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Monotherapy with Filgotinib, a JAK1-Selective Inhibitor, Reduces Disease Severity and Alters Immune Cell Subsets in the NZB/W F1 Murine Model of Lupus

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SESSION INFORMATION

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Session Type: ACR Poster Session C

Session Title: Systemic Lupus Erythematosus – Animal Models Poster

Session Time: 9:00AM-11:00AM

Background/Purpose: SLE is a heterogeneous autoimmune disease characterized by immune system hyper-activation leading to the production of autoantibodies and immune attack on multiple organs including skin and kidney. Interferon α/β (IFNα/β) alter immune cell populations and are risk factors for SLE. Antibody blockade of the IFNa receptor has demonstrated clinical efficacy in SLE and validates targeting this pathway. JAK1 mediates signaling downstream of IFNa/b, and therefore an inhibitor of JAK1 is anticipated to reduce IFN signaling, normalize immune cell subsets, and improve SLE disease activity. The JAK1 selective inhibitor, filgotinib (FIL) is currently being evaluated in Ph2 studies in cutaneous lupus and Sjogren's syndrome. This work characterizes the disease efficacy and mechanism-of-action of FIL in the NZB/W F1 murine model of lupus.

Methods: FIL was tested in the NZB/W F1 murine model of lupus at two concentrations (0.05% and 0.1%) formulated in chow and administered ad libitum from weeks 28-40. Cyclophosphamide was used as a positive control. Efficacy was determined by proteinuria, renal histopathology, clinical pathology, and survival. Splenic lymphocyte and myeloid subsets were analyzed by flow cytometry at study termination. Kidney gene expression was determined by qPCR, and serum cytokines by Luminex. An in vitro murine whole blood pSTAT assay and PK were used to establish a PD-PK-efficacy correlation.

Results: In the model, FIL dose-responsively decreased proteinurea and renal inflammation, improved glomerular morphology and renal function, and increased survival. Diseased mice had increased $CD11^{+}$ dendritic cells (DCs), decreased naive T cells, and increased ratio of memory:naive T cell populations versus non-diseased mice. FIL showed a reversal of these cell populations toward non-diseased levels. Consistent with the reduction of inflammation, FIL demonstrated reduction of pro-inflammatory cytokines (eg., TNFα, IL-6, IL-18, IL12p70, and IL9) and chemokines (eg., CXCL1, CXCL10, MIP1β, MCP1 and MCP3), and an increase of IL-4. FIL normalized renal expression of genes for structural damage, apoptosis, complement system, and nucleic acid sensing. Importantly, among the 16 type I interferon signature genes (ISGs) measured, 12 showed a dose-responsive decrease

with FIL treatment. Calculated whole blood pSTAT inhibition is consistent with FIL pSTAT coverage achieved in clinical studies.

Conclusion: FIL demonstrated efficacy in reducing disease activity in a murine model of lupus nephritis. This effect was coupled with normalization of splenic cell subsets, ISGs, and cytokines, and provides a mechanistic basis for the evaluation of FIL in the current clinical Phase 2 studies.

Disclosure: P. Han, Gilead Sciences, 1, 3; **C. Pohlmeyer**, Gilead Sciences, 1, 3; **C. Shang**, Gilead Sciences, 1, 3; **Z. Cui**, Gilead Sciences, 1, 3; **D. Lopez**, Gilead Sciences, 1, 3; **A. Clarke**, Gilead Sciences, 1, 3; **R. Jones**, Gilead Sciences, 1, 3; **N. Mollova**, Gilead Sciences, 1, 3; **I. Mikaelian**, Gilead Sciences, 1, 3; **D. Newstrom**, Gilead Sciences, 1, 3; **S. Zaboli**, Gilead Sciences, 1, 3; **A. Shauf**, Gilead Sciences, 1, 3; **J. Di Paolo**, Gilead Sciences, 1, 3.

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