Background: Systemic lupus erythematosus (SLE) clinical trials are challenged by high placebo response rates. Subgroup analyses of historic SLE clinical trial data have identified acute flares with normal complement levels as potential predictors of high placebo response.

Objectives: To assess the treatment effect of daprolizumab pegol (DZP; a polyethylene glycol conjugated antigen-binding fragment lacking a functional Fc domain, which inhibits the CD40–CD40 ligand interaction) in patients from the phase 2b trial in SLE.1 who fulfilled one or both of the characteristics identified as potential predictors of placebo response.

Methods: Post hoc analyses were performed on data from a phase 2b trial (NCT02804763), in which patients received placebo or DZP (6/24/45 mg/kg), alongside standard of care (SOC) for 24 weeks.1 Efficacy was compared between two subgroups: (1) acute flare with low C3/C4 or persistent disease activity, vs (2) acute flare without low C3/C4. In the subgroup analyses, disease activity screening was defined using British Isles Lupus Assessment Group (BILAG) 2004 item level scores either as acute flare (worsening/new symptoms) or persistent (symptoms rated as the same) based on the past 4 weeks compared with the 4 weeks prior to those, and low C3/C4 was defined as below the lower limit of normal at screening. Outcomes assessed were BILAG-based Composite Lupus Assessment (BICLA) response, SLE Responder Index-4 (SRI-4) response, and change from baseline in Physician's Global Assessment (PGA) at Week 24. Binary outcomes were analysed using logistic regression (p-values reported for odds ratio vs acute flare without low C3/C4), and continuous outcomes were analysed using mixed models with repeat measures (p-values reported for difference vs acute flare without low C3/C4).

Results: Figure 1a and 1b show BICLA responses in the subgroups over time; similar patterns were seen for the other outcomes. At Week 24, higher BICLA response rates were achieved across all treatment arms in the acute flare without low C3/C4 subgroup compared with the other subgroup (Figure 1c). This pattern was particularly evident in patients receiving SOC plus placebo, where there was a significant 3-fold difference in BICLA response rates between the subgroups (80.0% vs 24.2%; p=0.005). Patients who received SOC plus placebo in the acute flare without low C3/C4 subgroup also achieved numerically higher SRI-4 response rates than the acute flare with low C3/C4 or persistent disease activity subgroup. A similar pattern was observed for patients who received SOC plus 6 mg/kg DZP; however, comparable SRI-4 response rates were observed between subgroups in patients who received SOC plus 24/45 mg/kg DZP (Figure 1d). At Week 24, greater changes from baseline in PGA were achieved in patients receiving SOC plus placebo in the acute flare without low C3/C4 subgroup than in the acute flare with low C3/C4 or persistent disease activity subgroup (least squares mean: −42.0 vs −24.9; p=0.028). Comparable changes in PGA were seen between subgroups for patients receiving SOC plus DZP (Figure 1e).

Conclusion: Despite the limited sample size, patients with acute flare with normal complement levels were more likely to achieve responses to SOC plus placebo, diminishing the DZP treatment effect. These data suggest that SLE trial design may need to consider baseline clinical and serologic activity patterns to adequately assess treatment efficacy.

Keywords: Systemic lupus erythematosus, Clinical Trials

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Characteristics. This is clinically relevant given the lack of safe and effective therapies for patients with high proteinuria.

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**POS0117**

**REMBRIBUTIN SPECIFICダウンREGULATES MARKERS OF MEMORY B CELL SUBSETS IN SJÖGREN'S PATIENTS (SJS) IN THE LOUİSSe PHASE 2 CLINICAL TRIAL**

**Keywords:** Biomarkers, Sjögren syndrome, Clinical Trials

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**Background:** Remibrutinib is a selective, covalent and potent inhibitor of Bruton’s tyrosine kinase (BTK) in development for several autoimmune and auto-allergic indications showing promising clinical safety and efficacy (Kaul et al. 2021, Maurer et al. 2022). Sjögren’s (SJS) is a chronic autoimmune disorder characterized by dryness in the eyes and mouth, fatigue, joint pain, and reduced quality of life (Mariette et al. 2018). Remibrutinib may be particularly promising for the treatment of SJS due to its ability to target underlying B cell abnormalities and showed promising efficacy in a Ph2 SjS trial (Dörner et al. 2022).

**Objectives:** The aim of this exploratory biomarker study within the LOUİSSe trial was to identify protein and transcript signatures in the blood of patients with active SJS that are associated with remibrutinib treatment.

**Methods:** We conducted the LOUİSSe Ph2 clinical trial (NCT04335668) to evaluate the safety and efficacy of remibrutinib in patients with moderate to severe SJS. The study design was a randomized, double-blind, placebo-controlled, multi-center trial. Blood samples were collected at baseline and 24 weeks after treatment began. Protein profiles were generated using a Multiplex 7K aptamer profiling, and transcriptomics analysis was performed on RNA extracted from whole blood. By comparing the treatment and the placebo groups over time using multivariate linear regression models, we identified proteins and genes that were differentially modulated by remibrutinib. The gene signature identified by Yao et al. (2009) was used as a reference for the interferon signature.

**Results:** We observed a consistent downregulation of 35 proteins associated with B cell activity, including CD23, FCR1, FAIM3, and FCRL4, in all treatment groups receiving remibrutinib compared to the placebo group after 24 weeks of treatment. These modulated proteins are involved in multiple pathways related to B-cell activation and function, including B-cell receptor signaling, Fc receptor signaling, and platelet activation. Whole blood bulk mRNA sequencing revealed that remibrutinib treatment groups showed a significant downregulation of a 34-gene signature, most of which are known to be important for B-cell activation and immunoglobulin production. The top two most significantly downregulated genes, FCRL5 and SOX5, were previously identified as being highly enriched in a circulating tissue-like memory B-cell subset. This observation is also corroborated by the proteomics profiling analysis, where FCRL4 known to co-localize in the same memory B-cell subset (Verstappen et al. 2020, Götz et al. 2008), was strongly decreased by the treatment. Despite the specific and strong effects on B-cells, estimation of cell type proportions using RNA-seq revealed no significant changes, suggesting that remibrutinib does not affect the overall B-cell numbers and the relative proportions of its major subsets, like plasma cells, naïve and memory B-cells. Results from both proteomics and transcriptomics profiling suggest that remibrutinib treatment does not modify the interferon signature.

**Conclusion:** Our analysis of serum proteins and whole blood transcripts showed that remibrutinib treatment was associated with a significant downregulation of proteins and genes enriched in FCRL4+ B cells, a subset of tissue-resident memory B cells that are expanded in inflamed tissues and found in the salivary glands of SJS patients. These findings suggest that remibrutinib may have a particularly strong inhibitory effect on this subset. Additionally, many genes and proteins involved in B-cell activation, differentiation, and maturation were also downregulated, indicating that remibrutinib has a potent effect on multiple B-cell pathways.

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**POS0118**

**ADDING HYDROXYCHLOROQUINE IN REFRACTORY OBSTETRIC APS: OBSTETRIC OUTCOMES IN 182 PREGNANCIES**

**Keywords:** Anti-phospholipid syndrome, Pregnancy and reproduction

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**Background:** Pregnancy complications in obstetric APS (OAPS) include recurrent early pregnancy loss, fetal death, or premature birth due to preeclampsia,