# Efficacy and safety of deucravacitinib, an oral, selective, allosteric TYK2 inhibitor, in patients with active systemic lupus erythematosus: Results from a phase 2, randomized, double-blind, placebo-controlled study

Victoria P. Werth,[1] Marilyn Pike,[2] Joan T. Merrill,[3] Eric Morand,[4] Ronald van Vollenhoven,[5] Coburn Hobar,[6] Nikolay Delev,[6] Vaishali Shah,[6] Brian Sharkey,[6] Thomas Wegman,[6] Ian Catlett,[6] Subhashis Banerjee,[6] Shalabh Singhal[6]

[1]University of Pennsylvania and the Michael J. Crescenz VA Medical Center, Philadelphia, PA, USA; [2]MedPharm Consulting, Inc, Raleigh, NC, USA; [3]Oklahoma Medical Research Foundation, Oklahoma City, OK, USA; [4]Monash University, Victoria; Department of Rheumatology, Monash Health, Victoria, Australia; [5]Amsterdam University Medical Centers, Amsterdam, the Netherlands; [6]Bristol Myers Squibb, Princeton, NJ, USA

## Introduction

- Tyrosine kinase 2 (TYK2) mediates signaling of select immune cytokines, eg, Type I interferons, which play a key role in the pathogenesis of systemic lupus erythematosus (SLE)[1]
  - The related Janus kinases (JAK) 1/2/3 mediate signaling of a wider array of cytokines and mediators involved not only in broader inflammatory pathways, but also in developmental, metabolic, and hematopoietic pathways (see Supplemental Material)
- Deucravacitinib is an oral, selective, allosteric TYK2 inhibitor with a unique mechanism of action distinct from that of JAK 1/2/3 inhibitors
  - It selectively binds the TYK2 regulatory domain, locking the enzyme in the inactive state[1]
- Deucravacitinib is approved in the US, Canada, and Australia for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.[2-4] Deucravacitinib is also approved in Japan for the treatment of plaque psoriasis, generalized pustular psoriasis, and erythrodermic psoriasis[5]
  - Deucravacitinib was efficacious and well tolerated in a phase 2 trial in psoriatic arthritis[6]

## Objective

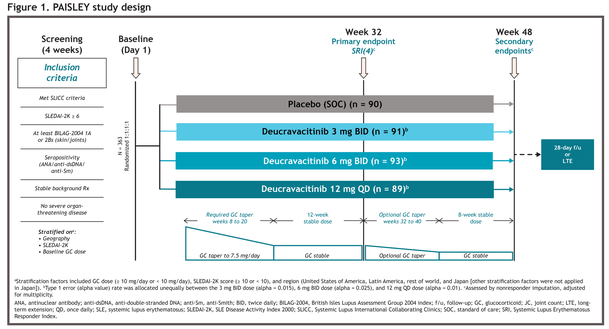
- Assess the efficacy and safety of deucravacitinib in patients with active SLE in a phase 2 study

## Methods

### Study design

- PAISLEY was a 48-week, randomized, double-blind, placebo-controlled, multicenter phase 2 trial in patients with active SLE with moderate to severe disease (Systemic Lupus Erythematosus Disease Activity Index 2000 [SLEDAI-2K] score ≥ 6), who have met the Systemic Lupus International Collaborating Clinics (SLICC) criteria (NCT03252587)
- Patients were randomized 1:1:1:1 to deucravacitinib (3 mg twice daily [BID], 6 mg BID, or 12 mg once daily [QD]) or placebo (**Figure 1**)

**Figure 1. PAISLEY study design**




aStratification factors included GC dose (≤ 10 mg/day or < 10 mg/day), SLEDAI-2K score (≤ 10 or < 10), and region (United States of America, Latin America, rest of world, and Japan [other stratification factors were not applied in Japan]). bType I error (alpha value) rate was allocated unequally between the 3 mg BID dose (alpha = 0.015), 6 mg BID dose (alpha = 0.025), and 12 mg QD dose (alpha = 0.01). cAssessed by nonresponder imputation, adjusted for multiplicity.

ANA, antinuclear antibody; anti-dsDNA, anti-double-stranded DNA; anti-Sm, anti-Smith; BID, twice daily; BILAG-2004, British Isles Lupus Assessment Group 2004 Index; f/u, follow-up; GC, glucocorticoid; JC, joint count; LTE, long-term extension; QD, once daily; SLE, systemic lupus erythematosus; SLEDAI-2K, SLE Disease Activity Index 2000; SLICC, Systemic Lupus International Collaborating Clinics; SOC, standard of care; SRI, Systemic Lupus Erythematosus Responder Index.

### Study endpoints

- Primary endpoint at week 32: Systemic Lupus Erythematosus Responder Index (SRI[4]) response
- Secondary endpoints at week 48:
  - SRI(4) response
  - British Isles Lupus Assessment Group–based Composite Lupus Assessment (BICLA) response
  - Decrease of ≥ 50% from baseline in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI-50) in patients with baseline CLASI Activity (CLASI-A) score ≥ 10
  - Lupus Low Disease Activity State (LLDAS)
  - Change from baseline in swollen, tender, and swollen + tender (active) joint counts
- Exploratory endpoints:
  - Time to SRI(4) response
  - Change from baseline in CLASI-A score over time
- Safety (adverse events [AEs] and laboratory parameters)

### Statistical methods

- Binary endpoints were analyzed using a logistic regression model with treatment group and stratification factors as covariates, and nonresponder imputation for missing values or patients who took prespecified medications. Continuous secondary endpoints were analyzed using a mixed model for repeated measures

## Results

### Patient disposition[7]

- Among 363 patients randomized, 275 (76%) completed 48 weeks of treatment (see Supplemental Material)
- Treatment discontinuations
  - Placebo: 24 (26.7%); 3 (3.3%) due to AEs
  - Deucravacitinib 3 mg BID: 20 (22.0%); 8 (8.8%) due to AEs
  - Deucravacitinib 6 mg BID: 17 (18.3%); 6 (6.5%) due to AEs
  - Deucravacitinib 12 mg QD: 27 (30.3%); 12 (13.5%) due to AEs

### Baseline patient characteristics and disease activity[7]

- Baseline demographic and clinical characteristics were balanced across treatment groups (**Table 1**)

**Table 1. Baseline patient characteristics and disease activity**

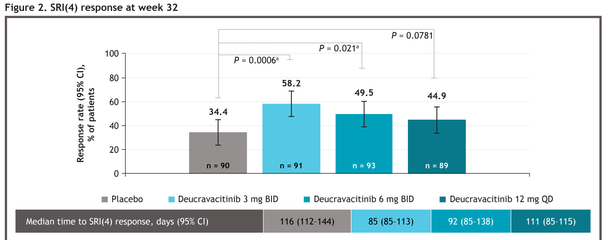
| | Total N = 363 | Placebo n = 90 | Deucravacitinib 3 mg BID n = 91 | Deucravacitinib 6 mg BID n = 93 | Deucravacitinib 12 mg QD n = 89 |
|---|---|---|---|---|---|
| **Age, years, mean** | 40.1 | 40.1 | 40.2 | 40.9 | 39.0 |
| **BMI, kg/m², mean** | 26.8 | 27.5 | 26.5 | 26.1 | 27.1 |
| **Gender, female, n (%)** | 334 (92.0) | 80 (88.9) | 85 (93.4) | 88 (94.6) | 81 (91.0) |
| **Race, n (%)** | | | | | |
| White | 234 (64.5) | 60 (66.7) | 62 (68.1) | 55 (59.1) | 57 (64.0) |
| Black or African American | 33 (9.1) | 6 (6.7) | 10 (11.0) | 8 (8.6) | 9 (10.1) |
| Asian | 44 (12.1) | 10 (11.1) | 9 (9.9) | 15 (16.1) | 10 (11.2) |
| **Use of glucocorticoids, antimalarials, and immunosuppressants, n (%)** | | | | | |
| Glucocorticoid | 292 (80.4) | 74 (82.2) | 74 (81.3) | 73 (78.5) | 71 (79.8) |
| ≥ 10 mg/day prednisone or equivalent | 181 (49.9) | 47 (52.2) | 45 (49.5) | 46 (49.5) | 43 (48.3) |
| Antimalarial | 315 (86.8) | 75 (83.3) | 81 (89.0) | 84 (90.3) | 75 (84.3) |
| Immunosuppressant | 188 (51.8) | 46 (51.1) | 53 (58.2) | 43 (46.2) | 46 (51.7) |
| Antimalarial, immunosuppressant, and glucocorticoid | 117 (32.2) | 26 (28.9) | 38 (41.8) | 26 (28.0) | 27 (30.3) |
| **SLEDAI-2K score, mean (SD)** | 10.8 (3.1) | 10.8 (3.1) | 11.1 (3.2) | 10.8 (3.2) | 10.7 (3.0) |
| **Overall BILAG-2004, at least one A, n (%)** | 197 (54.3) | 51 (56.7) | 51 (56.0) | 44 (47.3) | 51 (57.3) |
| **PGA, mean (SD)** | 1.83 (0.4) | 1.82 (0.4) | 1.80 (0.3) | 1.84 (0.4) | 1.86 (0.4) |
| **CLASI-A score, mean (SD)** | 8.3 (6.3) | 8.0 (5.1) | 8.6 (7.6) | 8.2 (6.5) | 8.4 (5.8) |
| **Active joint count, mean (SD)** | 9.0 (5.7) | 9.2 (6.0) | 8.6 (4.8) | 8.8 (6.1) | 9.4 (5.7) |

BID, twice daily; BILAG-2004, British Isles Lupus Assessment Group 2004 Index; BMI, body mass index; CLASI-A, Cutaneous Lupus Erythematosus Disease Area and Severity Index Activity; PGA, Physician's Global Assessment; QD, once daily; SD, standard deviation; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

### Efficacy

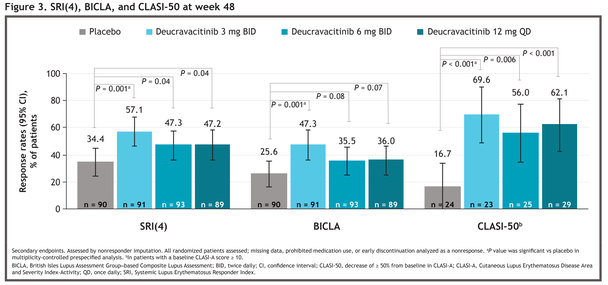
- The primary endpoint at week 32 was met, with significantly greater proportions of patients in the deucravacitinib 3 mg BID (58.2%) and 6 mg BID (49.5%) groups achieving SRI(4) responses compared with placebo (34.4%; $P < 0.001$ and $P = 0.02$, respectively)[7] (**Figure 2**)
  - The median time to SRI(4) response was 85 days with deucravacitinib 3 mg BID and 92 days with 6 mg BID versus 116 days with placebo[7]
- Patients treated with deucravacitinib demonstrated improvement across all secondary endpoints compared with placebo[7] (**Figure 3**)
  - SRI(4) response was sustained across all deucravacitinib groups up to 48 weeks
  - More patients treated with deucravacitinib had low disease activity (LLDAS) at week 48 compared with placebo (deucravacitinib 3 mg BID: 36.3%, $P < 0.001$ vs placebo; 6 mg BID: 23.7%, $P = 0.006$; and 12 mg QD: 25.8%, $P < 0.001$ vs placebo: 13.3%)
  - At week 48, a greater improvement from baseline was observed in active joint counts with deucravacitinib treatment compared with placebo (deucravacitinib 3 mg BID: -8.9, $P = 0.001$ vs placebo; 6 mg BID: -8.3, $P = 0.03$; and 12 mg QD: -8.7, $P = 0.005$ vs placebo: -7.6)

**Figure 2. SRI(4) response at week 32**




Assessed by nonresponder imputation. All randomized patients assessed; missing data, prohibited medication use, or early discontinuation analyzed as a nonresponse. aP value was significant vs placebo in multiplicity-controlled prespecified analysis.
BID, twice daily; CI, confidence interval; QD, once daily; SRI, Systemic Lupus Erythematosus Responder Index.

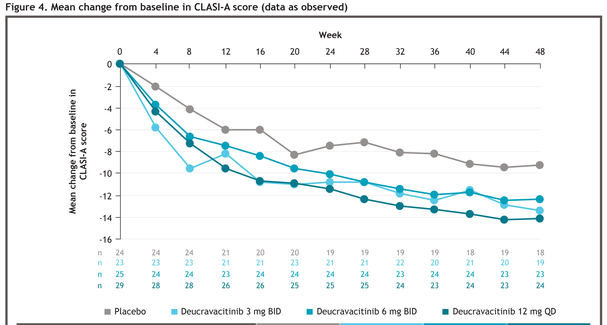
**Figure 3. SRI(4), BICLA, and CLASI-50 at week 48**




Secondary endpoints. Assessed by nonresponder imputation. All randomized patients assessed; missing data, prohibited medication use, or early discontinuation analyzed as a nonresponse. aP value was significant vs placebo in multiplicity-controlled prespecified analysis. bIn patients with a baseline CLASI-A score ≥ 10.
BICLA, British Isles Lupus Assessment Group–based Composite Lupus Assessment; BID, twice daily; CI, confidence interval; CLASI-50, decrease of ≥ 50% from baseline in CLASI-A; CLASI-A, Cutaneous Lupus Erythematosus Disease Area and Severity Index Activity; QD, once daily; SRI, Systemic Lupus Erythematosus Responder Index.

- In patients with a CLASI-A score ≥ 10 at baseline, greater mean changes from baseline in CLASI-A were observed with deucravacitinib treatment compared with placebo over 48 weeks (**Figure 4**)

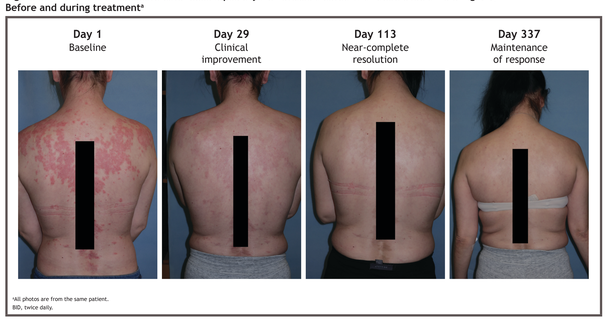
**Figure 4. Mean change from baseline in CLASI-A score (data as observed)**




No P values were calculated for exploratory endpoints.
BID, twice daily; CLASI-A, Cutaneous Lupus Erythematosus Disease Area and Severity Index Activity; QD, once daily; SD, standard deviation.

- Clearance of cutaneous lupus lesions was observed in patients treated with deucravacitinib 3 mg BID (**Figures 5A** and **5B**)

**Figure 5A. Patient with subacute cutaneous lupus erythematosus treated with deucravacitinib 3 mg BID: Before and during treatment[a]**




[a]All photos are from the same patient.
BID, twice daily.

**Figure 5B. Patient with discoid lupus erythematosus treated with deucravacitinib 3 mg BID: Before and during treatment[a]**


[a]All photos are from the same patient.
BID, twice daily.

### Serological markers of activity[7] (see Supplemental Material)

- Anti-double-stranded DNA (anti-dsDNA) antibodies were significantly reduced with deucravacitinib versus placebo
- Complement C4 was significantly increased with deucravacitinib versus placebo
  - These improvements with deucravacitinib occurred early and were maintained through the 48 weeks of treatment

### Safety[7]

- Deucravacitinib was generally well tolerated in patients in this study (**Table 2**)
  - Fewer serious AEs occurred with deucravacitinib compared with placebo
  - Upper respiratory tract infection, nasopharyngitis, urinary tract infections, and headache were the most common AEs (≥ 10%) in deucravacitinib-treated patients (see Supplemental Material)
  - There was no increase in incidence of influenza, coronavirus disease 2019 (COVID-19), or herpes zoster
  - Oral herpes and skin-related AEs were more frequent with deucravacitinib treatment, with acne and nondescript rash being more frequent with higher doses of deucravacitinib
  - There were no cases of tuberculosis, opportunistic infections, major adverse cardiac events, or thromboembolic events in any treatment group; malignancies were rare, with similar rates across all groups
- No meaningful abnormalities in mean levels of hematology and chemistry laboratory parameters were observed (see Supplemental Material)

**Table 2. Safety summary, weeks 0 to 48**

| AE, n[a] (%) | Placebo n = 90 | Deucravacitinib 3 mg BID n = 91 | Deucravacitinib 6 mg BID n = 93 | Deucravacitinib 12 mg QD n = 89 |
|---|---|---|---|---|
| **Deaths** | 0 | 0 | 0 | 0 |
| **AEs** | 79 (87.8) | 85 (93.4) | 81 (87.1) | 75 (84.3) |
| **SAEs** | 11 (12.2) | 7 (7.7) | 8 (8.6) | 7 (7.9) |
| Serious infections/infestations | 1 (1.1)[b] | 1 (1.1)[c] | 2 (2.2)[d] | 1 (1.1)[e] |
| **AEs leading to treatment discontinuation** | 3 (3.3) | 3 (3.3) | 6 (6.5) | 11 (12.4) |
| **AEs of interest** | | | | |
| **Overall infections/infestations** | 48 (53.3) | 60 (65.9) | 60 (64.5) | 45 (50.6) |
| Influenza | 1 (1.1) | 3 (3.3) | 1 (1.1) | 3 (3.4) |
| **COVID-19** | **3 (3.3)** | **3 (3.3)** | **5 (5.4)** | **3 (3.4)** |
| Tuberculosis | 0 | 0 | 0 | 0 |
| **Herpes zoster[f]** | **4 (4.4)** | **3 (3.3)** | **3 (3.2)** | **2 (2.2)** |
| Oral herpes | 0 | 4 (4.4) | 4 (4.3) | 5 (5.6) |
| **Skin-related AEs** | 12 (13.3) | 15 (16.5) | 32 (34.4) | 30 (33.7) |
| Acne | 4 (4.4) | 3 (3.3) | 8 (8.6) | 7 (7.9) |
| Rash | 0 | 2 (2.2) | 3 (3.2) | 7 (7.9) |
| **Malignancy events** | 1 (1.1)[g] | 1 (1.1)[h] | 0 | 1 (1.1)[i] |
| **MACE** | 0 | 0 | 0 | 0 |
| **Thromboembolic events** | 0 | 0 | 0 | 0 |

[a]n is the number of patients who experienced an event. [b]COVID-19 pneumonia. [c]Chronic pyelonephritis. [d]One patient with COVID-19 and one patient with herpes zoster. [e]Urinary tract infection. [f]Includes herpes zoster, herpes ophthalmic, genital herpes zoster. [g]Basal cell carcinoma. [h]Breast carcinoma. [i]Vaginal squamous cell carcinoma.
AE, adverse event; BID, twice daily; COVID-19, coronavirus disease 2019; MACE, major adverse cardiac events; QD, once daily; SAE, serious adverse event.

## Conclusions

- Deucravacitinib demonstrated sustained improvement in mucocutaneous activity as measured by CLASI-A
- Deucravacitinib showed significantly higher SRI(4) responses with sustained efficacy compared with placebo at week 32 and week 48
  - All secondary endpoints were achieved or meaningfully improved at week 48, including BICLA, CLASI-50, and LLDAS
- Deucravacitinib was well tolerated, and the safety profile was consistent with earlier trials in psoriasis and psoriatic arthritis[2,5,6]
  - There were no laboratory abnormalities characteristic of JAK 1/2/3 inhibitors
  - There were no increases in incidence of serious infections
  - There were numerical increases in cutaneous AEs and nonserious infections; however, the majority of cases were mild to moderate and did not lead to discontinuation
  - There was no increase in incidence of influenza, herpes zoster, or COVID-19 infections
- **Deucravacitinib shows promise as a novel therapy for SLE and warrants further investigation in phase 3 trials**

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Email for Dr Victoria Werth: werth@pennmedicine.upenn.edu