Dapirolizumab pegol treatment and improvement in laboratory markers of disease activity in patients with systemic lupus erythematosus: 48-week results from a phase 3 trial

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Objective

- **To evaluate changes from baseline and normalisation of levels of anti-dsDNA antibodies and complement proteins C3 and C4 in patients with systemic lupus erythematosus (SLE) treated with dapirolizumab pegol (DZP) in the phase 3 PHOENYCS GO trial.**

Introduction

- SLE is an autoimmune disease characterised by chronic inflammation and widespread organ damage, resulting from the immune system response to self-antigens.[1] Elevated anti-dsDNA antibodies and reduced complement proteins C3 and C4 are often associated with disease activity in SLE.[2]
- DZP is a novel CD40L inhibitor with broad modulatory effects on immune responses in SLE, including on B cells, T cells, antigen presenting cells, and type I and type II interferon signalling.[3,4] DZP consists of a polyethylene glycol (PEG)-conjugated antigen-binding fragment (Fab'), which lacks an Fc domain.
- In the phase 3 PHOENYCS GO trial (NCT04294667), the primary endpoint was met; DZP plus standard of care (DZP+SOC) resulted in a significantly higher rate of BICLA response versus placebo (PBO)+SOC at Week 48 (49.5% versus 34.6%; p=0.0110), alongside improvements in other clinical measures.[5] The PHOENYCS GO Primary manuscript is available now (see QR code in the bottom right corner). A confirmatory phase 3 trial (PHOENYCS FLY; NCT06617325) is ongoing (see QR code in the bottom left corner).

Methods

- PHOENYCS GO, a 48-week, randomised, double-blind, PBO-controlled trial, included patients aged ≥16 years with moderate-to-severe, active SLE characterised by persistently active or frequently flaring/relapsing-remitting disease activity despite stable SOC medication (antimalarials, glucocorticoids and/or immunosuppressants).
  - Patients were randomised 2:1 to intravenous DZP 24 mg/kg+SOC or PBO+SOC every 4 weeks.
- Anti-dsDNA antibody levels were measured using the Phadia EliA™ assay, and C3/C4 levels were measured using immunoturbidimetric assays.
  - Abnormal levels were defined as: anti-dsDNA >10 IU (ULN); C3 <830 mg/L (LLN); and C4 <150 mg/L (LLN).
- Analyses were conducted on the safety set, which included all randomised patients who received at least one dose of study medication; any data after treatment discontinuation or use of rescue treatment were set to missing.

Results

- The study was completed on treatment through Week 48 by 85.4% (182/213) of patients randomised to DZP+SOC and 79.6% (86/108) randomised to PBO+SOC.
- Baseline levels of anti-dsDNA, and complement proteins C3 and C4, were similar between the groups (**Table 1**).
- At baseline:
  - 42.7% of patients receiving DZP+SOC and 57.4% receiving PBO+SOC had abnormal levels of anti-dsDNA.
  - 30.5% of patients receiving DZP+SOC and 38.9% receiving PBO+SOC had abnormal levels of C3.
  - 54.9% of patients receiving DZP+SOC and 52.8% receiving PBO+SOC had abnormal levels of C4.
- Among patients with abnormal anti-dsDNA levels at baseline, improvements were greater with DZP+SOC compared with PBO+SOC (**Figure 1**).
  - Among these patients, a higher proportion of those receiving DZP+SOC (23.7%) achieved normal anti-dsDNA levels at Week 48 compared with those receiving PBO+SOC (7.9%; **Figure 2**).
- Similarly, among patients with abnormal baseline C3 and C4 levels, increases reflecting improvement were greater with DZP+SOC compared with PBO+SOC (**Figure 1**).
  - Among these patients, a higher proportion of those receiving DZP+SOC achieved normal C3 and C4 levels at Week 48 vs those receiving PBO+SOC (C3: 40.5% vs 28.6%; C4: 37.3% vs 18.8%; **Figure 2**).

Conclusions

Patients receiving DZP+SOC more frequently and consistently achieved normalisation of anti-dsDNA antibodies and complement proteins C3 and C4 than those receiving PBO+SOC.

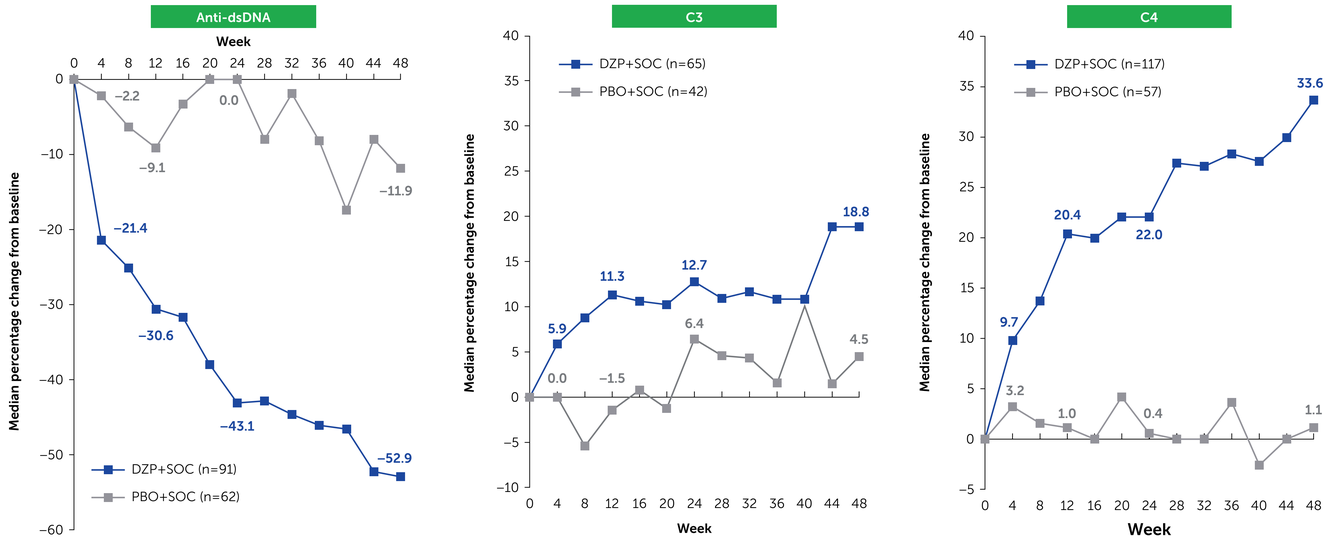
These findings build on previously reported data,[3,4] and suggest that DZP modulates important immune parameters in SLE, including anti-dsDNA, C3 and C4, which could help reduce deposition of immune complexes and complement activation.

Table 1 Baseline demographics, disease characteristics and immunologic parameters

	DZP+SOC n=208	PBO+SOC n=107
Age, years, mean (SD)	43.5 (12.3)	41.5 (12.4)
Female, n (%)	193 (92.8)	100 (93.5)
Time since diagnosis, years, mean (SD)	10.1 (7.9)	9.8 (8.5)
SLEDAI-2K total score, mean (SD)	10.7 (3.5)	11.2 (3.4)
SLEDAI-2K ≥10, n (%)	140 (67.3)	79 (73.8)
BILAG-2004 total score, mean (SD)	18.4 (4.0)	18.7 (4.4)
Concomitant SLE medications at baseline, n (%)		
Antimalarials	166 (79.8)	91 (85.0)
Systemic glucocorticoids	171 (82.2)	87 (81.3)
Immunosuppressants	129 (62.0)	70 (65.4)
Systemic glucocorticoid dose >7.5 mg/day,[a] n (%)	105 (50.5)	51 (47.7)
Anti-dsDNA[b]		
Level (IU), median (Q1, Q3)	8.0 (2.0, 39.0)	15.0 (3.0, 68.0)
>ULN, n (%)	91 (42.7)	62 (57.4)
C3[b]		
Level (mg/mL), median (Q1, Q3)	0.97 (0.76, 1.19)	0.94 (0.74, 1.19)
<LLN, n (%)	65 (30.5)	42 (38.9)
C4[b]		
Level (mg/L), median (Q1, Q3)	142.0(98.0, 199.0)	145.5 (95.5, 213.0)
<LLN, n (%)	117 (54.9)	57 (52.8)

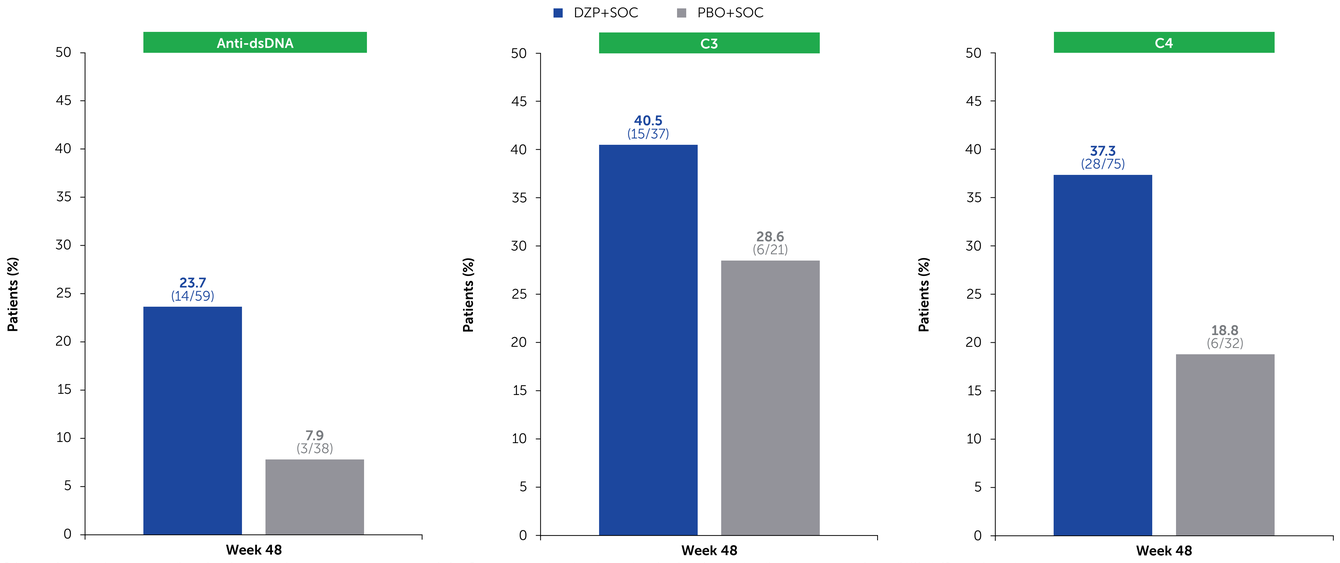
Full analysis set. [a] Prednisone equivalent dose. [b] Safety set; DZP+SOC: n=213; PBO+SOC: n=108.

Figure 1 Median percentage change from baseline of anti-dsDNA antibodies, C3 and C4 through Week 48 in patients with abnormal levels at baseline



Safety set. Any data after treatment discontinuation or use of rescue treatment were set to missing. Measurements below the limit of quantification were imputed as half the lower limit of quantification, while those above the limit were imputed as the upper quantification limit.

Figure 2 Proportion of patients who shifted from abnormal anti-dsDNA antibody, C3 and C4 levels at baseline to normal levels at Week 48



Safety set. Any data after treatment discontinuation or use of rescue treatment were set to missing. Percentages are based on the number of patients for each baseline value category with a valid Week 48 result for each treatment group.

For more information on PHOENYCS FLY, scan the QR code

BICLA: BILAG-based Composite Lupus Assessment; **BILAG:** British Isles Lupus Assessment Group; **C3:** complement 3; **C4:** complement 4; **dsDNA:** double-stranded deoxyribonucleic acid; **DZP:** dapirolizumab pegol; **Fab':** antigen-binding fragment; **IU:** international units; **LLN:** lower limit of normal; **PBO:** placebo; **PEG:** polyethylene glycol; **Q1:** first quartile; **Q3:** third quartile; **SLE:** systemic lupus erythematosus; **SLEDAI-2K:** Systemic Lupus Erythematosus Disease Activity Index-2K; **SOC:** standard of care; **ULN:** upper limit of normal.

References: [1]Ameer MA. Cureus 2022;14:e30330; [2]Swaak AJ. Ann Rheum Dis 1986;45:359–66; [3]Cutcutache I. Arthritis Rheumatol 2023;75 (suppl 9); [4]Powlesland AS. Ann Rheum Dis 2024;83 (suppl 1); [5]Clowse M. Arthritis Rheumatol 2024;76 (suppl 9).
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