



Abstract 8 Figure 2

Methods Patients with active (SLEDAI-2K \geq 6), autoantibody-positive SLE receiving standard therapy were randomised to weekly subcutaneous injections of atacicept (75 or 150 mg) or placebo for 24 weeks. **Results** In the ITT population (n=306), there was a trend towards improved SRI-4 response rates with both atacicept doses vs placebo at Week 24 (primary analysis, Screening as baseline). In a sensitivity analysis using Day 1 as baseline, both atacicept doses significantly increased SRI-4 responses (Table 1). In patients with high disease activity (HDA, n=158), serologically active (SA) disease (n=84), or both (HDA SA, n=69), enhanced improvements in SRI-4 and SRI-6 response rates were seen with atacicept (Tables 1 and 2; Figure 1). Atacicept significantly reduced severe flares in the ITT (75 mg: BILAG A p=0.019; 150 mg: SLEDAI flare index [SFI] p=0.002) and HDA populations (75 mg: BILAG A HR=0.1, SFI HR=0.3; 150 mg: BILAG A HR=0.3, SFI HR=0.2; all p<0.05). At Week 24, serum IgG was reduced from baseline by ~25% and ~30% with atacicept 75 and 150 mg, respectively (Figure 2); serum complement C3 and C4 increased while IgM, IgA, and anti-dsDNA antibodies decreased with atacicept. Risk of SAEs and serious/severe infections did not increase with atacicept (Table 3). **Conclusions** Atacicept demonstrated evidence of efficacy in SLE, particularly in HDA and SA patients, with reduction in disease activity and severe flares, and showed a favourable safety profile.

Plenary Session 4: Cutting edge science in SLE

9 BIM SUPPRESSES THE DEVELOPMENT OF SLE BY LIMITING MACROPHAGE INFLAMMATORY RESPONSES

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Background and aims There are numerous endogenous Bcl-2 antagonists that share similar homology, structure, topology and expression pattern, yet only the loss of Bim in mice is sufficient to lead to the development of a systemic autoimmunity.

Methods We investigated the contribution of Bim in monocytes/macrophages and its effect on systemic autoimmunity by establishing conditionally Bim-deleted mice in the monocyte/

macrophage compartment (Cre^{LysM}Bim^{fl/fl} mice) and examined the development of lupus-like disease over time.

Results Patients with lupus display decreased expression of Bim in circulating monocytes and reduced Bim expression in kidney macrophages. Cre^{LysM}Bim^{fl/fl} mice develop a lupus-like disease that mirrors aged Bim^{-/-} mice including loss of the marginal zone macrophages, splenomegaly, lymphadenopathy, autoantibodies including anti-DNA IgG, and a type I interferon signature as compared to control mice. Cre^{LysM}Bim^{fl/fl} mice also exhibit increased mortality attributed to immune complex deposition and increased numbers of kidney macrophages all of which contribute to glomerulonephritis. The loss of Bim in macrophages is sufficient to break tolerance as adoptive transfer of wild-type lymphocytes into Cre^{LysM}Bim^{fl/fl} Rag^{-/-} mice leads to systemic autoimmunity. We also identified that the loss of TLR signalling adaptor protein TRIF but not MyD88 is essential for progression to GN phase but is dispensable for systemic autoimmunity. RNA seq analysis of sorted kidney macrophages revealed a novel Bim and lupus specific signatures.

Conclusions These data add another facet to the conventional dogma that Bim's central role in autoimmune disease is to prevent the escape of autoreactive lymphocytes from apoptosis. Thus, Bim may be a novel therapeutic target for treating SLE.

10 SINGLE CELL EXPRESSION QUANTITATIVE TRAIT LOCI (EQTL) ANALYSIS OF ESTABLISHED LUPUS-RISK LOCI IN PATIENT MONOCYTES

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Background and aims While most of the confirmed SLE-risk loci are in or near genes with immune system function, a major unanswered question is how these loci influence diverse immune cell subsets.

Methods CD14⁺CD16⁻ classical monocytes (CL) and CD14^{dim}CD16⁺ non classical (NCL) monocytes from SLE patients were purified by magnetic separation. The Fluidigm C1 System was used for single cell capture and target gene pre-amplification and equal numbers of classical and non-