Dapirolizumab Pegol Impacts Important Immunologic Pathways in Systemic Lupus Erythematosus: Pharmacodynamic Analysis of T Cell and Antigen Presenting Cell Pathways from a Phase 2b Trial

Alex S. Powlesland,[1]* Ioana Cutcutache,[1] Andrew Skelton,[1] Anthony Shock,[1] Matthew Page,[1] Eris Bame,[2] Janine Gaiha-Rohrbach,[2] George Stojan,[3] Ania Skowera,[1] Christian Stach,[4] Thomas Dörner[5]

[1]UCB, Slough, UK; [2]Biogen, Cambridge, MA, USA; [3]UCB, Atlanta, GA, USA; [4]UCB, Monheim am Rheim, Germany; [5]Department of Medicine/Rheumatology and Clinical Immunology, Charité Universitätsmedizin Berlin, Berlin, Germany; *Affiliation at the time of publication development

To receive a copy of this poster, scan the QR code
Poster ID: 2430
Link expiration: February 17, 2025

Objective

To explore the impact of dapirolizumab pegol (DZP) on T cell responses and serum cytokine levels related to antigen-presenting cell (APC) pathways using molecular data from the phase 2b RISE trial in systemic lupus erythematosus (SLE).

Background

- CD40-CD40L interactions play a pivotal role in SLE pathogenesis by orchestrating a range of immune and inflammatory responses involving B cells, T cells, and APCs (**Figure 1**).[1]
- DZP is a novel, polyethylene glycol (PEG)-conjugated antigen-binding (Fab') fragment, lacking an Fc domain, that inhibits CD40L signaling,[2] and is under investigation in individuals with SLE in a phase 3 trial (PHOENYCS FLY; NCT04976322).
- This post hoc pharmacodynamic analysis explores the impact of DZP on T cell and APC pathways using molecular data from a subgroup of participants from the randomized, placebo (PBO)-controlled phase 2b trial in SLE (RISE; NCT02804763).[2]
  - In RISE, the primary objective of establishing a dose-response relationship was not met, however, DZP was associated with improvements in several measures of disease activity, including improved British Isles Lupus Assessment Group (BILAG)-Based Composite Lupus Assessment (BICLA) response rate and reduced BILAG severe flares from baseline.[2] DZP had an acceptable safety profile and was generally well tolerated.[2]

Methods

- In RISE, participants received PBO or DZP (6/24/45 mg/kg) alongside standard of care (SOC) for 24 weeks; adults with active SLE with moderate-to-severe disease manifestations, receiving stable doses of SOC treatments (corticosteroids, antimalarials, and immunosuppressants), were included in the trial.[2]
- Analyses presented here focused on a subgroup of participants from RISE similar to the PHOENYCS GO population, namely those who had acute flare with low complement or persistent disease activity (n=131), which were previously identified as predictors of a lower response to PBO+SOC.[3] Results are shown for the PBO and DZP 24 mg/kg arms.
- Protein analysis was conducted on serum samples at baseline and Weeks 2, 8, and 24, using the Olink® Target 96 Inflammation panel of protein biomarkers. RNA sequencing was performed on blood samples at baseline and Weeks 2, 4, 12, and 24.
- Gene expression changes were analyzed for pathways relevant to SLE immunopathology using competitive gene set tests.[4]
- Participants were stratified post hoc by baseline T cell-associated gene expression using a T cell gene signature derived from single cell gene expression data.[5]

Results

- Of the 92 proteins measured, DZP 24 mg/kg significantly downregulated key inflammatory proteins at various timepoints versus baseline, compared with PBO versus baseline (**Figure 2**).
  - Four proteins (CCL19, IL-12B, TNFRSF9 (CD137), and TNFA) were significantly downregulated across all timepoints and three proteins (TNFB, CXCL9, and CD6) were significantly downregulated at Week 2 and Week 8 (**Figure 3**).
  - Downregulated proteins were associated with T cell activation, including the co-stimulatory proteins IL12B (primarily produced by professional APCs)[6] and TNFSFR9 (CD137), and CCL19 and CXCL9 chemokines.
- Given the known heterogeneity of SLE samples, a subset of the cohort was selected based on T cell-associated gene expression to focus on participants with active T cell biology.
  - At baseline, across all treatment arms, a bimodal distribution was observed, with 54/120 (45%) participants showing high T cell-associated gene expression (**Figure 4A**).
  - In these participants, DZP 24 mg/kg significantly downregulated expression of genes related to biological pathways associated with T cell activation and related adaptive immune processes, including antigen processing/presentation and type II interferon (IFN-γ) responses (**Figure 4B**).
- All effects described across both analyses were observed as early as Week 2 following a single DZP dose.

Conclusions

Beyond the known effects of DZP in suppressing expression of gene sets related to B cell activation, immunoglobulin production, and type I IFN biology reported previously,[7] the data presented here demonstrate the targeted and rapid inhibitory effects of DZP on T cell activation, antigen processing/presentation, and pro-inflammatory cytokines, such as IFN-γ, involved in adaptive immune responses related to SLE. These findings support the broad mechanism of action of DZP in modulating multiple aspects of SLE immunopathology.

Figure 1 The CD40-CD40L pathway in SLE immunopathology

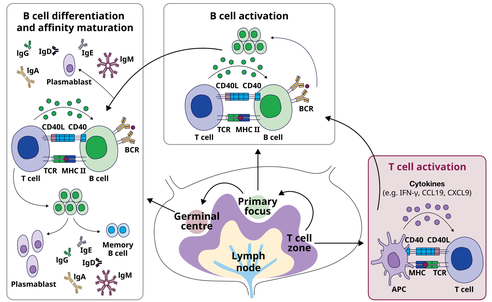
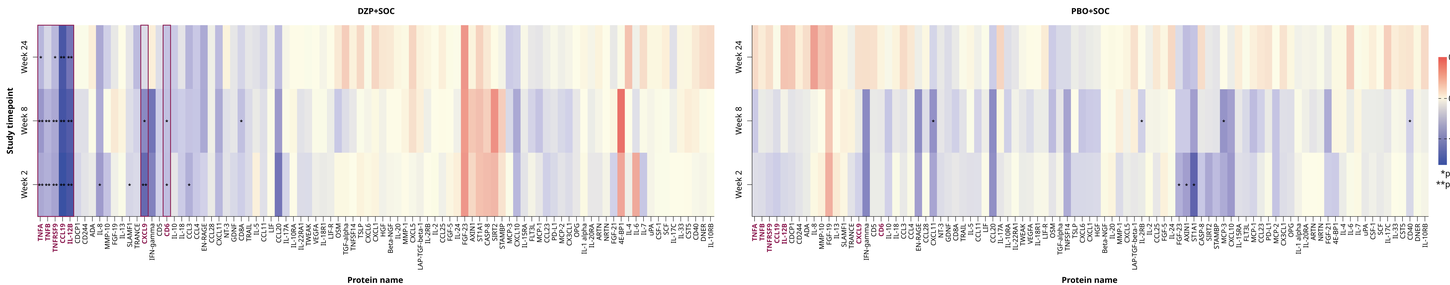
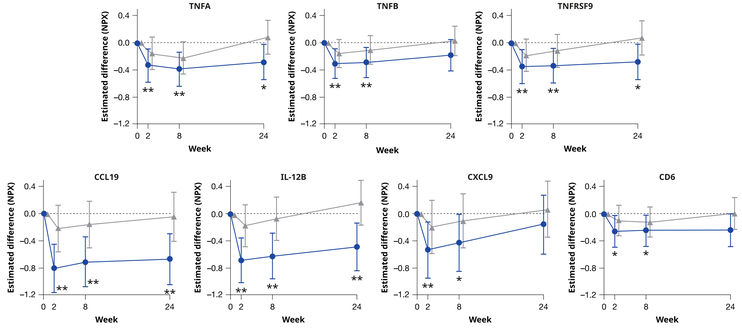


Figure 2 Heatmap presenting the effect of DZP+SOC compared with PBO+SOC on serum proteins



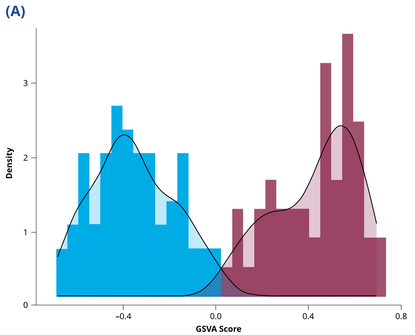
Serum samples taken at Weeks 0, 2, 8, and 24 were randomized prior to analysis, with all samples measured in a single testing batch. Protein values were corrected using extension controls, with an intensity-based normalization applied across the whole cohort in order to generate normalized expression values (NPX). Values presented in the heatmap correspond to the averaged standardized change of NPX with respect to baseline over time and by treatment. Dunnet adjusted p values are indicated for significant differences between DZP+SOC versus baseline and PBO+SOC versus baseline for each timepoint, with * indicating p<0.05 and ** indicating p<0.01. Proteins with significant differences compared to baseline at more than one timepoint with DZP+SOC are indicated with red labels and boxes.

Figure 3 Effect of DZP+SOC compared with PBO+SOC on serum proteins related to T cell and APC biology

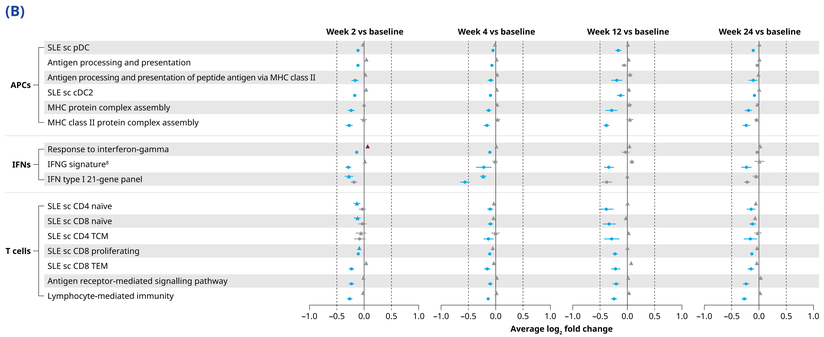


Serum samples taken at Weeks 0, 2, 8, and 24 were randomized prior to analysis, with all samples measured in a single testing batch. PBO+SOC and DZP+SOC: baseline: n=28; Week 2: n=28; Week 8: n=27; Week 24: n=26. Samples were not available for all participants at all timepoints. Protein values were corrected using extension controls, with an intensity-based normalization applied across the whole cohort, in order to generate NPX. Values presented correspond to the estimated difference in NPX value with respect to baseline over time, with error bars representing 95% CIs. Dunnet adjusted p values are indicated for significant differences between DZP+SOC versus baseline and PBO+SOC versus baseline for each timepoint, with * indicating p<0.05 and ** indicating p<0.01.

Figure 4 (A) Distribution of participant T cell-associated gene expression at baseline and (B) longitudinal effect of DZP+SOC and PBO+SOC on the expression of gene sets related to T cells and APCs in participants with high T cell-associated gene expression at baseline



The T cell gene signature was derived from an SLE single cell gene expression dataset.[5] Participants were stratified post hoc into two groups based on the baseline expression of this signature (GSVA scores) using k-means clustering. Black lines represent the density curves in the two subpopulations.



Pathways relevant to SLE immunopathology were selected from Gene Ontology Biological Processes and augmented with gene signatures that discriminate immune cell types in SLE.[4,9] DZP+SOC data were adjusted to account for SOC effects in an additive model via the PBO arm using the *limma* framework.[10] PBO+SOC: baseline: n=15; Week 2: n=15; Week 4: n=12; Week 12: n=14; Week 24: n=13. DZP+SOC: baseline: n=10; Week 2: n=10; Week 4: n=8; Week 12: n=10; Week 24: n=10. Each data point is a gene set, blue indicates significantly downregulated gene sets, red indicates significantly upregulated gene sets, and gray represents no significant change. The error bars represent the 95% CI; where error bars are not visible, this is due to small variability. Dashed lines represent 1.5-fold change; black lines at 0 represent 1-fold change. Only datapoints for which FDR<0.05 after treatment with DZP+SOC are shown.

APC: antigen-presenting cell; **BCR:** B cell receptor; **BICLA:** BILAG-Based Composite Lupus Assessment; **BILAG:** British Isles Lupus Assessment Group; **cDC2:** type 2 conventional dendritic cell; **CI:** confidence interval; **DZP:** dapirolizumab pegol; **FDR:** false discovery rate; **GSVA:** gene set variation analysis; **IFN:** interferon; **MHC:** major histocompatibility complex; **NPX:** normalized expression values; **PBO:** placebo; **pDC:** plasmacytoid dendritic cell; **sc:** single cell; **SLE:** systemic lupus erythematosus; **SOC:** standard of care; **TCM:** central memory T cell; **TCR:** T cell receptor; **TEM:** effector memory T cell.

References: [1]Ramanujam M. Autoimmun Rev 2020;19(1):102668; [2]Furie RA. Rheumatology (Oxford) 2021;60:5397–407; [3]Askanase A. Ann Rheum Dis 2023;82(suppl 1):272; [4]Wu D. Nucleic Acids Res 2012;40(17):e133; [5]Mandric I. Nat Commun 2020;11(1):5504; [6]Ullrich KA. EXCLI J 2020;19:1563–89; [7]Cutcutache I. Arthritis Rheumatol 2023;75(suppl 9); [8]Hall JC. Proc Natl Acad Sci 2012;109(43):17609–14; [9]Gene Ontology Consortium. Nucleic Acids Res 2021;49(D1):D325–34; [10]Ritchie ME. Nucleic Acids Res. 2015;43(7):e47. **Author Contributions:** Substantial contributions to study conception/design, or acquisition/analysis/interpretation of data: **ASP**, **IC**, **ASke**, **ASh**, **MP**, **EB**, **JGR**, **GS**, **ASko**, **CS**, **TD**; Drafting of the publication, or reviewing it critically for important intellectual content: **ASP**, **IC**, **ASke**, **ASh**, **MP**, **EB**, **JGR**, **GS**, **ASko**, **CS**, **TD**; Final approval of the publication: **ASP**, **IC**, **ASke**, **ASh**, **MP**, **EB**, **JGR**, **GS**, **ASko**, **CS**, **TD**. Please note that **ASP** is no longer employed by UCB, however, contributed to publication development. **Author Disclosures: ASP:** Former employee of UCB; **IC**, **ASke**, **ASh**, **MP**, **GS**, **ASko**, **CS:** Employees and shareholders of UCB; **EB**, **JGR:** Employees and shareholders of Biogen; **TD:** Speakers bureau for Novartis; consultant for AbbVie, Eli Lilly, Janssen, RocheGNE, and UCB. **Acknowledgments:** We would like to thank the participants and their caregivers in addition to all the investigators and their teams who contributed to this study. The authors acknowledge Agnes Koncz, MD, UCB, Brussels, Belgium, and Christine Nelson, PharmD, RPh, Biogen, Cambridge, MA, USA, for publication coordination; Sunandan Dhar, PhD, Patrick Cox, BSc, and Beverley Wilson, PhD, Costello Medical, UK for medical writing and editorial assistance, and the Costello Medical Creative team for graphic design assistance. This study was funded by UCB and Biogen. All costs associated with development of this presentation were funded by UCB and Biogen.