Efficacy and safety of the CD40 ligand inhibitor dapirolizumab pegol in systemic lupus erythematosus (PHOENYCS GO): a randomised, double-blind, placebo-controlled, phase 3 trial

*Megan E B Clowse, David A Isenberg, Joan T Merrill, Thomas Dörner, Michelle Petri, Edward M Vital, Eric F Morand, Zahi Touma, Anca D Askanase, Yiannis Ioannou, Stephen Brookes, Janine Gaiha-Rohrbach, E Dietlind Koch, Nour Zibian, Christophe Martin, Teri Jimenez, Annette Nelde, Christian Stach, on behalf of the PHOENYCS GO Study Investigators' Group**

Summary

Background Dapirolizumab pegol is a novel CD40 ligand inhibitor. In this phase 3 trial, we aimed to evaluate the efficacy and safety of dapirolizumab pegol in patients with systemic lupus erythematosus (SLE).

Methods PHOENYCS GO was a 48-week, randomised, double-blind, placebo-controlled, phase 3 trial conducted in 177 centres (hospitals, private practices, and trial centres) in 25 countries. Patients aged 16 years or older with moderate-to-severe, active SLE despite standard-of-care medication were randomly assigned (2:1), via an interactive web response system, to intravenous dapirolizumab pegol 24 mg/kg or placebo every 4 weeks in addition to standard of care. Patients, investigators, and funders were blinded to treatment assignments. The primary outcome was British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA) response at week 48. Efficacy analyses were conducted on a modified intention-to-treat population. Safety analyses included all randomly assigned patients who received at least one study medication dose. This trial is registered with ClinicalTrials.gov (NCT04294667) and is completed.

Findings Between Aug 12, 2020, and June 8, 2023, 643 patients were screened and 321 patients were randomly assigned to dapirolizumab pegol (n=213) or placebo (n=108) plus standard of care. All randomly assigned patients received at least one dose of study medication. Six patients were excluded due to non-compliance of one site with Good Clinical Practice guidelines; therefore, the full-analysis set included 315 patients (293 female, 22 male). A significantly greater proportion of patients receiving dapirolizumab pegol (50% [103/208]) versus placebo (35% [37/107]) had BICLA response at week 48 (p=0·011; difference 14·6; 95% CI 3·3–25·8). Treatment-emergent adverse events occurred in 83% (176/213) of patients receiving dapirolizumab pegol versus 75% (81/108) receiving placebo. Serious treatment-emergent adverse events occurred in 10% (21/213) of patients receiving dapirolizumab pegol versus 15% (16/108) receiving placebo. Hypersensitivity reactions during infusion occurred in 3% (6/213) of patients receiving dapirolizumab pegol. Serious infections occurred in 4% (8/213) and 6% (6/108) of patients receiving dapirolizumab pegol and placebo, respectively. One thromboembolic event (myocardial infarction) occurred in one patient in the dapirolizumab pegol group and one death (gangrene-related sepsis) occurred in another patient in the dapirolizumab pegol group.

Interpretation Dapirolizumab pegol was associated with significant improvement in disease activity in patients with SLE. These findings support the further investigation of dapirolizumab pegol as a treatment option for SLE.

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*Members listed in appendix 1 (pp 3–35)

Division of Rheumatology and Immunology, Duke University, Durham, NC, USA (Prof M E B Clowse MD); Department of Ageing, Rheumatology and Regenerative Medicine, Division of Medicine, University College London, London, UK (Prof D A Isenberg MD); Oklahoma Medical Research Foundation, Oklahoma City, OK, USA (Prof J T Merrill MD); Department of Medicine/Rheumatology and Clinical Immunology, Charité Universitätsmedizin Berlin, Berlin, Germany (Prof T Dörner MD); Johns Hopkins University School of Medicine, Baltimore, MD, USA (Prof M Petri MD); Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK (Prof E M Vital FRCP); NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK (Prof E M Vital FRCP); Centre for Inflammatory Diseases, Monash University and Monash Health, Melbourne, VIC, Australia (Prof E F Morand MBBS); Division of Rheumatology, University of Toronto Lupus Clinic, Schroeder Arthritis Institute, Krembil Research Institute, University Health Network, Toronto, ON, Canada (Z Touma MD); Columbia University Medical Center, New York, NY, USA (Prof A D Askanase MD); UCB,

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease driven by aberrant innate and adaptive immune responses.[1] SLE pathology is characterised by loss of tolerance to nuclear autoantigens, activation of antigen-presenting cells (APCs), and activation of autoreactive T and B cells, leading to autoantibody production.[1,2] Hallmarks of the disordered immune response are type I interferon pathway activation and immune-complex deposition, resulting in inflammation causing multisystem organ damage.[1,2] People with SLE frequently develop persistently active or relapsing-remitting disease despite receiving standard of care.[3,4] Due to its chronic symptoms, SLE can greatly affect patients' health-related quality of life, with fatigue being one of the most prevalent and debilitating symptoms.[1,5]

Standard-of-care treatment for SLE includes glucocorticoids, antimalarials, and other immune

Slough, UK (Y Ioannou PhD, C Martin MD)**; Biogen, Maidenhead, UK** (S Brookes MSc)**; Biogen, Cambridge, MA, USA** (J Gaiha-Rohrbach PhD)**; UCB, Monheim am Rhein, Germany** (E D Koch DrMed, C Stach MD)**; UCB, Colombes, France** (N Zibian PharmD)**; UCB, Raleigh, NC, USA** (T Jiminez MSc)**; Biogen, Baar, Switzerland** (A Nelde PhD)

Correspondence to: Prof Megan E B Clowse, Division of Rheumatology and Immunology, Duke University, Durham, NC 27710, USA **megan.clowse@duke.edu**

See **Online** for appendix 1

Research in context

Evidence before this study

We evaluated previous phase 3 trials assessing the efficacy and safety of interventions in patients with systemic lupus erythematosus (SLE) and searched PubMed using the term "systemic lupus erythematosus" for phase 3 clinical trial articles published between Jan 1, 2010, and April 30, 2025. Developing effective treatments for SLE has historically been challenging. Numerous potential treatments, including baricitinib, epratuzumab, blisibimod, ustekinumab, and tabalumab, have failed to show statistically significant efficacy in phase 3 trials. The only SLE-specific treatments approved over the past 60 years, in most regions, have been the biologics anifrolumab and belimumab. Other treatments include antimalarials and glucocorticoids, as well as multiple off-label immune modulators, including mycophenolate, azathioprine, methotrexate, and rituximab. Two treatments, voclosporin and obinutuzumab, have received approval from the US Food and Drug Administration for lupus nephritis. Long-term treatment with glucocorticoids is associated with multiple side-effects, and reducing doses to a minimum is therefore recommended.

Added value of this study

The phase 3 PHOENYCS GO trial assessed the efficacy and safety of dapirolizumab pegol 24 mg/kg versus placebo, in addition to standard-of-care medication and a background of glucocorticoid tapering, in patients with moderate-to-severe, active SLE. Dapirolizumab pegol is a novel CD40 ligand inhibitor, which consists of a polyethylene glycol-conjugated antigen-binding fragment lacking an Fc domain. The primary outcome of the PHOENYCS GO trial was met: a significantly greater proportion of patients receiving dapirolizumab pegol plus standard-of-care medication reached British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) response at week 48 compared with those receiving placebo plus standard of care. The key secondary outcome of BICLA response at week 24, tested by use of a gatekeeping procedure to control for multiplicity, was not met. However, results in favour of dapirolizumab pegol in other outcomes, not controlled for multiplicity, were seen, including prevention of severe BILAG flares, changes from baseline in SLE Disease Activity Index-2K, SLE Responder Index-4 response, achievement of Lupus Low Disease Activity State, and glucocorticoid tapering. In addition, patients treated with dapirolizumab pegol showed improvements in Functional Assessment of Chronic Illness Therapy–Fatigue scores. These results, observed across a broad range of outcomes, suggest potential clinical benefits for patients with moderate-to-severe, active SLE. Dapirolizumab pegol had an acceptable safety profile.

Implications of all the available evidence

As SLE immunopathology is complex and multifaceted, treatments targeting multiple immunological pathways and affecting a range of disease domains could provide benefit over current standard of care. The results of PHOENYCS GO reinforce the potential of targeting CD40–CD40 ligand interactions in the treatment of SLE, and support dapirolizumab pegol as a potential treatment option in patients with moderate-to-severe, active SLE. The ongoing open-label extension (ie, PHOENYCS GLIDE; NCT04976322), and a second confirmatory phase 3 trial (PHOENYCS FLY; NCT06617325) will further assess the efficacy and safety of dapirolizumab pegol in patients with SLE.

modulators.[4] Two biologics, belimumab (a monoclonal antibody to B-cell activating factor) and anifrolumab (a monoclonal antibody to type I interferon receptor subunit 1), are widely approved for use, and voclosporin (a calcineurin inhibitor) and obinutuzumab (a type II anti-CD20 monoclonal antibody) have been approved for lupus nephritis.[6–9] Other treatments (eg, rituximab [an anti-CD20 monoclonal antibody]), often used off label, expand management strategies to a limited extent.[10] Nevertheless, many people with SLE continue to require long-term glucocorticoids, which are associated with increased organ damage, and treatment guidelines recommend the minimisation of doses.[4,11,12] Therapies that provide broad and durable disease control across organ systems, improve patient symptoms, and minimise glucocorticoid use are therefore needed; however, development of treatments has proven difficult, with many phase 3 trial failures.[13]

A common mediator in many SLE inflammatory pathways is CD40–CD40 ligand signalling.[14] CD40–CD40 ligand interactions are required for B-cell activation, maturation, and survival; germinal centre formation; and production of antibodies, including autoantibodies.[14] CD40–CD40 ligand signalling is also key for cytokine secretion and coactivation of T cells and various APCs.[14] Dapirolizumab pegol is a novel, polyethylene glycol (PEG)-conjugated antigen-binding fragment (Fab') lacking an Fc domain.[15] Dapirolizumab pegol binds CD40 ligand, blocking CD40–CD40 ligand interactions, and has broad modulatory effects on SLE immunopathology, reducing B-cell and T-cell activation and downregulating activation of type I interferon pathways and other cytokines.[16,17] In a phase 2b trial of dapirolizumab pegol in SLE (NCT02804763), the primary endpoint of establishing a dose–response relationship was not met; however, dapirolizumab pegol was associated with improvements in multiple clinical and immunological disease activity measures.[15]

We report the results of the phase 3 PHOENYCS GO trial, which aimed to evaluate the efficacy and safety of dapirolizumab pegol in patients with moderate-to-severe, active SLE despite standard-of-care medication.

Methods

Study design

PHOENYCS GO was a 48-week, global, randomised, double-blind, placebo-controlled, parallel-group, phase 3 trial of dapirolizumab pegol plus standard-of-care medication versus placebo plus standard-of-care medication (appendix 1 p 48). After a 2–3-week screening period, patients entered a 48-week treatment period, after which they could enter an open-label extension or complete a 6-week safety follow-up.

The trial was conducted at 177 centres (hospitals, private practices, and trial centres) in 25 countries (appendix 1 pp 3–35), in accordance with ethical principles derived from international guidelines including the Declaration of Helsinki, Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable International Conference of Harmonisation Good Clinical Practice Guidelines, and other applicable laws and regulations. The trial was approved by the ethics committee or institutional review board of each site (appendix 1 pp 3–35).

The study protocol and statistical analysis plan are available in appendix 2; a summary of amendments to the protocol and statistical analysis plan are shown on pp 137–51 and pp 335–39. Two major amendments made to the statistical analysis plan are documented in appendix 1 (p 40). Important protocol deviations included inclusion or exclusion criteria deviations, prohibited concomitant medication use, incorrect treatment or dose, and procedural non-compliance.

Patients and patient organisations contributed to the study design, procedures, and endpoints included in the study via informal meetings. Patients contributed to the interpretation of the data via advisory boards.

This trial is registered with ClinicalTrials.gov (NCT04294667) and is completed.

Patients

Eligible patients were aged 16 years or older with moderate-to-severe, active SLE despite stable standard-of-care medication. Patients were required to meet the 2019 SLE European League Against Rheumatism/American College of Rheumatology classification criteria for SLE.[18] Serological evidence of SLE was required, with at least one of the following: (1) increased anti-double stranded (ds) DNA antibody concentrations (identified by Bio-Rad Autoimmune EIA anti-dsDNA assay [Hercules, CA, USA]); (2) complement C3 or C4 less than the lower limit of normal (LLN), or elevated erythrocyte-bound complement C4d; or (3) antinuclear antibodies with a titre of at least 1:80 in combination with at least one additional SLE autoantibody (eg, anti-Smith antibody, anti-Sjögren's syndrome antibody A or anti-Sjögren's syndrome antibody B, or a documented history of anti-dsDNA). Moderate-to-severe disease activity was defined as British Isles Lupus Assessment Group (BILAG)-2004 Grade B in at least two organ systems or BILAG-2004 Grade A in at least one organ system at screening and baseline (or both), and a Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K) score of at least 6 at screening. Patients qualified for the study via two potential patterns of SLE disease activity: active disease, defined as the presence of persistent symptoms (ie, chronic active), or frequently flaring or relapsing-remitting disease (acute flaring). To ensure that included patients had active disease without a high likelihood of spontaneous remission or remission with short-term treatment, patients who did not have persistent symptoms but had an acute flare at screening were excluded unless they had evidence of at least one of the following risk factors for flaring or relapsing-remitting disease: (1) at least one disease flare in the 24 weeks before screening; (2) anti-dsDNA positivity in combination with complement C3 less than the LLN; (3) complement C4 less than the LLN; (4) African American race; or (5) younger than 25 years. Patients were required to be taking a stable dose of at least one relevant standard-of-care medication, including glucocorticoids, antimalarials, or immunosuppressants (or combinations thereof). Race, ethnicity, and sex data were patient-reported via the case report form, with the following options provided: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, or other or mixed (for race); Hispanic or Latino, or not Hispanic or Latino (for ethnicity); and female, male, unknown, or undifferentiated (for sex). All patients provided written informed consent.

See Online for appendix 2

All inclusion and exclusion criteria are provided in the study protocol (appendix 2). Central review of clinical and laboratory data was conducted by a team of qualified physicians to provide feedback to investigators regarding whether eligibility criteria were fulfilled.

Randomisation and masking

Patients were randomly assigned (2:1) by the vendor of an interactive web response system (ie, Synapse version 19.03) to dapirolizumab pegol (24 mg/kg) or placebo; both groups also received standard-of-care medication. Randomisation was stratified based on known confounding variables in SLE clinical trials, including by pooled region (North America *vs* western Europe or Asia–Pacific *vs* Latin America or eastern Europe), disease activity at screening (chronic active *vs* acute flaring), and SLEDAI-2K score at screening (<10 *vs* ≥10).

All patients, investigators, and funders remained blinded to treatment assignments. To maintain blinding, an unblinded pharmacist or other suitably qualified site personnel prepared each dose and provided the blinded infusion (with an opaque infusion bag) to qualified site personnel for administration. Laboratory parameters that could cause unblinding and were therefore kept blinded from investigators were all autoantibodies, IgG, IgA,

IgM, IgE, complement C3 and C4, lactate dehydrogenase, plasma PEG pharmacokinetics and urine PEG pharmacokinetics, dapirolizumab pegol plasma pharmacokinetics, anti-drug antibodies, erythrocyte-bound complement C4d, and SARS-CoV-2 antibodies.

Procedures

Patients received study medication intravenously, as a 2 h infusion for the first administration and as 1 h infusions subsequently, every 4 weeks up to week 48, with the last infusion at week 44.

Investigators were required to initiate glucocorticoid tapering for patients on a dose exceeding 7·5 mg/day prednisone equivalent at baseline, aiming to reach no more than 7·5 mg/day by week 24 (per the European League Against Rheumatism 2019 treatment guidelines[19]), with tapering starting no later than week 8. Guidance was provided but the exact tapering regimen was at the investigator's discretion and could be adapted to the individual patient's disease state, and could therefore have continued beyond week 24. Antimalarials and immunosuppressants were kept stable, unless reductions were required per the investigator's discretion (eg, in cases of tolerability issues). Escape treatment, defined as initiating or increasing doses of concomitant glucocorticoids or immunosuppressants, was introduced if medically indicated. Patients undergoing escape treatment were not required to discontinue the study medication unless it presented a safety concern in combination with dapirolizumab pegol. Patients were encouraged to stay in the trial even if the study medication was permanently discontinued, but were subsequently considered a non-responder.

BILAG-2004, SLEDAI-2K, the Physician Global Assessment (PGA), and safety were assessed at every visit. Tender joint count (TJC), swollen joint count (SJC), and the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) were captured at baseline and weeks 4, 8, 12, 24, 36, and 48. The Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue was evaluated at baseline and weeks 12, 24, 36, and 48. Plasma samples to assess dapirolizumab pegol pharmacokinetics were taken at baseline and weeks 8, 16, 24, 32, 40, and 48, and at the safety follow-up visit at week 54 for patients not entering the open-label extension. Plasma samples to assess PEG pharmacokinetics were taken at baseline and weeks 24, 48, and 54.

Outcomes

The primary outcome was British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA) response at week 48 in patients receiving dapirolizumab pegol versus placebo.[20] The BICLA response required: (1) BILAG-2004 improvement without worsening (ie, BILAG-2004 grade As at baseline improved to B, C, or D; grade Bs at baseline improved to C or D; and no worsening in other BILAG-2004 organ systems, such that no new grade As were reported, nor >1 new grade B compared with baseline); (2) no worsening in SLEDAI-2K total score from baseline; and (3) no significant deterioration (<10 mm increase) from baseline in PGA.

Key secondary outcomes, tested with a gatekeeping procedure to control for multiplicity, in sequential testing order, were: BICLA response at week 24; prevention of severe BILAG flares (ie, severe BILAG flare-free) through week 48; achievement of Lupus Low Disease Activity State (LLDAS)[21] in at least 50% of visits through week 48, and change from baseline in SLEDAI-2K at week 48 (analysed in parallel in the sequential testing hierarchy with the Hochberg procedure, per the multiplicity adjustment strategy); and BICLA response at week 12 (appendix 1 p 49). Other secondary outcomes not controlled for multiplicity included: BILAG improvement without worsening at week 48, change from baseline in PGA at week 48, SLE Responder Index (SRI)-4 response at week 48, and moderate or severe BILAG flares through week 48. A complete list is available in appendix 2 (pp 35–36).

Tertiary outcomes (appendix 2 pp 36–40) not controlled for multiplicity included: remission (as confirmed by Definition of Remission in SLE [DORIS]); reduction in glucocorticoid dose from at least 7·5 mg/day prednisone equivalent at baseline to no more than 7·5 mg/day; LLDAS by visit; change from baseline and at least 50% decrease in TJC, SJC, and their combination (ie, tender and swollen joint count [TSJC]); change from baseline and at least 50% improvement in CLASI activity (CLASI-A) score; change from baseline in FACIT–Fatigue score; change from baseline in anti-dsDNA, complement C3, and complement C4; and pharmacokinetics, evaluated via dapirolizumab pegol and PEG plasma concentrations.

Adverse events (eg, treatment-emergent adverse events, serious treatment-emergent adverse events, adverse events of special interest, and adverse events of special monitoring) were reported throughout the trial and were coded by the Medical Dictionary for Regulatory Activities version 24.0. Further details of the recording, definitions, and severity grading of adverse events are available in appendix 1 (pp 36–38).

An independent data monitoring committee monitored the benefit–risk profile during the trial. The committee regularly reviewed data, met approximately every 6 months, and had access to unblinded data as needed. Certain aspects of the trial were adjudicated by blinded, independent adjudicators, including all BILAG-2004 grade A and Bs in the renal system, BILAG-2004 grade A and Bs due to rare SLE manifestations, intercurrent event escape treatment intervention, severe BILAG flares, and thromboembolic treatment-emergent adverse events.

Statistical analysis

The proposed sample size was 208 patients enrolled to receive dapirolizumab pegol and 104 to receive placebo.

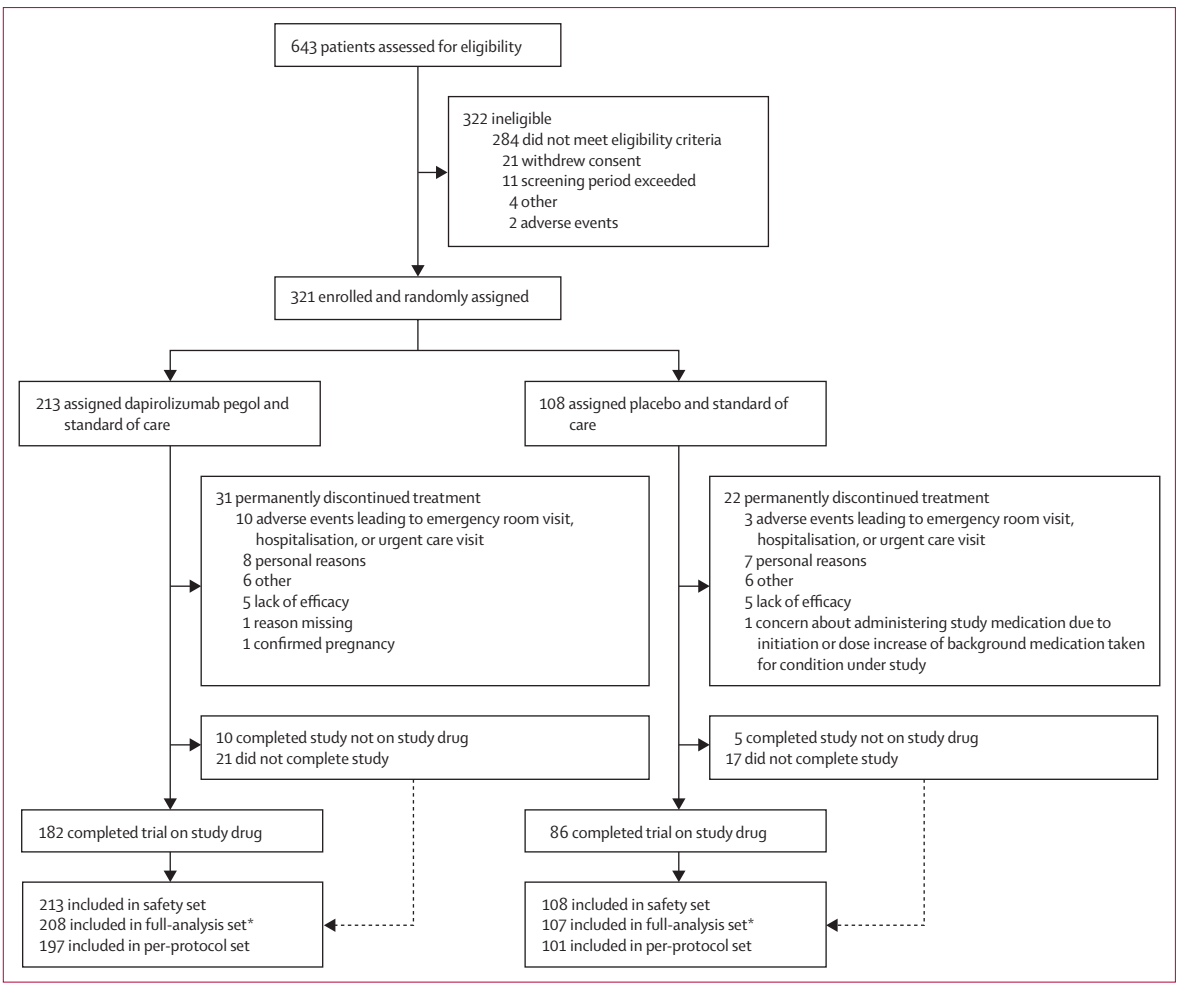

Figure 1: **Trial profile**
*Six patients were excluded from the full-analysis set due to non-compliance with Good Clinical Practice.

The 2:1 allocation ratio was chosen based on the consideration of risks for patients proceeding with standard of care only, without additional treatment intervention, for 48 weeks, and to collect sufficient safety data in patients treated with dapirolizumab pegol. The proposed sample size assumed a placebo responder rate of 32% and a dapirolizumab pegol responder rate of 52% (ie, a 20% improvement) to yield 90% power to confirm statistical significance by use of a two-sided 0·05 significance level test. These assumptions were based on phase 2b responder data at week 24, in patients fulfilling similar eligibility criteria as this phase 3 trial.[15] The originally proposed sample size was 450 patients; however, this was reduced given slow enrolment in the trial during and after the COVID-19 pandemic (see appendix 1 p 38 for further details).

The full-analysis set included all randomly assigned patients (excluding six patients; see Results) as a modified intention-to-treat analysis. Efficacy analyses were conducted on the full-analysis set, apart from the change from baseline in anti-dsDNA antibodies and complements C3 and C4, which were reported for the safety set. The per-protocol set consisted of patients in the full-analysis set who received at least one full dose of study medication and had no important protocol deviations. Pharmacokinetic analyses were conducted on the pharmacokinetic per-protocol set, which included all patients who received at least one dose of study medication and provided at least one quantifiable plasma concentration post-dose without important protocol deviations that would affect the concentration. The safety set included all randomly assigned patients who received at least one dose of study medication. All treatment-emergent adverse events were reported using the safety set. Treatment-emergent adverse events are reported as proportions of patients in each treatment group; risk difference and 95% CIs for the difference between dapirolizumab pegol versus placebo are presented for grouped adverse events.

	Dapirolizumab pegol (n=208)	Placebo (n=107)
Age, years	43·5 (36·0–52·0)	41·0 (32·0–50·0)
Sex		
Female	193 (93%)	100 (94%)
Male	15 (7%)	7 (7%)
Weight, kg	72·4 (17·9)	69·5 (14·8)
BMI, kg/m²	27·5 (6·0)	26·6 (5·3)
Race		
American Indian or Alaskan Native	20 (10%)	9 (8%)
Asian	18 (9%)	9 (8%)
Black or African American	11 (5%)	9 (8%)
Native Hawaiian or other Pacific Islander	1 (1%)	0
White	128 (62%)	63 (59%)
Other or mixed	30 (14%)	17 (16%)
Ethnicity		
Hispanic or Latino	77 (37%)	40 (37%)
Not Hispanic or Latino	131 (63%)	67 (63%)
Region		
North America	46 (22%)	24 (22%)
Eastern Europe	28 (14%)	8 (8%)
Western Europe	59 (28%)	31 (29%)
Asia–Pacific	16 (8%)	8 (8%)
Latin America	59 (28%)	36 (34%)
Time since SLE diagnosis, years	8·6 (3·7–14·5)	7·0 (3·8–14·0)
SLEDAI-2K score		
Mean	10·7 (3·5)	11·2 (3·4)
<10	68 (33%)	28 (26%)
≥10	140 (67%)	79 (74%)
BILAG-2004 score		
Mean	18·4 (4·0)	18·7 (4·4)
Either ≥1 BILAG-2004 grade A and/or ≥2 BILAG grade Bs	201 (97%)	106 (99%)
≥1 BILAG-2004 grade A	89 (43%)	48 (45%)
≥2 organ systems with BILAG-2004 grade A or B	184 (89%)	96 (90%)
SFI flare		
No flare	46 (22%)	24 (22%)
Mild flare	12 (6%)	6 (6%)
Moderate flare	93 (45%)	43 (40%)
Severe flare	56 (27%)	34 (32%)
Missing	1 (1%)	0
PGA score	58·9 (14·1)	59·7 (14·1)
CLASI-A score	7·0 (4·0–11·0)	6·0 (3·0–10·0)
CLASI-D score	0·0 (0·0–0·0)	0·0 (0·0–0·0)
(Table 1 continues in next column)		
(Continued from previous column)		
Tender joint count*	11·0 (7·0–15·0)	12·0 (5·0–16·0)
Swollen joint count*	7·0 (4·0–10·0)	6·0 (3·0–9·0)
LAMDA PGA of Arthritis	55·5 (18·0)	56·5 (18·7)
SLICC/ACR Damage Index total score	0·6 (0·9)	0·5 (1·1)
FACIT–Fatigue score	28·5 (11·2)	27·7 (10·5)
Concomitant SLE medications at baseline	208 (100%)	107 (100%)
Antimalarials†	166 (80%)	91 (85%)
Systemic glucocorticoids	171 (82%)	87 (81%)
Immunosuppressants	129 (62%)	70 (65%)
Systemic glucocorticoid dose		
Mean, mg/day	7·9 (5·9)	9·6 (8·1)
>7·5 mg/day	105 (51%)	51 (48%)
Anti-dsDNA‡ >10 IU	91 (44%)	62 (58%)
Anti-dsDNA‡ >10 IU and complement C3 <LLN	43 (21%)	34 (32%)
Antinuclear antibody titre§ ≥1:80	206 (99%)	102 (95%)
Complement C3 <LLN	65 (31%)	42 (39%)
Complement C4 <LLN	116 (56%)	57 (53%)
Any antiphospholipid antibodies¶	129 (62%)	64 (60%)
Lupus anticoagulant ratio >ULN‖	16 (8%)	13 (12%)

Data are mean (SD), n (%), or median (IQR). Both groups also received standard-of-care medication. Anti-dsDNA=anti-double stranded DNA. BILAG-2004=British Isles Lupus Assessment Group 2004. CLASI-A=Cutaneous Lupus Erythematosus Disease Area and Severity Index–Activity. CLASI-D=Cutaneous Lupus Erythematosus Disease Area and Severity Index–Damage. FACIT=Functional Assessment of Chronic Illness Therapy. IU=international unit. LAMDA=Lupus Arthritis and Musculoskeletal Disease Activity. LLN=lower limit of normal. PGA=Physician Global Assessment. SFI=Safety of Estrogen in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index Flare Index. SLE=systemic lupus erythematosus. SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index-2000. SLICC/ACR=Systemic Lupus International Collaborating Clinics/American College of Rheumatology. ULN=upper limit of normal. *Joint assessments were done on 28 joints. †204 (98%) patients receiving dapirolizumab pegol and 105 (98%) patients receiving placebo were either on antimalarials at baseline or had received antimalarials in the past. ‡Assessed through Phadia EliA. One patient receiving dapirolizumab pegol and one patient receiving placebo had missing data. §Assessed through Indirect Fluorescent Antibody testing with Bio-Rad Kallestad HEp-2 cell line substrate. ¶Antiphospholipid antibodies included anti-phosphatidylserine and anti-prothrombin; includes all patients with >0 antiphospholipid antibodies >ULN or lupus anticoagulant ratio >ULN. ‖The lupus anticoagulant ratio was based on confirmation testing.

Table 1: **Baseline demographics and disease characteristics of the full-analysis set**

Multiplicity-controlled analyses were conducted on primary and key secondary outcomes by use of an overall type I error rate α (two-sided 0·05; appendix 1 p 49). The primary outcome was conducted at the α level, and, if significant, comparisons were sequentially done on the key secondary outcomes (in the order listed in the Outcomes section). If at any point during multiplicity-controlled analyses the comparison was not significant at the α level, formal hypothesis testing was stopped.

The estimand framework, based on treatment condition, population, endpoint, intercurrent events, and population-level summary, dictated intercurrent event handling. For the primary outcome (appendix 1 p 50), a composite strategy was used for intercurrent events

(ie, escape treatment, premature withdrawal from the study, or permanent discontinuation of study medication while remaining in the study), and patients were assigned as non-responders from the day following the event. Following intercurrent event handling, the primary approach for handling missing data of responder outcomes was non-responder imputation. For analysis of severe BILAG flares through week 48, missing data were handled by multiple imputation–missing at random. For changes from baseline and other continuous outcomes, missing data were handled using mixed models for repeated measurements (see appendix 1 p 38 for more information). Further details regarding intercurrent event handling and escape treatment are available in appendix 1 (pp 38–39).

Six sensitivity analyses were conducted for the primary outcome, details of which are provided in appendix 1 (pp 39–40).

Statistical analyses were conducted with SAS version 9.4 or higher.

Role of the funding source

The funders had a role in study design, data collection, data analysis, and data interpretation, and in writing, review, and approval of the manuscript. Medical writers, employed by the funders, assisted with manuscript preparation under the authors' direction.

Results

Between Aug 12, 2020, and June 8, 2023, 643 patients were screened and 321 were enrolled, with 213 randomly assigned to dapirolizumab pegol plus standard of care and 108 to placebo plus standard of care (figure 1). All randomly assigned patients received at least one dose of study medication. The full-analysis set included 208 patients receiving dapirolizumab pegol and 107 receiving placebo; six randomly assigned patients from one site were excluded due to non-compliance with Good Clinical Practice. A summary of important protocol deviations and excluded patients from the per-protocol set is provided in appendix 1 (p 43). The safety set comprised 213 patients receiving dapirolizumab pegol and 108 receiving placebo. Trial completion rates on study medication were similar between dapirolizumab pegol (85% [182/213]) and placebo (80% [86/108]). The final patient visit occurred on June 4, 2024.

Baseline demographics were similar between treatment groups and representative of patients with moderate-to-severe, active SLE (table 1). At baseline, similar proportions of patients receiving dapirolizumab pegol and placebo were on glucocorticoids at a dose exceeding 7·5 mg/day. A lower proportion of patients receiving dapirolizumab pegol versus placebo had a baseline anti-dsDNA concentration exceeding 10 international units and a complement C3 level less than the LLN.

The primary outcome was met, with 50% (103/208) of patients receiving dapirolizumab pegol reaching BICLA response at week 48 versus 35% (37/107) receiving placebo (p=0·011; difference 14·6; 95% CI 3·3–25·8; figures 2, 3). Results of sensitivity analyses were consistent with the results of the primary efficacy analysis, showing that a greater proportion of patients receiving dapirolizumab pegol reached BICLA response at week 48 versus those receiving placebo, including across imputation methods, exclusion of patients who potentially became unblinded, and when partly available data were handled by an alternative method (appendix 1 pp 44, 51). At week 24, 47% (97/208) of patients receiving dapirolizumab pegol reached BICLA response versus 38% (41/107) receiving placebo (p=0·18; difference 7·9; −3·6 to 19·4; figures 2, 3). As this first key secondary outcome was not met, the multiplicity-controlled analyses were stopped. At week 12, a greater proportion of patients receiving dapirolizumab pegol reached BICLA response than patients receiving placebo (figures 2, 3). Reasons for failure to reach BICLA response by visit are provided in appendix 1 (p 45).

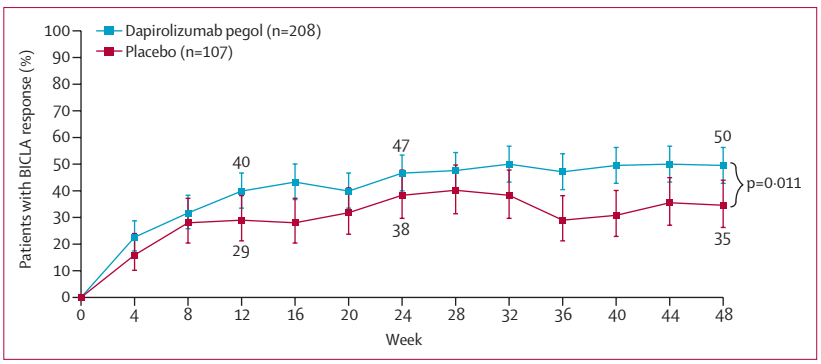

Figure 2: **BICLA response over time in the full-analysis set**
Error bars represent 95% CIs. BICLA=British Isles Lupus Assessment Group-based Composite Lupus Assessment.

A lower proportion of patients receiving dapirolizumab pegol had severe BILAG flares through week 48 compared with those receiving placebo (figures 3, 4A). Lower proportions of patients also had moderate or severe BILAG flares through week 48 in the dapirolizumab pegol group versus the placebo group (figure 3). The proportion of patients who had improvements in BILAG without worsening was greater in the dapirolizumab pegol group compared with the placebo group (figure 3).

LLDAS was reached in at least 50% of study visits through week 48 in 24% (49/208) of patients receiving dapirolizumab pegol and 16% (17/107) receiving placebo (figure 3). A greater proportion of patients receiving dapirolizumab pegol reached DORIS remission and LLDAS at week 48 compared with those receiving placebo (figures 3, 4B). Greater decreases from baseline in both SLEDAI-2K and PGA at week 48 were seen in patients receiving dapirolizumab pegol than in those receiving placebo (figures 3, 4C). A higher proportion of patients receiving dapirolizumab pegol reached SRI-4 response

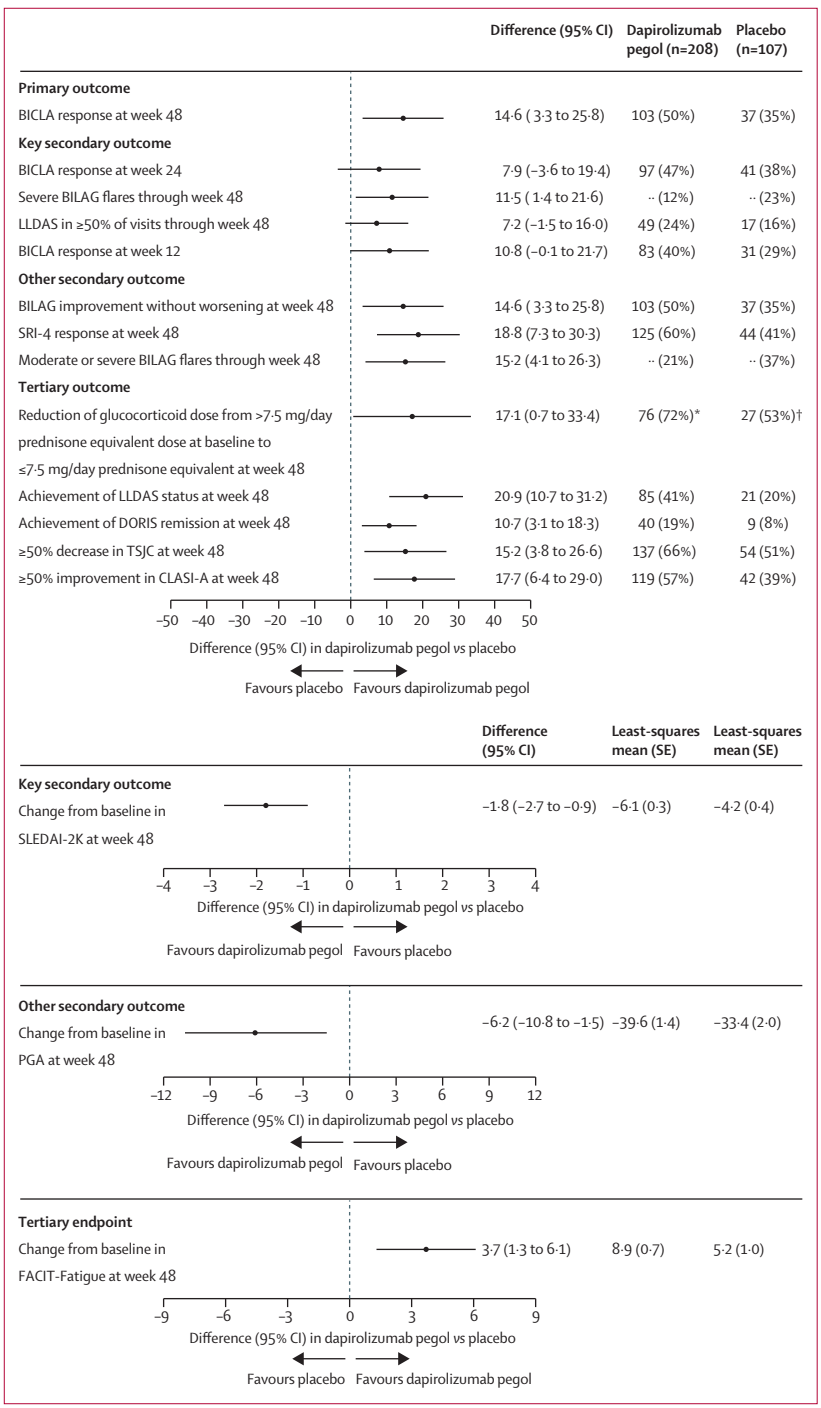

Figure 3: **Primary, secondary, and tertiary outcomes in the full-analysis set**
For BILAG flare outcomes, only percentages are provided and exact patient numbers are not available, given the multiple imputation–missing at random method used. Patients with intercurrent events or missing data cannot be assumed to not have had a flare. BICLA=British Isles Lupus Assessment Group-based Composite Lupus Assessment. BILAG=British Isles Lupus Assessment Group. CLASI-A=Cutaneous Lupus Erythematosus Disease Area and Severity Index–Activity. DORIS=Definition of Remission in Systemic Lupus Erythematosus. FACIT=Functional Assessment of Chronic Illness Therapy. LLDAS=Lupus Low Disease Activity State. PGA=Physician Global Assessment. SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index-2000. SRI-4=Systemic Lupus Erythematosus Responder Index-4. TSJC=tender and swollen joint count. *n=105. †n=51.

at week 48 compared with those receiving placebo (figures 3, 4D). For patients with a glucocorticoid dose exceeding 7·5 mg/day at baseline, a greater proportion of those receiving dapirolizumab pegol reduced their dose to 7·5 mg/day or less by week 48, compared with those receiving placebo (figures 3, 4E).

At week 48, a higher proportion of patients receiving dapirolizumab pegol had a 50% or greater reduction in TSJC compared with those receiving placebo (figure 3). Results were similar for TJC (ie, 64% in the dapirolizumab pegol group *vs* 45% in the placebo group; difference 18·4; 95% CI 7·1–29·7) and SJC (65% *vs* 50%; difference 15·6; 4·1–27·1). By week 48, a higher proportion of patients receiving dapirolizumab pegol had a 50% or greater improvement in their CLASI-A scores compared with the placebo group (figure 3). Changes in TJC, SJC, TSJC, and CLASI-A scores from baseline are presented in appendix 1 (p 41).

Improvements in FACIT–Fatigue scores were seen with dapirolizumab pegol: at week 48 the least-squares mean improvement from baseline was greater for patients receiving dapirolizumab pegol than for those receiving placebo (figure 3).

In patients with anti-dsDNA antibodies above the upper limit of normal at baseline, 25% (19/75) receiving dapirolizumab pegol had normalised levels (<10 international units) at week 48 compared with 7% (4/54) of patients receiving placebo. Furthermore, the median percentage decrease at week 48 was greater in patients receiving dapirolizumab pegol than in those receiving placebo (ie, a 53% decrease [IQR –72·7 to –35·7] *vs* a 16% decrease [–50·0 to 20·0]). For patients whose complement C3 at baseline was less than the LLN, 37% (22/59) of the dapirolizumab pegol group versus 29% (10/35) in the placebo group had normalised levels at week 48. Similarly, for those with complement C4 less than the LLN at baseline, 33% (34/104) of patients in the dapirolizumab pegol group versus 15% (7/46) in the placebo group had normalised levels at week 48. The median percentage increase in complement C3 and C4 from baseline levels less than the LLN was greater in patients receiving dapirolizumab pegol than in those receiving placebo (ie, complement C3: 20% increase [IQR 3·7 to 34·7] *vs* 7% increase [–6·4 to 17·1]; complement C4: 32% increase [9·7 to 60·0] *vs* 5% increase [–13·6 to 17·6]). Pharmacokinetic results are presented in appendix 1 (p 46).

Treatment-emergent adverse events occurred in 83% (176/213) of patients receiving dapirolizumab pegol compared with 75% (81/108) receiving placebo (table 2), and serious treatment-emergent adverse events occurred in 10% (21/213) and 15% (16/108) of patients, respectively. The three most common treatment-emergent adverse events in patients receiving dapirolizumab pegol were COVID-19, urinary tract, and upper respiratory tract infections; all treatment-emergent adverse events with a frequency of 5% or more, in any treatment group, are

presented in table 2. The proportion of patients who permanently discontinued the study medication or trial due to treatment-emergent adverse events was similar in those receiving dapirolizumab pegol and placebo. Treatment-emergent adverse events that were assessed as being related to the study medication by the investigator occurred in similar proportions of patients receiving dapirolizumab pegol and placebo. Protocol-specified treatment-emergent adverse events of special interest included Hy's law (indicating drug-induced liver injury) and malignancies. No cases of potential Hy's law were reported. A lung adenocarcinoma was reported in one patient who received placebo.

3% (6/213) of patients receiving dapirolizumab pegol developed hypersensitivity reactions during the infusion, based on the narrow Standardised Medical Dictionary for Regulatory Activities Query of hypersensitivity. A summary table providing an overview of these six events is available in appendix 1 (p 47). Events were immediately treated by site personnel in line with protocol-specified recommendations (ie, antihistamines or glucocorticoids, or both). All patients improved quickly; none were referred to an emergency room or hospitalised. Of these reactions, two were serious, and five were considered related to study medication, with one event of urticaria considered not related. Four of the patients permanently discontinued treatment, one patient temporarily discontinued treatment (but completed the study on treatment), and the other patient had no changes and completed the study on treatment. Anaphylactic reactions meeting Sampson's criteria occurred in 1% (3/213) of patients receiving dapirolizumab pegol; these patients were part of the six patients with hypersensitivity reactions described above.

A higher proportion of infections was observed in patients receiving dapirolizumab pegol than in those receiving placebo. Most infections were mild or moderate in severity. Mild infections were observed in 45% (95/213) of patients receiving dapirolizumab pegol versus 32% (35/108) of those receiving placebo, and moderate infections were seen in 31% (66/213) versus 33% (36/108), respectively. Severe infections were observed in 1% (3/213) of patients receiving dapirolizumab pegol and 4% (4/108) receiving placebo. Viral herpes infections, including those classified as opportunistic and non-opportunistic, were less frequent in patients receiving dapirolizumab pegol versus placebo (6% [13/213] *vs* 13% [14/108])

Opportunistic infections, based on the narrow Standardised Medical Dictionary for Regulatory Activities

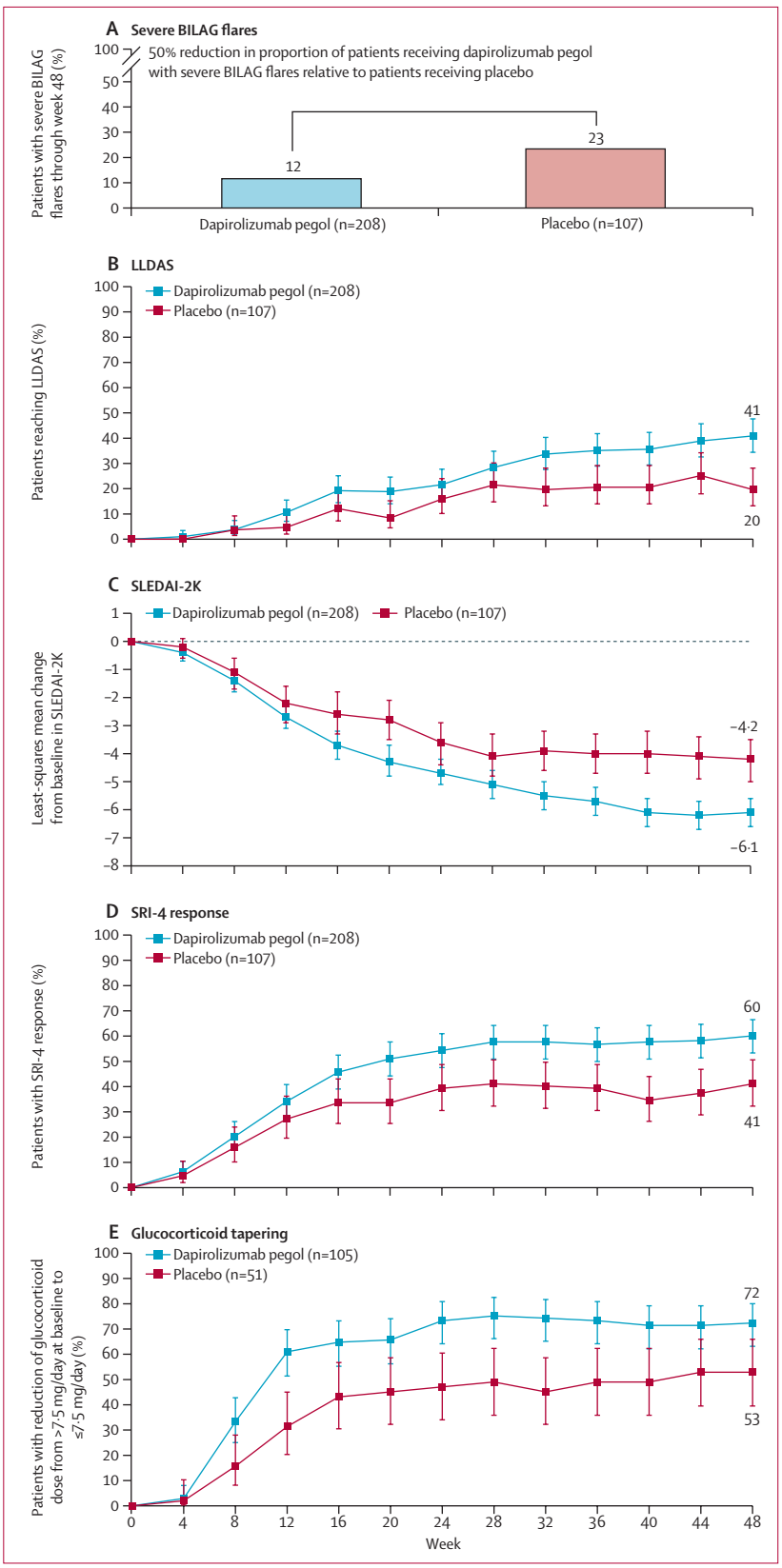

Figure 4: **Select efficacy outcomes over time up to week 48 in the full-analysis set**

Error bars represent 95% CIs. BILAG=British Isles Lupus Assessment Group. LLDAS=Lupus Low Disease Activity State. SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index-2000. SRI-4=Systemic Lupus Erythematosus Responder Index-4.

	Dapirolizumab pegol (n=213)	Placebo (n=108)	Risk difference (95% CI)
Any treatment-emergent adverse event	176 (83%)	81 (75%)	7·6 (−1·5 to 17·6)
Serious treatment-emergent adverse events	21 (10%)	16 (15%)	−5·0 (−13·5 to 2·3)
Anticipated serious adverse events*			
Lower respiratory tract and lung infections	0	2 (2%)	..
Lupus erythematosus	3 (1%)	1 (1%)	..
Urinary tract infections	1 (1%)	0	..
Nephritis	0	0	..
Pain and discomfort	0	1 (1%)	..
Abdominal and gastrointestinal infections	0	2 (2%)	..
Bacterial infections	2 (1%)	1 (1%)	..
Peripheral embolism and thrombosis	0	0	..
Ischaemic coronary artery disorders	1 (1%)	0	..
Herpes viral infections	2 (1%)	1 (1%)	..
Severe treatment-emergent adverse events	13 (6%)	11 (10%)	−4·1 (−11·6 to 1·9)
Permanent discontinuation of drug or study discontinuation due to treatment-emergent adverse events	10 (5%)	4 (4%)	1·0 (−4·8 to 5·3)
Treatment-related treatment-emergent adverse events†	50 (24%)	24 (22%)	1·3 (−8·9 to 10·4)
Deaths‡	1 (1%)	0	0·5 (−3·0 to 2·6)
Most common treatment-emergent adverse events (≥5% of any treatment group by preferred term)			
COVID-19	44 (21%)	17 (16%)	..
Urinary tract infection	29 (14%)	9 (8%)	..
Upper respiratory tract infection	20 (9%)	8 (7%)	..
Nasopharyngitis	18 (9%)	13 (12%)	..
Diarrhoea	15 (7%)	10 (9%)	..
Headache	15 (7%)	7 (7%)	..
Bronchitis	11 (5%)	5 (5%)	..
Nausea	9 (4%)	6 (6%)	..
Herpes zoster	4 (2%)	7 (7%)	..
Oral herpes	4 (2%)	6 (6%)	..
Chest pain	1 (1%)	6 (6%)	..
Treatment-emergent adverse events of special interest	0	1 (1%)	−0·9 (−5·1 to 1·0)
Potential Hy's law§	0	0	..
Malignancies	0	1 (1%)	..
Treatment-emergent adverse events of special monitoring	78 (37%)	26 (24%)	12·5 (1·7–22·3)
Severe infections	3 (1%)	4 (4%)	..
Opportunistic infections¶	6 (3%)‖	1 (1%)**	..
Hypersensitivity treatment-emergent adverse events starting on the day of or the day after an infusion	6 (3%)	0	..
Hypersensitivity treatment-emergent adverse events leading to permanent discontinuation of study treatment	4 (2%)	0	..
Anaphylactic reactions¶††	1 (1%)	0	..
Thromboembolic treatment-emergent adverse events confirmed by adjudication	1 (1%)	0	..
Acute myocardial infarction	1 (1%)	0	..
Neurological events‡‡	0	0	..

(Table 2 continues on next page)

Query of opportunistic infections (which classifies severe, but not all, herpes zoster infections as opportunistic), occurred in 3% (6/213) and 1% (1/108) of patients receiving dapirolizumab pegol and placebo, respectively. In the dapirolizumab pegol group, there were two cases of ophthalmic herpes zoster, one of herpes ophthalmic, two of disseminated cutaneous herpes zoster, and one case of joint tuberculosis. One patient receiving placebo had a case of disseminated cutaneous herpes zoster. Full details of these opportunistic infections are in appendix 1 (p 41). All opportunistic herpes zoster infections responded to antiviral therapy (ie, systemic or topical treatment, or both) and resolved without occurrence of further similar events.

One thromboembolic treatment-emergent adverse event confirmed by adjudication was reported in a patient receiving dapirolizumab pegol (exposure-adjusted incidence rate 0·5 per 100 patient-years [95% CI 0·0–2·8]). This severe, non-ST-elevation myocardial infarction occurred in a 53-year-old patient with a predisposing medical history of triple positive antiphospholipid antibodies, smoking, and a sedentary lifestyle at study entry. The patient was treated with a drug-eluting stent; full details are in appendix 1 (pp 41–42).

One death was reported in a patient who received dapirolizumab pegol. The patient developed gangrene following trauma to the foot, and the cause of death determined at autopsy was heart failure on the grounds of sepsis. The death occurred 57 days after the final dose of dapirolizumab pegol. The patient had a medical history of multiple cardiac, arterial, and venous comorbidities, including occlusive arterial disease (full details in appendix 1 p 42).

One pregnancy occurred in a patient receiving dapirolizumab pegol. Maternal exposure to dapirolizumab pegol occurred before and during pregnancy (one administration was delivered during pregnancy). Dapirolizumab pegol was discontinued upon detection of pregnancy, and the patient completed the study. The patient delivered a healthy baby by caesarean section at 38 weeks gestation, and during follow-up 6 months after birth, the baby was reported to be healthy with no congenital anomalies.

Discussion

In the PHOENYCS GO trial, dapirolizumab pegol treatment in addition to standard of care significantly improved disease activity in patients with SLE compared with placebo plus standard of care, meeting the primary outcome of BICLA response at week 48. Because the first key secondary outcome (ie, BICLA response at week 24) was not met, subsequent key secondary outcomes were not controlled for multiplicity. However, results in favour of dapirolizumab pegol were observed across clinical outcomes, including reduction in severe BILAG flares,

reduction in SLEDAI-2K, increased SRI-4 response, increased achievement of LLDAS and glucocorticoid tapering, and improvement in FACIT–Fatigue score. Serological improvements were also seen with dapirolizumab pegol in concentrations of anti-dsDNA antibodies and complement C3 and C4.

The study protocol required initiation of glucocorticoid tapering no later than week 8. Of patients with a glucocorticoid dose exceeding 7·5 mg/day at baseline, greater proportions receiving dapirolizumab pegol versus placebo reduced their dose to 7·5 mg/day or less over the 48-week trial. This result suggests a glucocorticoid-sparing effect of dapirolizumab pegol, alongside superior control of disease activity, potentially mitigating the damage associated with extended exposure to high glucocorticoid doses and enabling dosage reductions per treatment guidelines.[4,11,12] Imbalances across treatment groups in glucocorticoid tapering might have confounded efficacy outcomes by permitting greater responses in the placebo group. Although the first key secondary outcome (ie, BICLA response at week 24) was not met, separation between the treatment arms in favour of dapirolizumab pegol was seen at week 16. However, the placebo response rate increased from weeks 20 to 32, before decreasing at week 36, whereas the dapirolizumab pegol response rate appeared comparatively stable from weeks 24 to 48. Reasons for this endpoint not being met are not definitive; however, patients in the placebo group had slower tapering of glucocorticoids compared with those in the dapirolizumab pegol group, potentially obscuring the treatment effect of dapirolizumab pegol.

The BICLA and SRI-4 composite outcomes both assess changes in disease activity but differ in some respects. BICLA requires clinically relevant improvement—but not necessarily resolution—of all active disease manifestations, whereas SRI-4 is based primarily on SLEDAI improvements, requiring complete resolution within at least one descriptor, but not across all present disease manifestations.[22] Although some treatments investigated in previous phase 3 trials have shown efficacy in one outcome and not the other,[23] results in favour of dapirolizumab pegol were observed across both outcomes in this trial.

Fatigue is a prominent and debilitating symptom in SLE, affecting up to 80% of patients.[5] Patients receiving dapirolizumab pegol had a greater change from baseline to week 48 in FACIT–Fatigue score compared with those receiving placebo, suggesting a positive effect of dapirolizumab pegol on fatigue. The mean improvement in FACIT–Fatigue score was greater than previously proposed thresholds for minimal clinically important differences,[5] suggesting that treatment with dapirolizumab pegol could have meaningful clinical impacts, although individual patient scores were not assessed.

Dapirolizumab pegol had an acceptable safety profile. Incidence of hypersensitivity reactions was low with dapirolizumab pegol; reactions were successfully managed with treatment with antihistamines or glucocorticoids (or both), and none resulted in hospitalisation. Although rates of mild infections were higher in patients receiving dapirolizumab pegol than in those receiving placebo, no increase was observed for moderate, severe, or serious infections. The finding of fewer severe and serious infections in the dapirolizumab pegol group compared with the placebo group could potentially be related to glucocorticoid tapering or reduced SLE disease activity.[24] Herpes viral infections, including herpes zoster infections, were more common in patients receiving placebo, but three ophthalmic herpes cases occurred in patients receiving dapirolizumab pegol. No ophthalmic herpes cases have been observed in previous trials of dapirolizumab pegol, across a total of 187 patients.[15,25,26]

One thromboembolic treatment-emergent adverse event (myocardial infarction), confirmed by adjudication, was observed in a patient receiving dapirolizumab pegol with a predisposing medical history. In the phase 2b trial of dapirolizumab pegol, thromboembolic treatment-emergent adverse events were less common in patients receiving dapirolizumab pegol (1/137; 1%) than in those receiving placebo (3/45; 7%).[15] Patients with SLE are at higher risk of thromboembolic events compared with the general population.[19] Patients enrolled in PHOENYCS

	Dapirolizumab pegol (n=213)	Placebo (n=108)	Risk difference (95% CI)
(Continued from previous page)			
Infections and infestations	131 (62%)	56 (52%)	9·7 (−1·7 to 20·9)
Mild	95 (45%)	35 (32%)	..
Moderate	66 (31%)	36 (33%)	..
Severe	3 (1%)	4 (4%)	..
Serious	8 (4%)	6 (6%)	..
Herpes viral infections	13 (6%)	14 (13%)	−6·9 (−14·9 to −0·4)
Herpes zoster	4 (2%)	7 (7%)	..
Ophthalmic herpes zoster	2 (1%)§§	0	..
Herpes ophthalmic	1 (1%)¶¶	0	..

Data are n (%) or risk difference (95% CI). Both groups also received standard-of-care medication. ALP=alkaline phosphatase. ALT=alanine aminotransferase. AST=aspartate aminotransferase. SMQ=Standardised Medical Dictionary for Regulatory Activities Queries. SLE=systemic lupus erythematosus. ULN=upper limit of normal. *The specific serious adverse events displayed are protocol-defined serious adverse events—defined as serious adverse events that can be anticipated in a patient with SLE, irrespective and independent of the study treatment or drug exposure—which were summarised to alert investigators to the possibility of these events occurring in the study population. †Considered related by investigator. ‡Death due to gangrene-related sepsis, which was considered not related to treatment by the investigator. However, per the sponsor, the causal role of the study medication in the final outcome of sepsis could not be completely ruled out. §Potential Hy's law, defined as ALT or AST ≥3 times ULN, with coexisting total bilirubin ≥2 times ULN, in the absence of ALP ≥2 times ULN, with no alternative explanation for the biochemical abnormality. ¶Definition based on the narrow SMQ v24.0. ||In patients receiving dapirolizumab pegol, there were two cases of ophthalmic herpes zoster, one of herpes ophthalmic, two of disseminated cutaneous herpes zoster, and one case of joint tuberculosis. **One patient receiving placebo had a case of disseminated cutaneous herpes zoster. ††Three patients receiving dapirolizumab pegol had anaphylaxis reactions meeting Sampson's criteria; two patients had infusion-related reactions and one patient had an anaphylactic reaction. ‡‡Prespecified neurological events: severe or serious headache, positional headache, cranial nerve dysfunction, and signs or symptoms of meningitis. §§The two events were reported as "herpes zoster over left eyelid and forehead, V1" and "left herpes zoster ophthlamicus (dermatome V1/V2)". ¶¶Reported as "herpetic queratitis".

Table 2: **Adverse events in the safety set**

GO were at high risk of thromboembolic events, with a high proportion (61%) having antiphospholipid antibodies at baseline. Historically, the development of first-generation anti-CD40 ligand antibodies was terminated due to thrombotic events that were thought to be a consequence of cross-linking between CD40 ligand-positive cells or cell fragments (eg, platelets) and those carrying Fc receptors.[27] Dapirolizumab pegol is a PEG-conjugated antigen-binding fragment lacking an Fc domain. In a previous in-vivo study in rhesus monkeys, the risk of thromboembolic events was not higher in those treated with dapirolizumab pegol compared with the control group, and dapirolizumab pegol failed to activate platelets in vitro.[27] The data presented here, and in the phase 2b trial,[15] further support the theory that the absence of the Fc domain in dapirolizumab pegol could mitigate the risk of thromboembolic events.[27]

Results from PHOENYCS GO reinforce the potential of targeting CD40–CD40 ligand interactions in the treatment of SLE. CD40–CD40 ligand interactions are important in the adaptive immune response, including in cytokine and autoantibody production, and in the expansion of autoreactive B and T cells in SLE. Targeting the CD40–CD40 ligand pathway can disrupt early-stage immune activation and broadly modulate multiple inflammatory pathways implicated in SLE pathology.[14] Dapirolizumab pegol has been shown to reduce B-cell activation, autoantibody production, T-cell activation, and APC function.[16,17] Dapirolizumab pegol has also been shown to suppress type I and type II interferon pathways, and reduce levels of key pro-inflammatory cytokines related to APC function.[16,17] In line with broad immune response effects, patients treated with dapirolizumab pegol in the PHOENYCS GO trial had reductions in anti-dsDNA antibodies and increases in serum complement C3 and C4 concentrations.

A limitation of this trial is that, as in other phase 3 SLE trials, all patients continued to receive standard-of-care medication, potentially hindering measurement of the full treatment effect of dapirolizumab pegol.[7,28] Variable glucocorticoid doses could have confounded results, with different levels of glucocorticoid use between treatment arms. However, the glucocorticoid tapering regimen could also be seen as a key strength of the study design, as it allowed evaluation of disease activity against background glucocorticoid tapering, in line with treatment guidelines.[19] An additional strength of the trial is that data were adjudicated by blinded independent expert adjudicators; thus, the quality of data collected was carefully considered. The level of missing data for the primary outcome was low, with minimal bias expected to be introduced due to missing data; sensitivity analyses further support that the primary outcome was robust to missing data. In addition, the non-responder imputation method used to handle missing data is a conservative approach and could have underestimated the true response rates. Despite these points, the trial was limited by the reduction in the sample size because of the COVID-19 pandemic, which impacted the safety assessment given the reduced total exposure. Furthermore, only data up to week 48 are presented; additional studies are required to confirm the long-term efficacy and tolerability of dapirolizumab pegol.

In summary, in the PHOENYCS GO trial, dapirolizumab pegol plus standard of care showed statistically significant improvement in disease activity versus placebo plus standard of care, as measured by BICLA response at week 48, against a background of glucocorticoid tapering. The ongoing open-label extension, PHOENYCS GLIDE (NCT04976322), will continue to assess the long-term safety and tolerability of dapirolizumab pegol, and a second phase 3 trial, PHOENYCS FLY (NCT06617325), has been initiated to confirm the results of PHOENYCS GO. The results of PHOENYCS GO reinforce the therapeutic potential of targeting CD40–CD40 ligand interactions, which could add a unique mechanism of action to the available treatment options for patients with moderate-to-severe, active SLE.

Contributors

MEBC, DAI, TD, EFM, ZT, YI, JG-R, CM, AN, and CS contributed to study conception. TD, EFM, YI, ADA, SB, EDK, CM, TJ, AN, and CS contributed to the study design. MEBC, DAI, JTM, TD, MP, EMV, EFM, ZT, ADA, YI, SB, JG-R, EDK, NZ, CM, TJ, AN, and CS contributed to the data analysis. All authors contributed to drafting and review of the manuscript for important intellectual content. MEBC, YI, SB, JG-R, EDK, NZ, CM, TJ, AN, and CS had access to and verified all the included data in the study. All authors provided approval and had final responsibility for the decision to submit for publication.

Declaration of interests

MEBC has been a consultant for AstraZeneca, GSK, and UCB, and received grant or research support from GSK and UCB. DAI has been a consultant for AstraZeneca, Autolus, Eli Lilly, GSK, Merck Serono, Novartis, Servier, and UCB, and reports honoraria passed to a local arthritis charity (the Rheumatology Discretionary Fund UCL Charity). JTM has been a consultant for AbbVie, Amgen, AstraZeneca, Aurinia, Biogen, BMS, Boehringer Ingelheim, Eli Lilly, EMD Serono, Genentech, GSK, Merck, Novartis, RemeGen, Sanofi, UCB, and Zenas; reports speakers bureaus for AbbVie, Biogen, BMS, Sanofi, and Zenas; received grant or research support from AstraZeneca, BMS, and GSK; and received medical writing support from AbbVie, BMS, and UCB. TD has been a consultant for AbbVie, Eli Lilly, Janssen, Roche/GNE, and UCB, and reports speakers bureaus for Novartis. MP has been a consultant for Amgen, AnaptysBio, Annexon Bio, AstraZeneca, Atara Biosciences, Aurinia, Autolus, Bain Capital, Baobab Therapeutics, Biocryst, Biogen, Boxer Capital, Cabaletta Bio, Caribou Biosciences, CTI Clinical Trial and Consulting Services, CVS Health, DualityBio, Eli Lilly, EMD Serono, Emergent Biosolutions, Escient Pharmaceuticals, Exo Therapeutics, Gentibio, GSK, iCell Gene Therapeutics, Innovaderm Research, IQVIA, Kezar Life Sciences, Kira Pharmaceuticals, Nexstone Immunology, Nimbus Lakshmi, Novartis, Ono Pharma, PPD Development, Proviant, Regeneron, Seismic Therapeutic, Senti Biosciences, Sinomab Biosciences, Steritas, Takeda, Tenet Medicines, TG Therapeutics, UCB, Variant Bio, Worldwide Clinical Trials, and Zydus; reports speakers bureaus for Arthros–FocusMedEd, AstraZeneca, and Aurinia; and received grant or research support from AstraZeneca, Aurinia, Eli Lilly, Exagen, GSK, and Janssen. EMV has been a consultant for AbbVie, Alpine, Amgen, Artiva, AstraZeneca, Aurinia, BMS, Dianthus, Eli Lilly, Kymerva, Merck, Mescapse, NICE, Novartis, Otsuka, Pfizer, Roche, Ventus, UCB, and Zenas; has been a paid instructor for Novartis; reports speakers bureaus for AstraZeneca, Novartis, and Otsuka; received grant or research support from CESAS, Novartis, and Roche;

received royalties from the University of Leeds; has received payment for expert testimony from the National Institute for Health and Care Excellence; received support for attending meetings and/or travel from Merck and UCB; participated on a Data Safety Monitoring Board or Advisory Board for Aurinia and Dianthus; and reports a leadership or fiduciary role at SLEuro. EFM has been a consultant for AstraZeneca, Biogen, BMS, Cabaletta, Cullinan, Dragonfly, Eli Lilly, EMD Serono, Galapagos, GSK, Novartis, Orna, Quell, RemeGen, UCB, and Zenas; reports speakers bureaus for AstraZeneca, BMS, EMD Serono, Novartis, and Viatris; received grant or research support from AbbVie, Amgen, AstraZeneca, Biogen, BMS, Eli Lilly, EMD Serono, Genentech–Hoffman La Roche, GSK, Janssen, Novartis, Takeda, and UCB; received support for attending meetings and/or travel from AstraZeneca and EMD Serono; planned pending or issued patents with AstraZeneca and Monash University; and holds stock or stock options in Dragonfly. ZT has been a consultant for AbbVie, AstraZeneca, BMS, GSK, Roche, and UCB/Biogen, and received grant or research support from AstraZeneca and GSK. ADA has been a consultant for AstraZeneca, GSK, and Novartis; received grant or research support from Alumis, AstraZeneca, BMS, Cabaletta, Idorsia, NKARTA, Sanofi, and UCB; and has participated on a Data Safety Monitoring Board or Advisory Board for Amgen and Janssen. YI, EDK, NZ, CM, TJ, and CS are employees and shareholders of UCB. SB, JG-R, and AN are employees and shareholders of Biogen.

Data sharing

Underlying data from this Article can be requested by qualified researchers 6 months after product approval in the USA and Europe, or global development is discontinued, and 18 months after trial completion. Investigators can request access to anonymised individual patient-level data and redacted trial documents, which can include analysis-ready datasets, the study protocol, annotated case-report form, statistical analysis plan, dataset specifications, and clinical study report. Before use of the data, proposals must be approved by an independent review panel at https://vivli.org/ and a signed data-sharing agreement will need to be completed. All documents are available in English only, for a prespecified time, typically 12 months, on a password-protected portal.

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