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Dapirolizumab Pegol Demonstrated Significant Improvement in Systemic Lupus Erythematosus Disease Activity: Efficacy and Safety Results of a Phase 3 Trial

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PHOENYCS GO

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Disclosures

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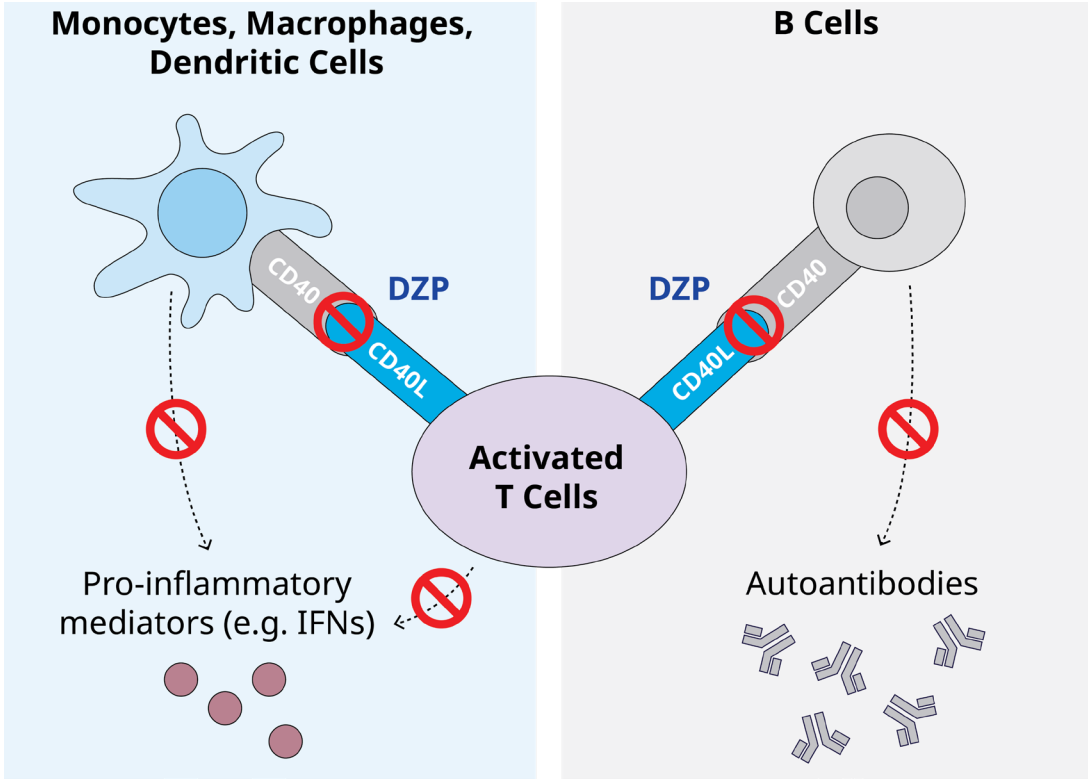
Background & objective

- **Systemic lupus erythematosus (SLE)** remains associated with a high disease burden and unmet need[1–4]
  - Ongoing inflammatory symptoms
  - Long-term toxicity from corticosteroid use
- **Dapirolizumab pegol (DZP)** is a novel, polyethylene glycol (PEG)-conjugated antigen-binding (Fab') fragment, lacking an Fc domain, that **inhibits CD40L signaling**
- DZP has **broad modulatory effects on SLE immunopathology**, including reducing B and T cell activation and downregulating interferon pathways[5–7]



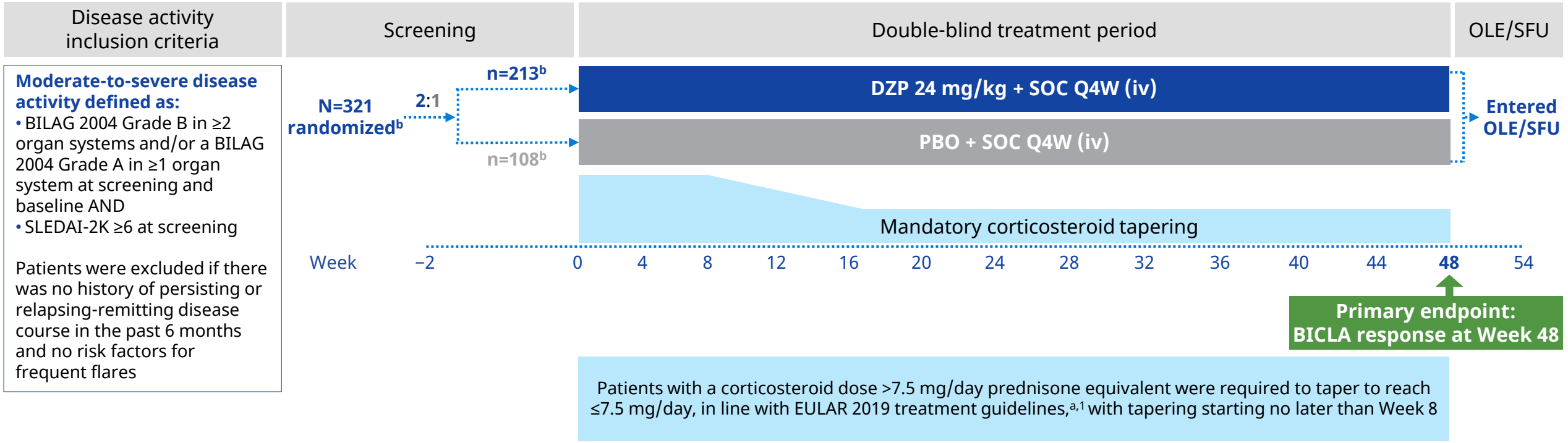
Objective

To evaluate the **efficacy and safety of DZP** in patients with **moderate-to-severe, active SLE** in the **phase 3 PHOENYCS GO trial** (NCT04294667)

[1]Fanouriakis A. Ann Rheum Dis 2021;80:14–25; [2]Fanouriakis A. Ann Rheum Dis 2024;83:15–29; [3]Györi N. Lupus Sci Med 2017;4:e000192; [4]Mehta B. Ann Intern Med 2019;171:164–71; [5]Cutcutache I. Arthritis Rheumatol 2023;75 (suppl 9); [6]Powlesland A. Ann Rheum Dis 2024;83:261; [7]Rowley T. Arthritis Rheumatol 2024;76 (suppl 9). DZP: dapirolizumab pegol; Fab': antigen-binding fragment; IFN: interferon; PEG: polyethylene glycol; SLE: systemic lupus erythematosus.

Study design

- PHOENYCS GO was a **48-week, global, randomized**, **double-blind**, **placebo (PBO)-controlled** trial
- Patients aged ≥16 years with moderate-to-severe SLE characterized by **persistently active or frequently flaring/relapsing-remitting disease activity despite stable standard of care (SOC) medication** (antimalarials, corticosteroids, and/or immunosuppressants) were enrolled



[a] Guidelines available at the time of study design; [b] Randomized set. [1]Fanouriakis A. Ann Rheum Dis 2019;78:736–45. BICLA: British Isles Lupus Assessment Group-based Composite Lupus Assessment; BILAG: British Isles Lupus Assessment Group; DZP: dapirolizumab pegol; EULAR: European Alliance of Associations for Rheumatology; iv: intravenous; OLE: open-label extension; PBO: placebo; Q4W: every 4 weeks; SFU: safety follow up; SLE: systemic lupus erythematosus; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index-2K; SOC: standard of care.

Baseline demographics and disease characteristics

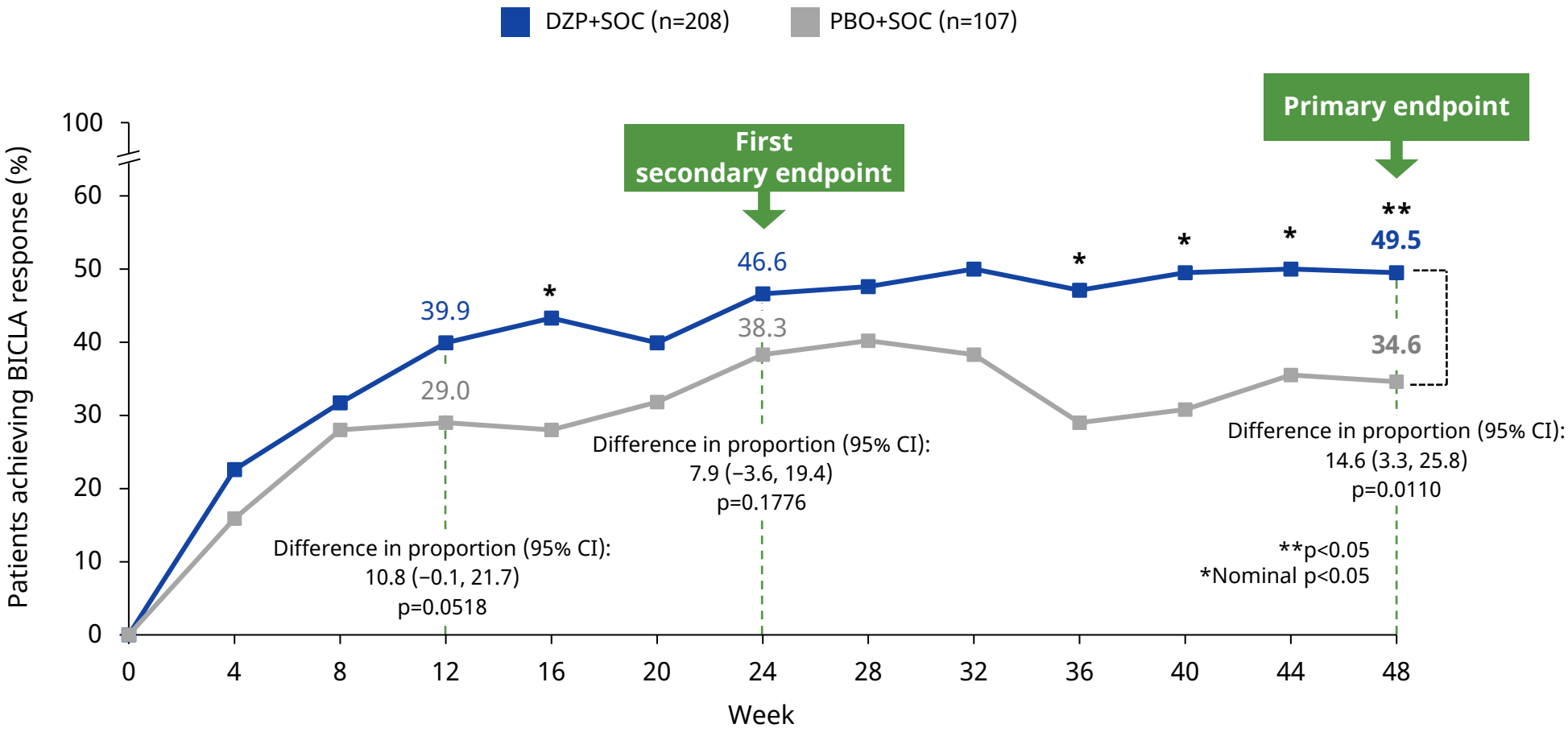
	DZP+SOC n=208	PBO+SOC n=107
Age, years, mean (SD)	**43.5** (12.3)	**41.5** (12.4)
Female, n (%)	193 **(92.8%)**	100 **(93.5%)**
SLEDAI-2K ≥10, n (%)	145 **(69.7%)**	76 **(71.0%)**
anti-dsDNA (EliA) >10 IU, n (%)	91 **(43.8%)**	62 **(57.9%)**
C3 or C4 <LLN, n (%)	124 **(59.6%)**	66 **(61.7%)**
Concomitant SLE medications at baseline, n (%)	208 **(100.0%)**	107 **(100.0%)**
Antimalarials, n (%)	166 **(79.8%)**	92 **(86.0%)**
Immunosuppressants, n (%)	128 **(61.5%)**	70 **(65.4%)**
Systemic corticosteroids, n (%)	171 **(82.2%)**	88 **(82.2%)**
Systemic corticosteroid dose >7.5 mg/day, n (%)	105 **(50.5%)**	51 **(47.7%)**
Any aPLs,[a] n (%)	129 **(62.0%)**	64 **(59.8%)**

Full analysis set. [a] aPLs include anti-phosphatidylserine and anti-prothrombin. Anti-dsDNA: anti-double stranded DNA; aPLs: antiphospholipid antibodies; C3: complement 3; C4: complement 4; DZP: dapirolizumab pegol; IU: international unit; LLN: lower limit of normal; PBO: placebo; SD: standard deviation; SLE: systemic lupus erythematosus; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index-2K; SOC: standard of care.

BICLA response

Significantly more patients receiving DZP+SOC compared with PBO+SOC achieved BICLA response at Week 48

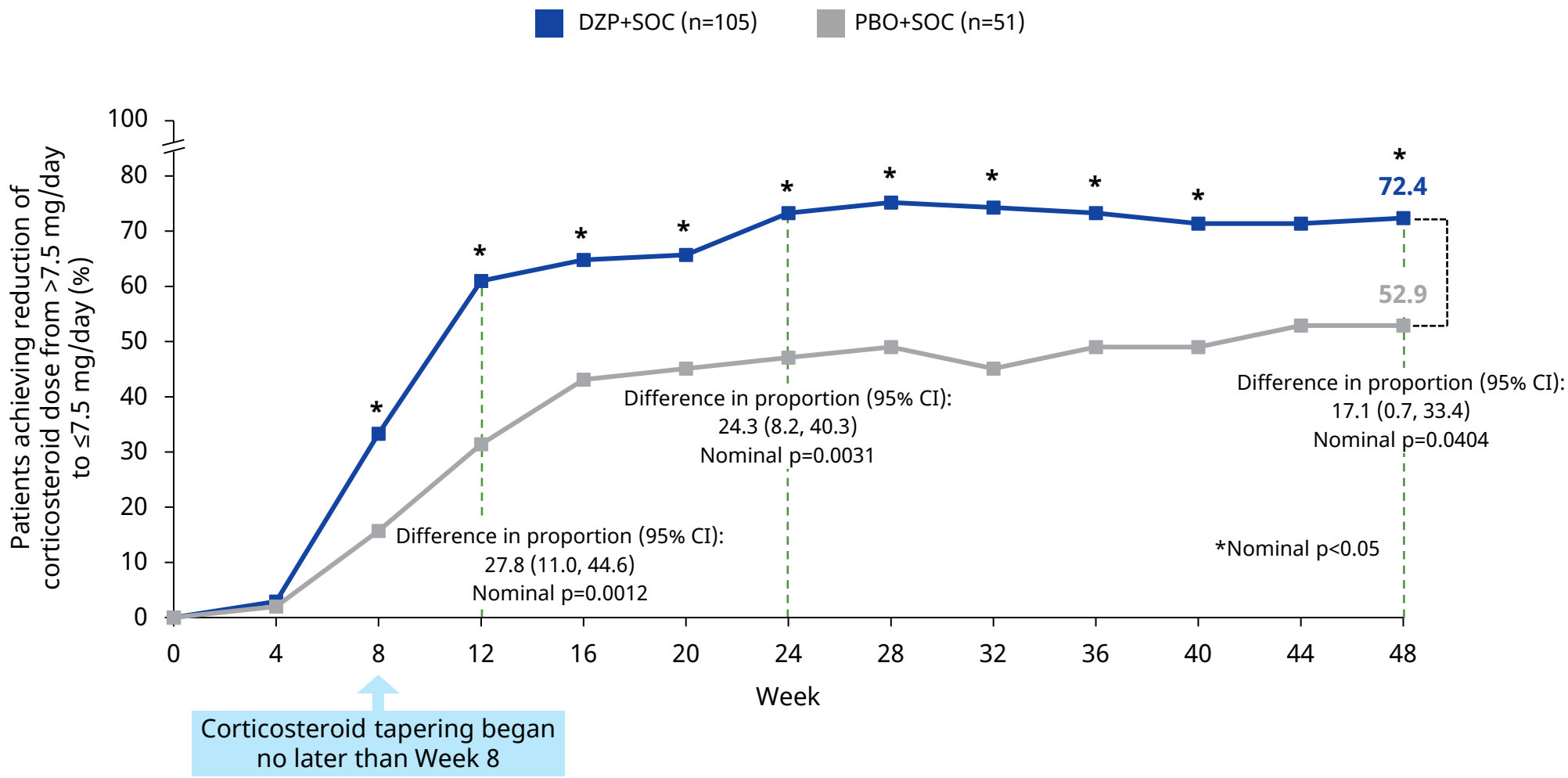
- **85.4%** of patients receiving DZP+SOC and **79.6%** receiving PBO+SOC **completed the study to Week 48 on treatment**[a]



Full analysis set. Secondary endpoints were controlled for multiplicity using a hierarchical testing procedure. As the second step of the hierarchical testing was BICLA response at Week 24 and the p value was >0.05 for this time point, all other secondary endpoints cannot be considered statistically significant. A composite strategy was used for intercurrent events (escape treatment, premature withdrawal from the study, or permanent discontinuation of study medication while remaining in the study) and patients were assigned as a non-responder from the day after the intercurrent event occurred. After intercurrent event handling, any remaining missing data were handled using NRI. Difference in proportion responding between DZP+SOC and PBO+SOC, 95% CI for difference in proportions, and p-values were estimated and tested using the CMH risk difference estimate controlling for stratification factors (pooled region [North America vs Western Europe/Asia-Pacific vs Latin America/Eastern Europe], baseline disease activity pattern [chronic active vs acute flaring], and baseline SLEDAI-2K score [<10 vs ≥10]). [a] Of all randomized patients. BICLA: British Isles Lupus Assessment Group-based Composite Lupus Assessment; CI: confidence interval; CMH: Cochran-Mantel-Haenszel; DZP: dapirolizumab pegol; NRI: non-responder imputation; PBO: placebo; SLEDKAI-2K: Systemic Lupus Erythematosus Disease Activity Index-2K; SOC: standard of care.

Corticosteroid tapering in subgroup of patients on high dose steroids

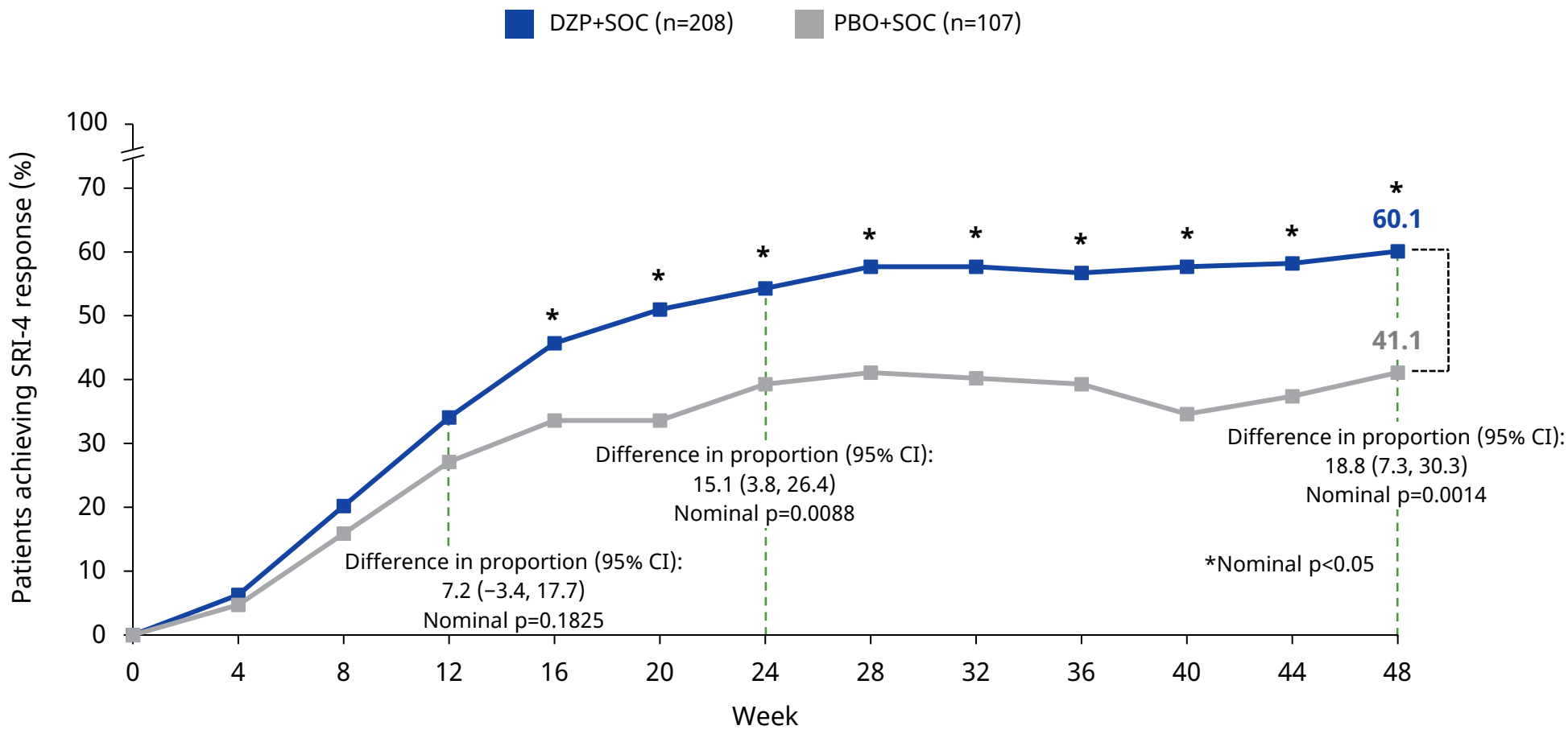
A higher proportion of patients receiving DZP+SOC compared with PBO+SOC reduced their corticosteroid dose from >7.5 mg/day at baseline to ≤7.5 mg/day at Week 48



Full analysis set. A composite strategy was used for intercurrent events (escape treatment, premature withdrawal from the study, or permanent discontinuation of study medication while remaining in the study) and patients were assigned as a non-responder from the day after the intercurrent event occurred. After intercurrent event handling, any remaining missing data were handled using NRI. Difference in proportion responding between DZP+SOC and PBO+SOC, 95% CI for difference in proportions, and p-values were estimated and tested using the CMH risk difference estimate controlling for stratification factors (pooled region [North America vs Western Europe/Asia-Pacific vs Latin America/Eastern Europe], baseline disease activity pattern [chronic active vs acute flaring], and baseline SLEDAI-2K score [<10 vs ≥10]). CI: confidence interval; CMH: Cochran-Mantel-Haenszel; DZP: dapirolizumab pegol; NRI: non-responder imputation; PBO: placebo; SLEDKAI-2K: Systemic Lupus Erythematosus Disease Activity Index-2K; SOC: standard of care.

SRI-4 response

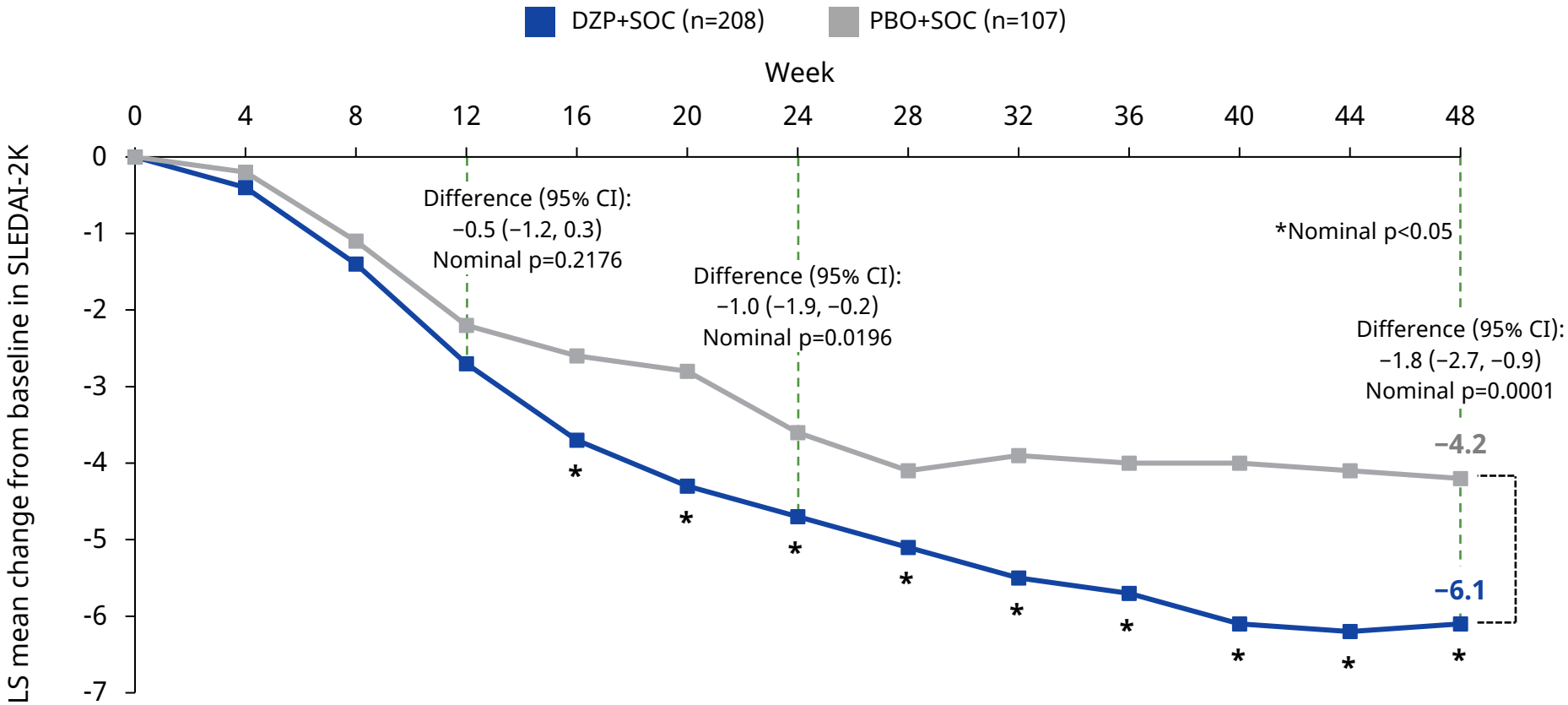
A higher proportion of patients receiving DZP+SOC compared with PBO+SOC achieved SRI-4 response at Week 48



Full analysis set. A composite strategy was used for intercurrent events (escape treatment, premature withdrawal from the study, or permanent discontinuation of study medication while remaining in the study) and patients were assigned as a non-responder from the day after the intercurrent event occurred. After intercurrent event handling, any remaining missing data were handled using NRI. Difference in proportion responding between DZP+SOC and PBO+SOC, 95% CI for difference in proportions, and p-values were estimated and tested using the CMH risk difference estimate controlling for stratification factors (pooled region [North America vs Western Europe/Asia-Pacific vs Latin America/Eastern Europe], baseline disease activity pattern [chronic active vs acute flaring], and baseline SLEDAI-2K score [<10 vs ≥10]). CI: confidence interval; CMH: Cochran-Mantel-Haenszel; DZP: dapirolizumab pegol; NRI: non-responder imputation; PBO: placebo; SLEDKAI-2K: Systemic Lupus Erythematosus Disease Activity Index-2K; SOC: standard of care; SRI-4: Systemic Lupus Erythematosus Responder Index-4.

SLEDAI-2K

A greater change from baseline in SLEDAI-2K was seen in patients receiving DZP+SOC compared with PBO+SOC at Week 48

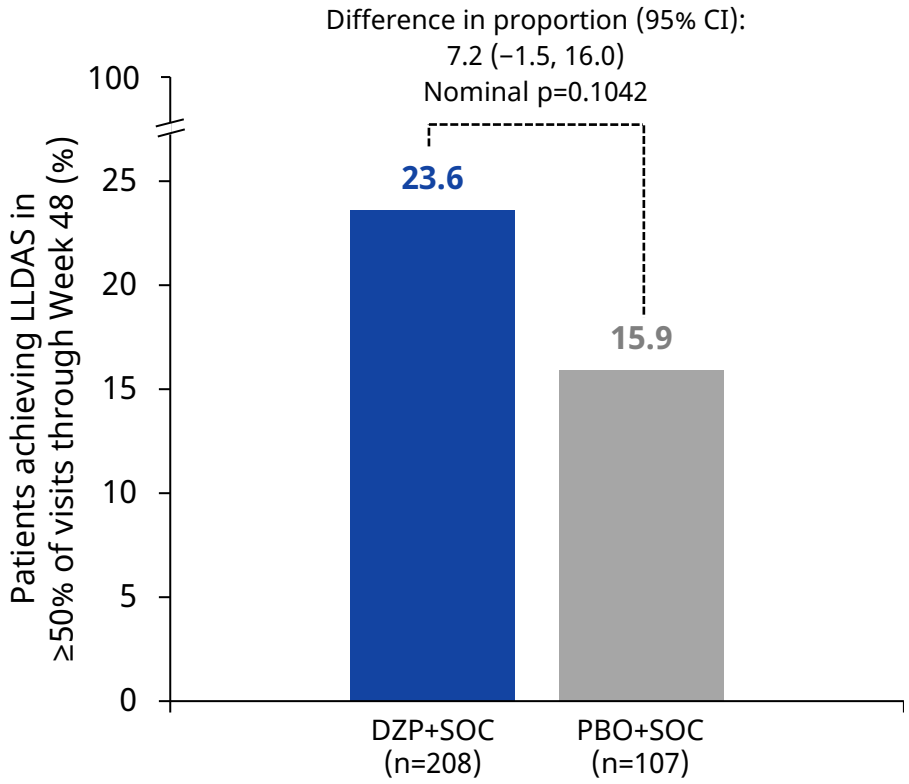


Full analysis set. A hypothetical strategy was used for intercurrent events (escape treatment, premature withdrawal from the study, or permanent discontinuation of study medication while remaining in the study) where data were set as missing. After intercurrent event handling, MMRM with fixed effects for treatment, stratification factors, baseline value, visit, treatment by study week interaction, and baseline value by study week interaction was conducted on the remaining data. The LS mean, the difference (DZP+SOC versus PBO+SOC), and the 95% CI were computed from the MMRM. CI: confidence interval; DZP: dapirolizumab pegol; LS: least square; MMRM: mixed model for repeated measurements; PBO: placebo; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index-2K; SOC: standard of care.

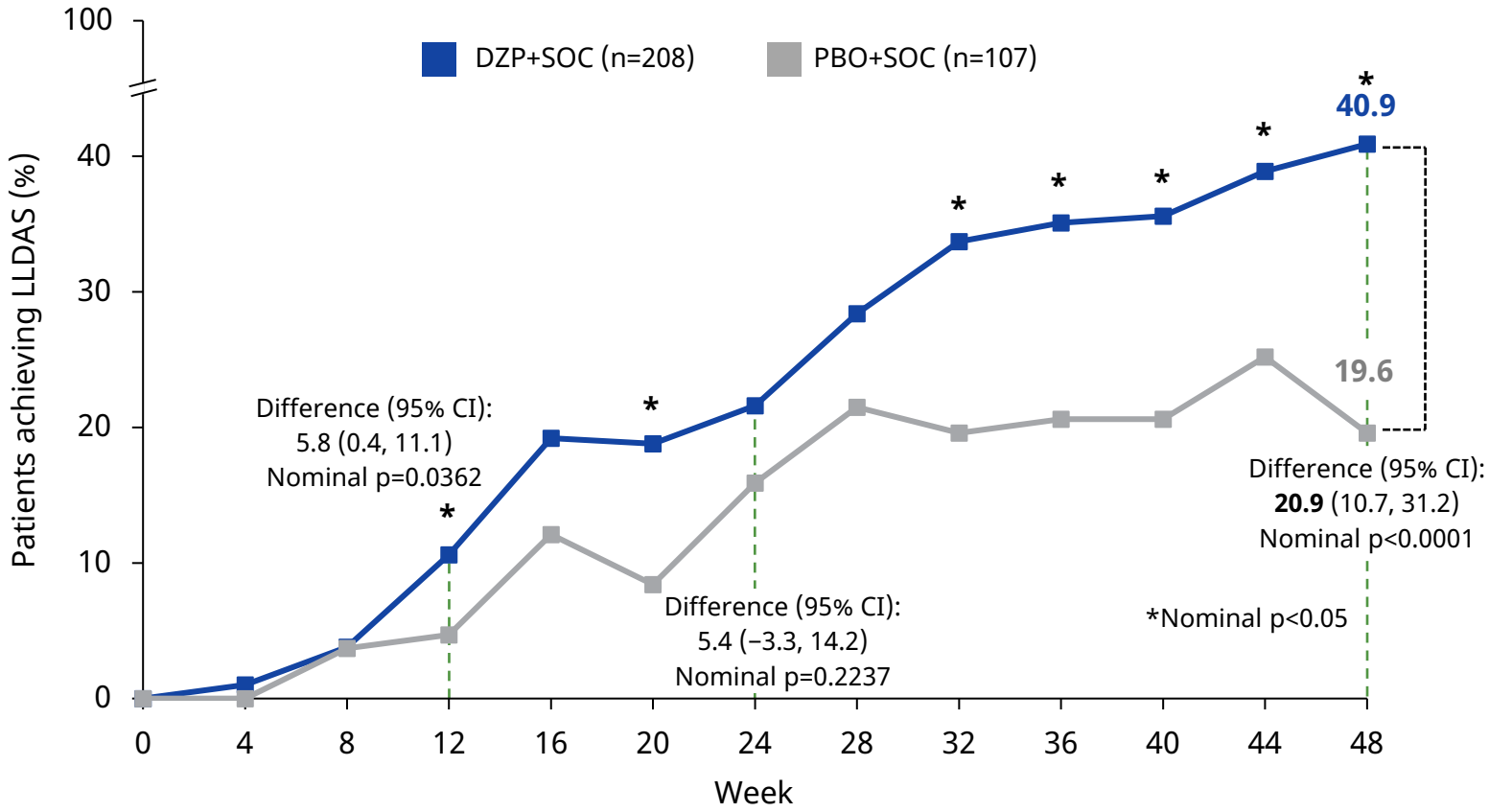
Lupus Low Disease Activity State (LLDAS)

A higher proportion of patients receiving DZP+SOC compared with PBO+SOC achieved LLDAS through Week 48

LLDAS in ≥50% of visits through Week 48



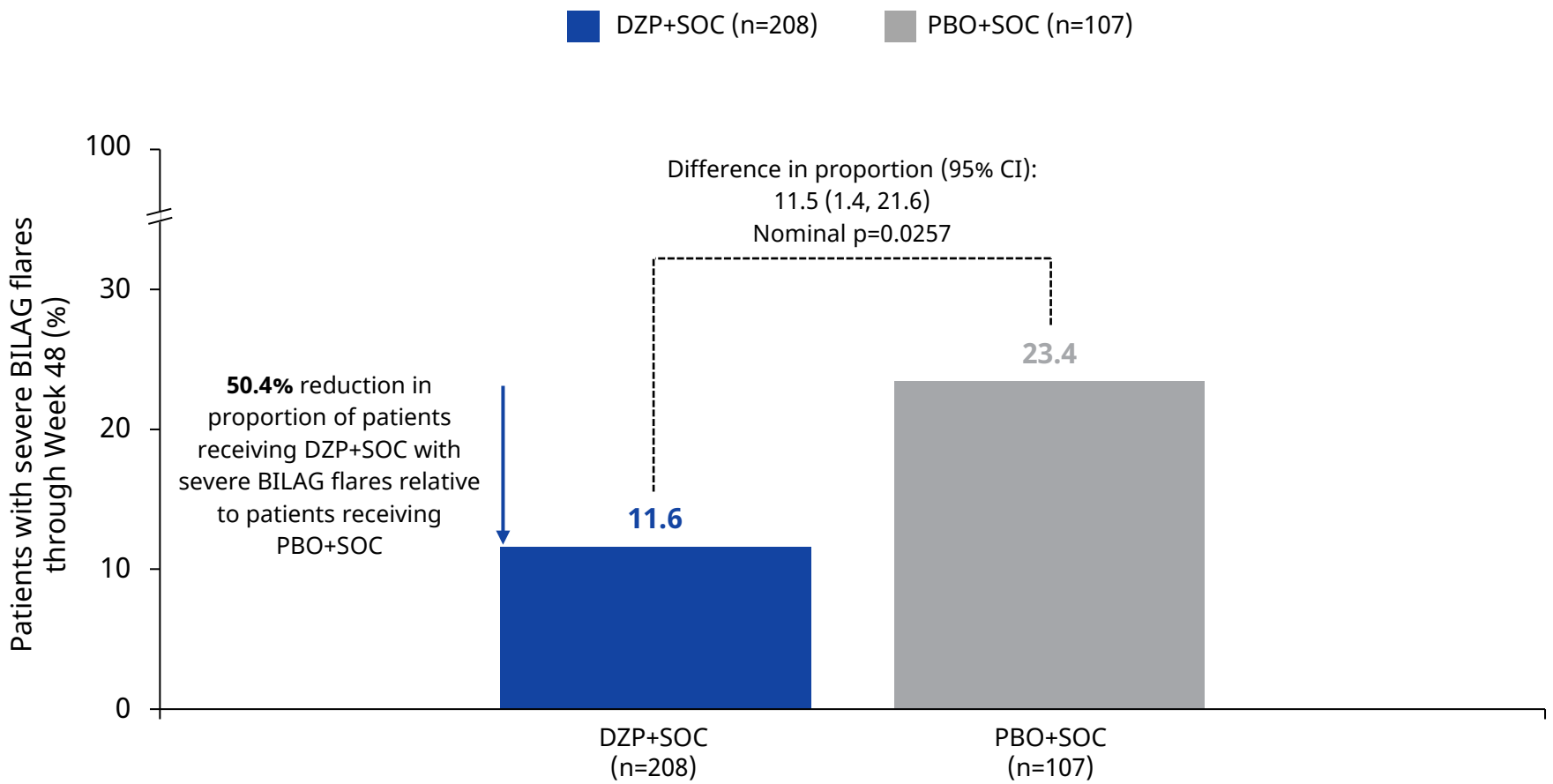
LLDAS status by visit



Full analysis set. A composite strategy was used for intercurrent events (escape treatment, premature withdrawal from the study, or permanent discontinuation of study medication while remaining in the study) and patients were counted as not in LLDAS. After intercurrent event handling, any remaining missing data was not counted as LLDAS (analogous to using NRI). Difference in proportion responding between DZP+SOC and PBO+SOC, 95% CI for difference in proportions, and p-values were estimated and tested using the CMH risk difference estimate controlling for stratification factors (pooled region [North America vs Western Europe/Asia-Pacific vs Latin America/Eastern Europe], baseline disease activity pattern [chronic active vs acute flaring], and baseline SLEDAI-2K score [<10 vs ≥10]). CI: confidence interval; CMH: Cochran-Mantel-Haenszel; DZP: dapirolizumab pegol; LLDAS: Lupus Low Disease Activity State; NRI: non-responder imputation; PBO: placebo; SLEDKAI-2K: Systemic Lupus Erythematosus Disease Activity Index-2K; SOC: standard of care.

Severe BILAG flares

There was a 50.4% reduction in the proportion of patients receiving DZP+SOC with severe BILAG flares compared with patients receiving PBO+SOC through Week 48



Full analysis set. A composite strategy was used for escape treatment, where patients were assigned as non-responders (counted as a flare) at the time point of the intercurrent event, even if the intercurrent event was after permanent discontinuation of study medication, as long as the intercurrent event was ≤5 weeks after the last infusion. A hypothetical strategy was used for permanent discontinuation of study drug or premature withdrawal from study, where data >5 weeks after the last infusion were set to missing. After intercurrent event handling, any remaining missing data will be handled using MI-MAR. Difference in proportion responding between DZP+SOC and PBO+SOC, 95% CI for difference in proportions, and p-values were estimated and tested using the CMH risk difference estimate controlling for stratification factors (pooled region [North America vs Western Europe/Asia-Pacific vs Latin America/Eastern Europe], baseline disease activity pattern [chronic active vs acute flaring], and baseline SLEDAI-2K score [<10 vs ≥10]). BILAG: British Isles Lupus Assessment Group; CMH: Cochran-Mantel-Haenszel; CI: confidence interval; DZP: dapirolizumab pegol; MI-MAR: multiple imputation assuming missing at random; PBO: placebo; SLEDKAI-2K: Systemic Lupus Erythematosus Disease Activity Index-2K; SOC: standard of care.

Safety

DZP was generally well tolerated over 48 weeks; the safety profile was generally consistent with previous DZP studies and with that seen in study patients with SLE receiving an immunomodulator[1–3]

n, (%)	DZP+SOC n=213	PBO+SOC n=108
Any TEAE	176 **(82.6%)**	81 **(75.0%)**
Serious TEAEs	21 **(9.9%)**	16 **(14.8%)**
Permanent discontinuation of drug or study discontinuation due to TEAEs	10 **(4.7%)**	4 **(3.7%)**
Hypersensitivity TEAEs starting on the day of or the day after an infusion	6 **(2.8%)**	0 **(0.0%)**
Infections and infestations	131 **(61.5%)**	56 **(51.9%)**
Mild	95 **(44.6%)**	35 **(32.4%)**
Moderate	66 **(31.0%)**	36 **(33.3%)**
Severe	3 **(1.4%)**	4 **(3.7%)**
Serious	8 **(3.8%)**	6 **(5.6%)**
Herpes viral infections	13 **(6.1%)**	14 **(13.0%)**
Herpes zoster	4 (**1.9%**)	7 **(6.5%)**
Ophthalmic herpes zoster	2 **(0.9%)**[a]	0 **(0.0%)**
Herpes ophthalmic	1 **(0.5%)**[b]	0 **(0.0%)**
Thromboembolic TEAEs confirmed by an adjudication committee	1 **(0.5%)**	0 **(0.0%)**
Acute myocardial infarction	1 **(0.5%)**	0 **(0.0%)**
Deaths	1 **(0.5%)**	0 **(0.0%)**
Gangrene-related sepsis	1 **(0.5%)**	0 **(0.0%)**

Safety set. MedDRA v24.0. [a] The two events were reported as "herpes zoster over left eyelid and forehead, V1" and "left herpes zoster ophthlamicus (dermatome V1/V2)"; [b] Reported as "herpetic queratitis".
[1]Furie RA. Rheumatology (Oxford) 2021;60:5397–407; [2]Chamberlain C. Ann Rheum Dis 2018;77:787–88; [3]Tocoian A. Lupus 2015;24:1045–56. DZP: dapirolizumab pegol; MedDRA: Medical Dictionary for Regulatory Activities; PBO: placebo; SLE: systemic lupus erythematosus; SOC: standard of care; TEAE: treatment-emergent adverse event.

Conclusions

Treatment with DZP, a novel CD40L inhibitor, resulted in improvement in disease activity and corticosteroid tapering in patients with SLE and was generally well tolerated; a second phase 3 trial is being initiated

- The **PHOENYCS GO** trial of DZP in SLE **met its primary endpoint**; significantly more patients who received DZP+SOC compared with PBO+SOC achieved BICLA response at Week 48
    - Against a background of corticosteroid tapering, efficacy of DZP was **observed across multiple measures**, including SRI-4, SLEDAI-2K, LLDAS, and severe BILAG flares
- DZP treatment was generally **well tolerated** in the PHOENYCS GO trial
- DZP may represent a novel treatment option for SLE, with **broad immunomodulatory effects**; treatments that target diverse mechanisms and options for treatment combinations are needed for heterogenous diseases such as SLE
- Additional efficacy data for DZP across a **broad spectrum of measures**, **including patient-reported outcomes**, will be presented in future publications

BICLA: British Isles Lupus Assessment Group-based Composite Lupus Assessment; BILAG: British Isles Lupus Assessment Group; DZP: dapirolizumab pegol; LLDAS: Lupus Low Disease Activity State; PBO: placebo; SLE: systemic lupus erythematosus; SLEDAI -2K: Systemic Lupus Erythematosus Disease Activity Index-2K; SOC: standard of care; SRI: Systemic Lupus Erythematosus Response Index.