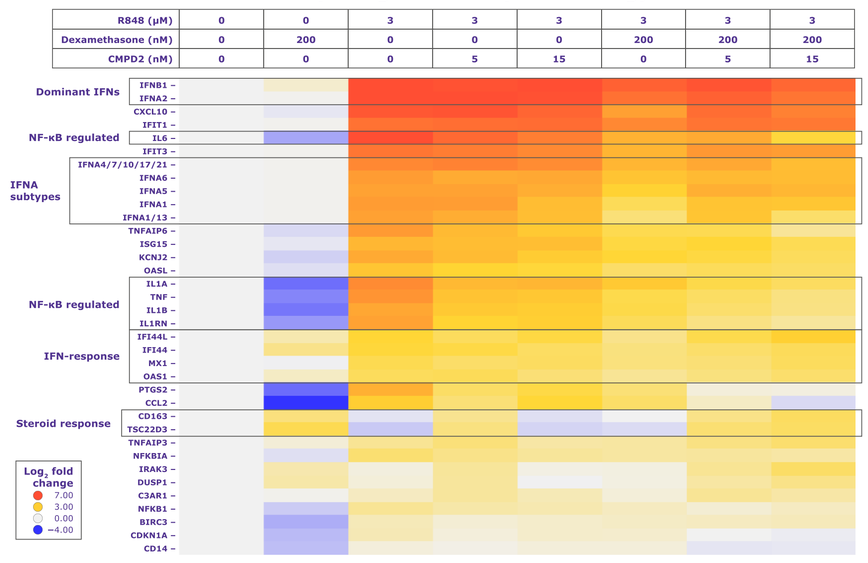
Figure 2. R848-stimulated IL-6 and TNFα inhibition by combination of dexamethasone and CMPD2 (A). Tables show mean (SD) 50% inhibitory concentration (μM) for R848-induced IL-6 and TNFα inhibition by dexamethasone alone or with 0.0078 μM CMPD2 (B). Loewe matrix plots of R848-stimulated IL-6 and TNFα inhibition, revealing synergy between dexamethasone and CMPD2 (C)



Gene expression

- R848 strongly induced canonical NF-κB and IFN-I response genes and overrode suppression by dexamethasone alone. Dexamethasone-induced steroid response genes were suppressed by R848 **(Figure 3)**
- **Reversal of R848-induced effects** was maximized by TLR7/8i and dexamethasone together, particularly for NF-κB-regulated genes

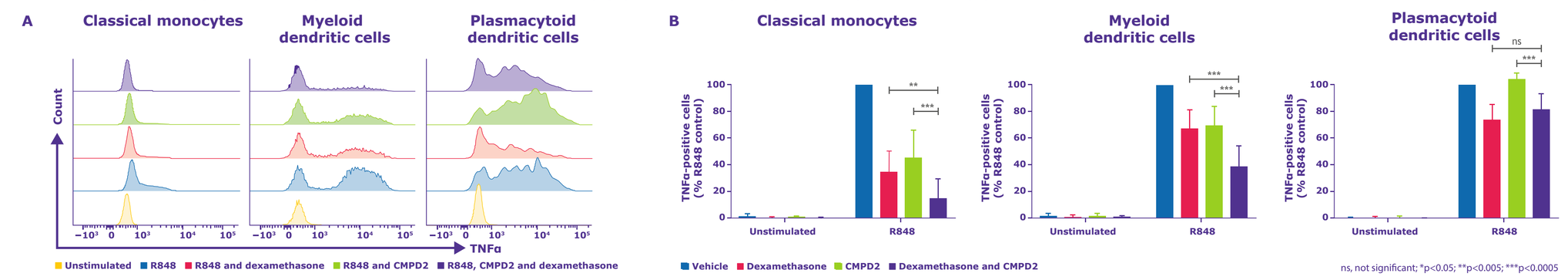
Figure 3. Gene expression analysis of R848-stimulated (1.5 h) PBMCs treated with dexamethasone and CMPD2 (data generated by NanoString)



Immune cells

- **Benefit of combination treatment** with low dose TLR7/8i and dexamethasone was best seen in **monocytes (Figure 4)**

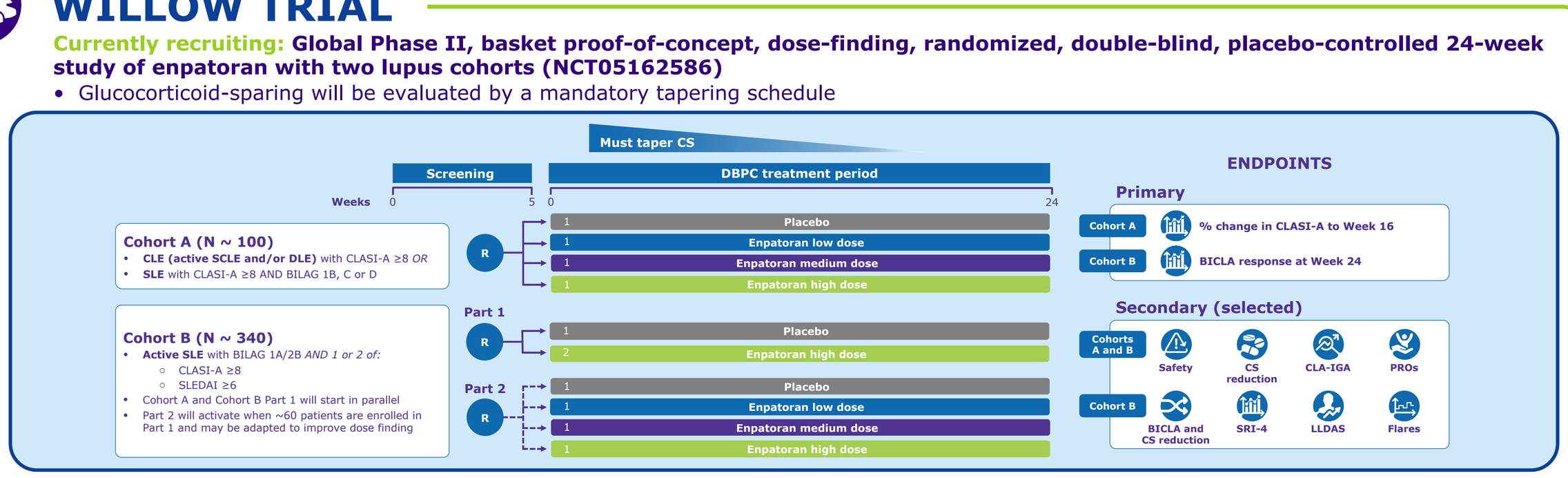
Figure 4. PBMCs were stimulated with R848 (3 μM, 4 h) and TNFα-positive immune cells were measured by flow cytometry (N=14) following single or combination treatment with low dose dexamethasone (200 nM) and CMPD2 (5 nM). Mean fluorescence intensity (A) and the frequency of TNFα-positive cells (B) were evaluated



WILLOW TRIAL

Currently recruiting: Global Phase II, basket proof-of-concept, dose-finding, randomized, double-blind, placebo-controlled 24-week study of enpatoran with two lupus cohorts (NCT05162586)

- Glucocorticoid-sparing will be evaluated by a mandatory tapering schedule



Abbreviations: BICLA, BILAG-Based Composite Lupus Assessment; **BILAG**, British Isles Lupus Assessment Group; **CLA-IGA**, Cutaneous Lupus Activity Investigator's Global Assessment; **CLASI**, Cutaneous Lupus Erythematosus Disease Area and Severity Index; **CLE**, cutaneous lupus erythematosus; **CMPD2**, compound 2; **COVID-19**, coronavirus disease 2019; **DBPC**, double-blind placebo-controlled; **DLE**, discoid lupus erythematosus; **DMSO**, dimethylsulfoxide; **IFN(-I)**, interferon (-type I); **IRAK1/4**, interleukin-1 receptor-associated kinase 4; **IRF7**, interferon regulatory factor 7; **IL-6**, interleukin-6; **LLDAS**, Lupus Low Disease Activity State; **MYD88**, myeloid differentiation primary response 88; **NETosis**, neutrophil extracellular trap death; **PBMCs**, peripheral blood mononuclear cells; **PROs**, patient reported outcomes; **R**, randomized; **SCLE**, subacute cutaneous lupus erythematosus; **SARS-CoV-2**, severe acute respiratory syndrome coronavirus 2; **SD**, standard deviation; **SLE**, systemic lupus erythematosus; **SLEDAI**, Systemic Lupus Erythematosus Disease Activity Index; **SRI-4**, SLE Responder Index-4; **ssRNA**, single-stranded RNA; **TLR7/8(i)**, toll-like receptor 7/8 (inhibitor); **TNFα**, tumor necrosis factor alpha

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