Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: Efficacy and safety results from the 52-week, randomized, double-blinded, placebo-controlled phase 3 POETYK PSO-1 trial

April W. Armstrong, MD, MPH,[a] Melinda Gooderham, MD,[b] Richard B. Warren, MD,[c] Kim A. Papp, MD, PhD,[d] Bruce Strober, MD, PhD,[e] Diamant Thaçi, MD,[f] Akimichi Morita, MD, PhD,[g] Jacek C. Szepietowski, MD, PhD,[h] Shinichi Imafuku, MD,[i] Elizabeth Colston, MD, PhD,[j] John Throup, PhD,[j] Sudeep Kundu, PhD,[j] Steve Schoenfeld, MD,[j] Misti Linaberry, MPH,[j] Subhashis Banerjee, MD,[j] and Andrew Blauvelt, MD, MBA[k]

Background: Effective, well-tolerated oral psoriasis treatments are needed.

Objective: To compare the efficacy and safety of deucravacitinib, an oral, selective, allosteric tyrosine kinase 2 inhibitor, versus placebo and apremilast in adults with moderate to severe plaque psoriasis.

Methods: Participants were randomized 2:1:1 to deucravacitinib 6 mg every day (n = 332), placebo (n = 166), or apremilast 30 mg twice a day (n = 168) in the 52-week, double-blinded, phase 3 POETYK PSO-1 trial (NCT03624127). Coprimary end points included response rates for ≥75% reduction from baseline in Psoriasis Area and Severity Index (PASI 75) and static Physician's Global Assessment score of 0 or 1 (sPGA 0/1) with deucravacitinib versus placebo at week 16.

Results: At week 16, response rates were significantly higher with deucravacitinib versus placebo or apremilast for PASI 75 (194 [58.4%] vs 21 [12.7%] vs 59 [35.1%]; $P < .0001$) and sPGA 0/1 (178 [53.6%] vs 12 [7.2%] vs 54 [32.1%]; $P < .0001$). Efficacy improved beyond week 16 and was maintained through week 52. Adverse event rates with deucravacitinib were similar to those with placebo and apremilast.

From the Department of Dermatology, Keck School of Medicine, University of Southern California, Los Angeles, California[a]; SKiN Centre for Dermatology, Department of Dermatology at Queen's University, and Probity Medical Research, Peterborough, Ontario, Canada[b]; Dermatology Centre at Salford Royal NHS Foundation Trust Hospital, NIHR Manchester Biomedical Research Centre at the University of Manchester, Manchester, United Kingdom[c]; K Papp Clinical Research and Probity Medical Research, Waterloo, Ontario, Canada[d]; Department of Dermatology, Yale University School of Medicine, New Haven, and Central Connecticut Dermatology Research, Cromwell, Connecticut[e]; Comprehensive Center for Inflammation Medicine, University of Lübeck, Lübeck, Germany[f]; Department of Geriatric and Environmental Dermatology, Nagoya City University Graduate School of Medical Sciences, Nagoya City, Aichi, Japan[g]; Department of Dermatology, Venereology and Allergology, Wroclaw Medical University, Wrocław, Poland[h]; Dermatology, Faculty of Medicine, Fukuoka University, Fukuoka, Japan[i]; Bristol Myers Squibb, Princeton, New Jersey[j]; and Oregon Medical Research Center, Portland, Oregon.[k]

Funding sources: This clinical trial was sponsored by Bristol Myers Squibb.

IRB approval status: The study protocol and patient informed consent received appropriate approval before initiation of the study at each site by an institutional review board and/or independent ethics committee.

Accepted for publication July 1, 2022.

Reprints not available from the authors.

Correspondence to: April W. Armstrong, MD, MPH, Department of Dermatology, Keck School of Medicine, University of Southern California, 1520 San Pablo St, Los Angeles, CA 90033. E-mail: aprilarmstrong@post.harvard.edu.

Published online July 9, 2022.

0190-9622

https://doi.org/10.1016/j.jaad.2022.07.002

Limitations: One-year duration, limited racial diversity.

Conclusion: Deucravacitinib was superior to placebo and apremilast across multiple efficacy end points and was well tolerated in moderate to severe plaque psoriasis. (J Am Acad Dermatol 2023;88:29-39.)

Key words: apremilast; clinical trial; deucravacitinib; efficacy; phase 3; psoriasis; Psoriasis Area and Severity Index; safety; skin diseases; static Physician's Global Assessment.

INTRODUCTION

Tyrosine kinase 2 (TYK2) mediates signaling of interleukin 23 (IL-23) and other cytokines involved in psoriasis pathogenesis (eg, type I interferons).[1-4] Individuals with loss-of-function genetic polymorphisms of *TYK2* have lower risk of developing psoriasis and other immune-mediated diseases, without substantial safety concerns.[1,4-7] These features make TYK2 an attractive target for novel psoriasis treatments.[1-4]

CAPSULE SUMMARY

- Deucravacitinib is a selective allosteric tyrosine kinase 2 inhibitor under investigation for the treatment of multiple immune-mediated inflammatory diseases.
- Here, in a pivotal phase 3 study, deucravacitinib was shown to be superior to both placebo and apremilast for the treatment of patients with moderate to severe plaque psoriasis.

Deucravacitinib is an oral, selective TYK2 inhibitor under investigation for the treatment of multiple immune-mediated inflammatory diseases, including plaque psoriasis, psoriatic arthritis, inflammatory bowel disease (Crohn's disease and ulcerative colitis), and systemic lupus erythematosus.[1,2] Deucravacitinib inhibits TYK2 via an allosteric mechanism by selectively binding to the unique regulatory or pseudokinase rather than the active catalytic domain of the enzyme.[1] In a phase 2 trial of patients with psoriasis, deucravacitinib demonstrated superior efficacy versus placebo based on ≥75% reduction from baseline in Psoriasis Area and Severity Index (PASI 75) over 12 weeks.[8] In a phase 2 trial of patients with psoriatic arthritis, deucravacitinib was more efficacious than placebo in improving joint and skin manifestations over 16 weeks.[9] In both studies, deucravacitinib was well tolerated with no clinically meaningful treatment-related laboratory abnormalities observed.[8,9] This report describes results from the pivotal phase 3 POETYK PSO-1 study of deucravacitinib in patients with moderate to severe plaque psoriasis.

METHODS

Study design and participants

POETYK PSO-1 was a 52-week, randomized, double-blinded, double-dummy, placebo-controlled and active comparator—controlled trial conducted at 154 sites in Canada, China, Germany, Japan, Poland, Russia, South Korea, Spain, Taiwan, the United Kingdom, and the United States, in accordance with the Declaration of Helsinki and the International Council for Harmonization Good Clinical Practice guideline. Independent institutional review board approvals were obtained. All participants provided written informed consent.

Individuals ≥18 years of age with moderate to severe psoriasis (static Physician's Global Assessment [sPGA] ≥3, PASI ≥12, and body surface area involvement ≥10%) for ≥6 months before screening were enrolled. Complete inclusion and exclusion criteria are provided in the Supplementary Material, available via Mendeley at https://data.mendeley.com/datasets/vpb6m7gmhn/.

Patients were randomized 2:1:1 to deucravacitinib 6 mg every day, placebo, or apremilast twice a day on day 1 (Supplemental Fig 1, available via Mendeley at https://data.mendeley.com/datasets/vpb6m7gmhn/). Apremilast was titrated as per label in a blinded manner from 10 mg every day to 30 mg twice a day over the first 5 days of dosing; apremilast was not used in China where it was not approved at the start of the study. Randomization was stratified by geographic region (United States, Japan, China, and rest of world), previous biologic use (for psoriasis, psoriatic arthritis, or other inflammatory diseases only; yes/no), and body weight (≥90 kg and <90 kg). Body weight stratum was not applied in Japan or China due to lower expected body weights in these countries.

Deucravacitinib-randomized patients maintained their initial treatment through week 52. At week 16, patients randomized to placebo crossed over to deucravacitinib. At week 24, patients randomized to apremilast who did not achieve ≥50% reduction from baseline in PASI (PASI 50) switched to deucravacitinib, whereas those who achieved PASI 50 continued apremilast through week 52. Investigative site staff, the study sponsor and

Abbreviations used:

AEs:	adverse events
IL:	interleukin
PASI 50:	≥50% reduction from baseline in Psoriasis Area and Severity Index
PASI 75:	≥75% reduction from baseline in Psoriasis Area and Severity Index
PASI 90:	≥90% reduction from baseline in Psoriasis Area and Severity Index
PASI 100:	100% reduction from baseline in Psoriasis Area and Severity Index
PGA-F 0/1:	Physician's Global Assessment of Fingernail score of 0 or 1
PSSD:	Psoriasis Symptoms and Signs Diary
PY:	person-years
QoL:	quality of life
SAEs:	serious adverse events
sPGA 0/1:	static Physician's Global Assessment score of 0 or 1
ss-PGA 0/1:	scalp-specific Physician's Global Assessment score of 0 or 1
TYK2:	tyrosine kinase 2

designated personnel, and patients and their families remained blinded to all treatment assignments and treatment switches.

Procedures

This trial included a 4-week screening period before study entry, a 16-week placebo- and apremilast-controlled period, an 8-week apremilast-controlled period, and a 28-week maintenance period (Supplementary Fig 1, available via Mendeley at https://data.mendeley.com/datasets/vpb6m7gmhn/). Most efficacy and safety assessments were performed at baseline and at weeks 1, 2, 4, 8, 12, 16, and every 4 weeks thereafter through week 52 at investigative sites; the Psoriasis Symptoms and Signs Diary (PSSD) was completed daily by patients through week 52 (24-hour recall). Patients completing 52 weeks of treatment could enroll in a single-arm, open-label, long-term extension trial where they received deucravacitinib 6 mg once daily. Patients who discontinued or did not enroll in the long-term extension study were followed for 4 weeks after the last dose.

Outcome measures

Coprimary efficacy end points were achievement of PASI 75 and sPGA 0/1 (clear/almost clear) with a ≥2-point improvement from baseline for deucravacitinib versus placebo at week 16. Key secondary end points included sPGA 0 (clear), ≥90% and 100% reductions from baseline in PASI (PASI 90 and PASI 100), scalp-specific Physician's Global Assessment score of 0 or 1 (ss-PGA 0/1) (clear or almost clear), and Physician's Global Assessment of Fingernails score of 0 or 1 (PGA-F 0/1) (clear or almost clear); additional outcomes and hierarchical testing details are presented in Supplementary Table I, available via Mendeley at https://data.mendeley.com/datasets/vpb6m7gmhn/. Patient-reported symptoms and signs of psoriasis were evaluated using the PSSD.[10,11] Quality of life (QoL) was assessed using the Dermatology Life Quality Index. Safety data included adverse events (AEs) (Medical Dictionary for Regulatory Activities version 23.0), serious AEs (SAEs), and standard laboratory analytes. An external data monitoring committee periodically conducted safety assessments, and blinded external adjudication committees reviewed specific types of AEs, including infections, cardiovascular events, and suicidal ideation and behavior.

Statistical analysis

Sample size calculations were based on superiority testing of deucravacitinib for PASI 75 and sPGA 0/1 at week 16 versus placebo (coprimary end points) and versus apremilast. Expected response rates were 60%, 10%, and 35% for deucravacitinib, placebo, and apremilast, respectively, based on deucravacitinib phase 2 study results, published placebo response rates, and apremilast prescribing information.[12] Using these assumptions, a sample size of 600 patients was determined to have sufficient statistical power for analysis of efficacy outcomes and safety exposure data with deucravacitinib.

Efficacy analyses were performed using the full analysis set (all randomized patients). Missing data were imputed by nonresponder imputation for the coprimary end points; note, as this study was conducted during the global SARS-CoV2 (COVID-19) pandemic, PASI 75 and sPGA 0/1 analyses during weeks 24-52 excluded patients at visits that were missed solely due to COVID-19, as advised by the US Food and Drug Administration.[13] The modified baseline-observation-carried-forward method was used to impute missing data for continuous secondary end points for patients who discontinued study treatment before week 16 due to lack of efficacy or AEs. Patients who discontinued study treatment before week 16 for other reasons had their last valid observation carried forward (including the baseline value as applicable).

A stratified Cochran-Mantel-Haenszel test was used to compare PASI 75 and sPGA 0/1 response rates at week 16 in the deucravacitinib versus placebo groups. Both coprimary end points needed to demonstrate statistical significance using a 2-sided α level of 0.05 for the study to be considered successful, and statistical analysis of the key secondary end points was performed in a hierarchical manner only if between-

group differences in both coprimary end points were significant (Supplementary Table I, available via Mendeley at https://data.mendeley.com/datasets/vpb6m7gmhn/). Testing of additional end points not in the hierarchy was considered nominal.

Safety analyses were performed using the as-treated population (all patients who received ≥1 dose of study treatment). Week 52 safety data are reported as exposure-adjusted incidence rates per 100 person-years (PY) to account for variable periods of treatment exposure in the 3 treatment groups. All analyses were performed using SAS software (SAS Institute Inc), version 9.4 or higher.

RESULTS

Study participants

Between August 7, 2018, and July 5, 2019, a total of 666 patients were randomly assigned to treatment with deucravacitinib 6 mg every day (n = 332), placebo twice a day (n = 166), or apremilast 30 mg twice a day (n = 168) (Supplementary Fig 2, available via Mendeley at https://data.mendeley.com/datasets/vpb6m7gmhn/). Baseline patient demographics and disease characteristics were similar across groups and were typical for patients with moderate to severe plaque psoriasis (Table I).

Treatment outcomes

Response rates for the 2 coprimary end points were significantly higher with deucravacitinib versus placebo: PASI 75 was achieved in 194 (58.4%) versus 21 (12.7%) patients ($P < .0001$), and sPGA 0/1 was achieved in 178 (53.6%) versus 12 (7.2%) patients ($P < .0001$) at week 16 (Table II; Fig 1). Response rates for PASI 75 and sPGA 0/1 continued to improve through week 24 and were higher with deucravacitinib versus apremilast at weeks 16 and 24 ($P < .0001$ for each end point; Table II). Deucravacitinib responses were maintained to week 52 with continuous treatment (Fig 2).

Deucravacitinib achieved statistical significance for multiple other secondary end points versus placebo and apremilast (Table II, Supplementary Table I, available via Mendeley at https://data.mendeley.com/datasets/vpb6m7gmhn/, Supplementary Fig 3, available via Mendeley at https://data.mendeley.com/datasets/vpb6m7gmhn/). A greater percentage of patients treated with deucravacitinib achieved PASI 90 versus patients in the placebo and apremilast groups at week 16 (35.5% vs 4.2% and 19.6%, respectively; $P < .0001$ vs placebo; $P = .0002$ vs apremilast) and versus the apremilast group at week 24 (42.2% vs 22.0%; $P < .0001$). Photographs illustrating PASI 90 response in a representative patient are provided in Supplementary Fig 4, available via Mendeley at https://data.mendeley.com/datasets/vpb6m7gmhn/. Statistical significance was also achieved for deucravacitinib versus placebo and apremilast on measures of complete skin clearance, including sPGA 0 (17.5% vs 0.6% and 4.8%; $P < .0001$ for both) and PASI 100 (14.2% vs 0.6% and 3.0%; $P < .0001$ for both) at week 16. In patients with moderate to severe scalp psoriasis (ss-PGA ≥3) at baseline (deucravacitinib, n = 209; placebo, n = 121; apremilast, n = 110), 70.3% treated with deucravacitinib achieved ss-PGA 0/1 at week 16 versus 17.4% and 39.1% of patients treated with placebo and apremilast, respectively ($P < .0001$ for both). In the few patients with moderate to severe fingernail psoriasis (PGA-F ≥3) at baseline (deucravacitinib, n = 43; placebo, n = 34), response rates for PGA-F 0/1 at week 16 were numerically higher with deucravacitinib (20.9%) than with placebo (8.8%).

Greater reduction from baseline in PSSD symptom scores was observed at week 16 with deucravacitinib versus placebo and apremilast (adjusted mean change from baseline [SE], −26.7 [1.8] vs −3.6 [2.1] and −17.8 [2.2]; $P < .0001$ for both); significant improvements with deucravacitinib versus placebo were observed by week 2. The proportion of patients who achieved a PSSD symptom score of 0 (symptom-free) with deucravacitinib at week 16 (7.9%) was significantly higher versus placebo (0.7%; $P = .0013$) and was numerically higher versus apremilast (4.4%; $P = .17$) (Table II). Deucravacitinib-treated patients reported greater QoL improvements than the other treatment groups, with a significantly greater Dermatology Life Quality Index 0/1 response rate at week 16 (41.0%) versus patients who received placebo (10.6%; $P < .0001$) or apremilast (28.6%; $P = .0088$); significant improvements versus placebo were observed by week 2.

In patients who crossed over from placebo to deucravacitinib treatment at week 16, clinical responses at week 52 were comparable to patients who received continuous deucravacitinib treatment from day 1. This was observed for PASI 75 and sPGA 0/1 (Fig 2) and for change from baseline in PASI (−80.5% vs −78.4%), ss-PGA 0/1 (69.7% vs 65.6%), and Dermatology Life Quality Index 0/1 (46.1% vs 43.2%), respectively.

Safety

Over 52 weeks, total exposure was 419.1 PY for deucravacitinib, 46.9 PY for placebo, and 115.8 PY for apremilast. For the weeks 0-16 and weeks 0-52 assessment periods, AE rates overall were similar across all 3 treatment groups, and the most frequent AEs in deucravacitinib-treated patients were nasopharyngitis and upper respiratory tract infection,

Table I. Baseline patient demographics and disease characteristics

Parameter	Placebo (*n* = 166)	Deucravacitinib 6 mg every day (*n* = 332)	Apremilast 30 mg twice a day (*n* = 168)	Total (*N* = 666)
Age, mean (SD), y	47.9 (14.0)	45.9 (13.7)	44.7 (12.1)	46.1 (13.4)
Weight, mean (SD), kg	89.1 (22.3)	87.9 (21.8)	87.5 (21.1)	88.1 (21.7)
BMI, mean (SD), kg/m^2	30.2 (7.4)	29.8 (7.0)	29.6 (6.7)	29.9 (7.0)
Sex, *n* (%)				
Male	113 (68.1)	230 (69.3)	110 (65.5)	453 (68.0)
Female	53 (31.9)	102 (30.7)	58 (34.5)	213 (32.0)
Race, *n* (%)				
White	128 (77.1)	267 (80.4)	139 (82.7)	534 (80.2)
Black or African American	3 (1.8)	2 (0.6)	1 (0.6)	6 (0.9)
Asian	34 (20.5)	59 (17.8)	28 (16.7)	121 (18.2)
Other	1 (0.6)	4 (1.2)	0 (0.0)	5 (0.8)
Age at disease onset, mean (SD), years	31.5 (14.7)	29.6 (15.1)	27.8 (13.1)	29.6 (14.6)
Duration of disease, mean (SD), years	17.3 (12.8)	17.1 (12.4)	17.7 (11.8)	17.3 (12.3)
Psoriasis-related history, *n* (%)				
Scalp	155 (93.4)	298 (89.8)	156 (92.9)	609 (91.4)
Nails	76 (45.8)	138 (41.6)	64 (38.1)	278 (41.7)
Psoriatic arthritis	26 (15.7)	64 (19.3)	31 (18.5)	121 (18.2)
Prior systemic treatment use, *n* (%)				
Yes	109 (65.7)	200 (60.2)	109 (64.9)	418 (62.8)
Biologic*	63 (38.0)	130 (39.2)	66 (39.3)	259 (38.9)
Nonbiologic	46 (27.7)	70 (21.1)	43 (25.6)	159 (23.9)
No	57 (34.3)	132 (39.8)	59 (35.1)	248 (37.2)
sPGA score (0-4), *n* (%)				
3 (moderate)	128 (77.1)	257 (77.4)	139 (82.7)	524 (78.7)
4 (severe)	37 (22.3)	75 (22.6)	29 (17.3)	141 (21.2)
PASI (0-72), mean (SD)	20.7 (8.0)	21.8 (8.6)	21.4 (9.0)	21.4 (8.6)
BSA involvement, mean (SD), %	25.3 (16.9)	26.6 (15.9)	26.6 (16.1)	26.3 (16.2)
DLQI (0-30), mean (SD)	11.4 (6.6)	12.0 (6.7)	12.4 (6.8)	12.0 (6.7)
PSSD symptom score (0-100), mean (SD)	51.4 (26.8)	51.7 (25.2)	56.2 (25.2)	52.8 (25.6)
ss-PGA ≥3, *n* (%)	121 (72.9)	209 (63.0)	110 (65.5)	440 (66.1)

BMI, Body mass index; *BSA*, body surface area; *DLQI*, Dermatology Life Quality Index; *IL*, interleukin; *PASI*, Psoriasis Area and Severity Index; *PSSD*, Psoriasis Symptoms and Signs Diary; *sPGA*, static Physician's Global Assessment; *ss-PGA*, scalp-specific Physician's Global Assessment.
*Including tumor necrosis factor inhibitors or antibodies to IL-23p19, IL-12/23p40, or IL-17.

whereas headache, diarrhea, and nausea were more common with apremilast than in other treatment groups (Table III).

The frequency of SAEs during weeks 0−16 was lowest in the deucravacitinib group (2.1% vs 5.5% with placebo and 2.4% with apremilast). The incidence rates of SAEs during weeks 0−52 were 7.5/100 PY with deucravacitinib and 5.2/100 PY with apremilast. All SAEs over 52 weeks occurred in single patients, except for pericarditis and cholecystitis, which each occurred in 2 deucravacitinib-treated patients. Discontinuations due to AEs over weeks 0−52 were lower with deucravacitinib (3.3/100 PY) versus placebo (14.7/100 PY) and apremilast (10.3/100 PY). No AEs leading to discontinuation occurred in >1 patient receiving deucravacitinib (Supplementary Table II, available via Mendeley at https://data.mendeley.com/datasets/vpb6m7gmhn/). One death occurred in the placebo group on Day 23 due to hypertensive cardiovascular disease; no deaths occurred with deucravacitinib or apremilast (Table III). Incidence rates for AEs of interest, including skin events (Table III), herpes zoster (Table III), serious infections (Table III, Supplementary Table III, available via Mendeley at https://data.mendeley.com/datasets/vpb6m7gmhn/), and malignancies and cardiovascular events (Supplementary Table IV, available via Mendeley at https://data.mendeley.com/datasets/vpb6m7gmhn/), were low.

Laboratory parameters

No clinically meaningful changes from baseline were observed for laboratory parameters through week 16 (Supplementary Fig 5, available via

Table II. Outcomes at weeks 16 and 24

	Outcomes at weeks 16 and 24						
End point	**Placebo**	**Deucravacitinib**	**Apremilast**	**Difference vs placebo (95% CI)**	***P* value vs placebo**	**Difference vs apremilast (95% CI)**	***P* value vs apremilast**
PASI 75, *n* (%)							
Week 16	21/166 (12.7)*	194/332 (58.4)*	59/168 (35.1)	46.1 (38.9-53.2)	<.0001	23.0 (14.1-31.8)	<.0001
Week 24	NA	230/332 (69.3)	64/168 (38.1)	NA	NA	31.0 (22.2-39.8)	<.0001
PASI 90, *n* (%)							
Week 16	7/166 (4.2)	118/332 (35.5)	33/168 (19.6)	31.6 (25.8-37.5)	<.0001	15.8 (8.2-23.5)	.0002
Week 24	NA	140/332 (42.2)	37/168 (22.0)	NA	NA	20.0 (11.9-28.2)	<.0001
PASI 100, *n* (%)							
Week 16	1/166 (0.6)	47/332 (14.2)	5/168 (3.0)	13.7 (9.8-17.6)	<.0001	11.3 (6.8-15.8)	<.0001
Week 24	NA	58/332 (17.5)	11/168 (6.5)	NA	NA	11.1 (5.6-16.6)	.0007
sPGA 0/1, *n* (%)							
Week 16	12/166 (7.2)*	178/332 (53.6)*	54/168 (32.1)	46.7 (40.2-53.2)	<.0001	21.4 (12.7-30.1)	<.0001
Week 24	NA	195/332 (58.7)	52/168 (31.0)	NA	NA	27.5 (18.8-36.2)	<.0001
sPGA 0, *n* (%)							
Week 16	1/166 (0.6)	58/332 (17.5)	8/168 (4.8)	17.1 (12.8-21.3)	<.0001	12.9 (7.7-18.0)	<.0001
Week 24	NA	60/332 (18.1)	11/168 (6.5)	NA	NA	11.7 (6.2-17.3)	.0004
Change from baseline PSSD symptom score, adjusted mean (SE)†							
Week 16	−3.6 (2.1)	−26.7 (1.8)	−17.8 (2.2)	−23.1 (2.0) [−27.0, −19.1]	<.0001	−8.8 (2.0) [−12.8, −4.9]	<.0001
Week 24	NA	−31.9 (2.0)	−20.7 (2.4)	NA	NA	−11.2 (2.0) [−15.2, −7.3]	<.0001
PSSD symptom score 0, *n* (%)							
Week 16	1/149 (0.7)	24/305 (7.9)	7/158 (4.4)	7.4 (4.1-10.7)	.0013	3.3 (−1.0 to 7.7)	.1702
Week 24	NA	30/305 (9.8)	8/158 (5.1)	NA	NA	4.7 (0.0-9.5)	.0787
DLQI 0/1, *n* (%)							
Week 16	17/160 (10.6)	132/322 (41.0)	46/161 (28.6)	30.5 (23.4-37.6)	<.0001	12.3 (3.4-21.1)	.0088
Week 24	NA	155/322 (48.1)	39/161 (24.2)	NA	NA	24.3 (15.7-32.8)	<.0001
ss-PGA 0/1, *n* (%)							
Week 16	21/121 (17.4)	147/209 (70.3)	43/110 (39.1)	52.8 (43.7-62.0)	<.0001	29.6 (18.7-40.6)	<.0001
Week 24	NA	151/209 (72.2)	47/110 (42.7)	NA	NA	29.0 (17.8-40.2)	<.0001

Missing data were imputed with nonresponder imputation, with the exception of PSSD, in which missing data were imputed using the modified baseline-observation-carried-forward method.

DLQI, Dermatology Life Quality Index; *NA*, not applicable; *PASI*, Psoriasis Area and Severity Index; *PSSD*, Psoriasis Symptoms and Signs Diary; *sPGA*, static Physician's Global Assessment; *ss-PGA*, scalp-specific Physician's Global Assessment.

*Coprimary end point.

†Data shown are adjusted mean difference (SE).

Mendeley at https://data.mendeley.com/datasets/vpb6m7gmhn/; Supplementary Table V, available via Mendeley at https://data.mendeley.com/datasets/vpb6m7gmhn/). The most common laboratory abnormality reported as an AE was increased blood creatine phosphokinase in all 3 treatment groups (exposure-adjusted incidence rates: 3.8/100 PY for deucravacitinib, 2.1/100 PY for placebo, and 3.4/100 PY for apremilast), which was typically associated with recent physical exertion and resolved without treatment in most cases.

DISCUSSION

Findings from POETYK PSO-1 demonstrated superiority of deucravacitinib on PASI 75 and sPGA 0/1 at week 16 versus placebo (coprimary end points) and apremilast. Response rates continued to increase through week 24 in deucravacitinib-treated patients and were maintained through week 52. Deucravacitinib treatment was also associated with significantly greater improvements compared with placebo and apremilast across multiple ranked secondary efficacy end points, including

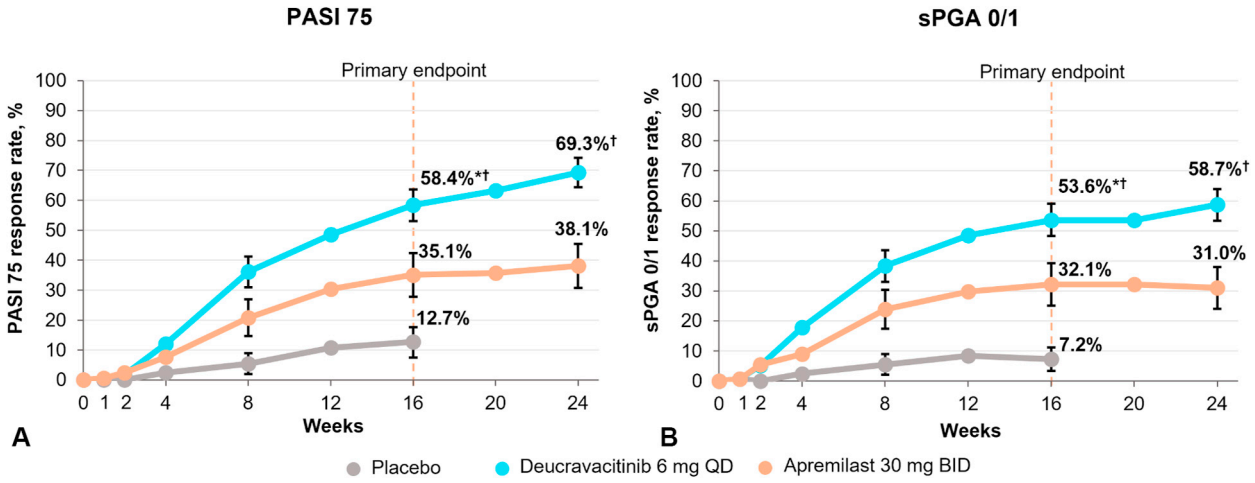

Fig 1. Efficacy measures through week 24. **A,** Coprimary end point: percentage of patients achieving PASI 75. (**B**) Coprimary end point: percentage of patients achieving an sPGA 0/1 with ≥2-point improvement from baseline. Error bars represent 95% confidence intervals. *$P < .0001$ vs placebo. †$P < .0001$ vs apremilast. *PASI 75*, ≥75% reduction from baseline in Psoriasis Area and Severity Index; *sPGA 0/1*, static Physician's Global Assessment score of 0 or 1.

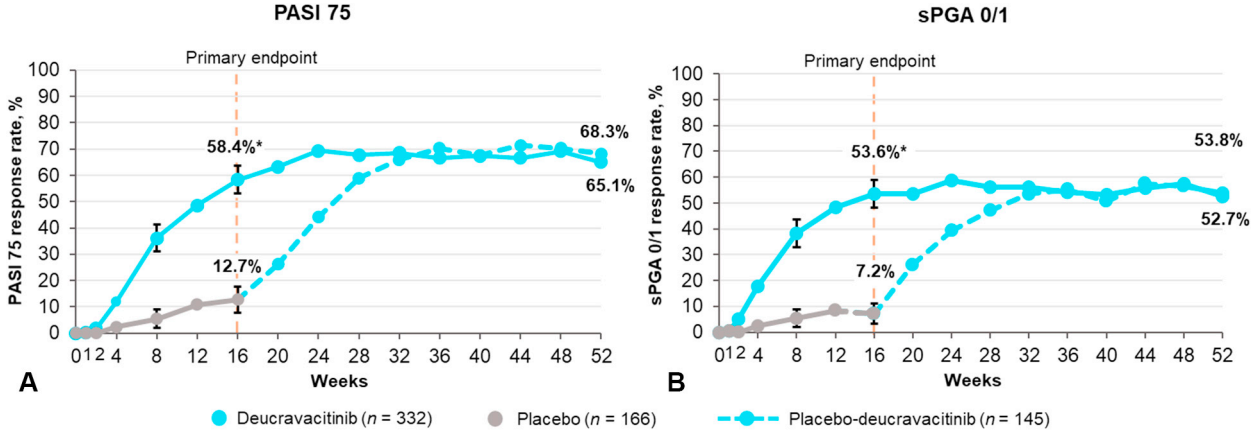

Fig 2. Efficacy responses with deucravacitinib through week 52. **A,** Percentage of patients achieving PASI 75. **B,** Percentage of patients achieving sPGA 0/1 with ≥2-point improvement from baseline. Error bars represent 95% confidence intervals. *$P < .0001$ vs placebo. *PASI 75*, ≥75% reduction from baseline in Psoriasis Area and Severity Index; *sPGA 0/1*, static Physician's Global Assessment.

measures of clear skin and improvements in scalp psoriasis, psoriasis symptoms, and QoL. Efficacy outcomes for apremilast in this trial were similar to those reported with this agent in earlier phase 3 trials in psoriasis.[14,15]

Types and rates of AEs, SAEs, and AEs resulting in treatment discontinuation were generally comparable among patients receiving deucravacitinib, placebo, or apremilast. The most common AEs with apremilast and those leading to discontinuation were not unexpected given its known safety profile. Exposure-adjusted AE incidence was consistent in the week 0-16 and week 0-52 assessment periods, and no new relevant AEs emerged with continued deucravacitinib exposure.

An increased rate of viral infections, most notably herpes zoster reactivation, has been documented among patients receiving other immunomodulatory agents, including anti-interferon-I antibodies, anti-IL-23p19 or IL-12/23p40 antibodies, JAK 1/2/3 inhibitors, and anti—tumor necrosis factor agents.[16] In this study, herpes zoster infections occurred at a low rate in the deucravacitinib arm (exposure-adjusted incidence rate, 1.2/100 PY; 95% CI, 0.4-2.8; $n = 5$, including 3 Asian patients); all cases were mild to moderate, localized, followed a benign clinical course, were not serious, and did not lead to discontinuation. There was no evidence indicating an increased risk of SARS-CoV-2 infection or severe COVID-19 outcomes with deucravacitinib treatment

Table III. Overall safety summary, weeks 0-16 and weeks 0-52

AE category	Weeks 0-16		
	Placebo (*n* = 165), *n* (%)	Deucravacitinib (*n* = 332), *n* (%)	Apremilast (*n* = 168), *n* (%)
Any AE	70 (42.4)	176 (53.0)	93 (55.4)
Serious AEs	9 (5.5)	7 (2.1)	4 (2.4)
Treatment-related AEs	20 (12.1)	65 (19.6)	36 (21.4)
AE leading to discontinuation	7 (4.2)	6 (1.8)	10 (6.0)
Deaths	1* (0.6)	0 (0.0)	0 (0.0)
Most common AEs†			
Nasopharyngitis	7 (4.2)	21 (6.3)	14 (8.3)
Upper respiratory tract infection	6 (3.6)	21 (6.3)	3 (1.8)
Headache	5 (3.0)	16 (4.8)	17 (10.1)
Diarrhea	6 (3.6)	13 (3.9)	17 (10.1)
Nausea	4 (2.4)	7 (2.1)	19 (11.3)

	Weeks 0-52					
	Placebo (*n* = 165), total PY = 46.9		Deucravacitinib (*n* = 531), total PY = 419.1		Apremilast (*n* = 168), total PY = 115.8	
AE category	*n*	EAIR/100 PY‡	*n*	EAIR/100 PY‡	*n*	EAIR/100 PY‡
Any AE	70	202.5	395	211.8	127	234.3
Serious AEs	9	19.2	31	7.5	6	5.2
Treatment-related AEs	20	45.2	117	33.1	45	46.9
AE leading to discontinuation	7	14.7	14	3.3	12	10.3
Deaths	1*	2.1	0	0.0	0	0.0
Most common AEs§						
Nasopharyngitis	7	14.7	96	25.4	26	24.3
Upper respiratory tract infection	6	12.5	50	12.5	6	5.2
Headache	5	10.5	35	8.6	23	21.7
Diarrhea	6	12.7	30	7.3	19	17.6
Nausea	4	8.4	7	1.7	21	19.9
Arthralgia	2	4.1	22	5.3	6	5.2
Cough	3	6.3	15	3.6	2	1.7
Hypertension	0	0.0	14	3.4	9	7.9
Psoriasis	7	14.8	9	2.1	5	4.3
Dyspepsia	0	0.0	3	0.7	6	5.2
Myalgia	0	0.0	3	0.7	6	5.2
AEs of interest						
Skin event						
Acne	0	0.0	15	3.6	0	0.0
Folliculitis	0	0.0	9	2.1	2	1.7
Infections and infestations						
Serious infections	1	2.1	6	1.4	3	2.6
Herpes zoster	0	0.0	5‖	1.2‖	0	0.0

AE, Adverse event; *EAIR*, exposure-adjusted incidence rate; *PY*, person-years.

*A 57-year-old White female patient in the placebo group died on day 23 due to sudden cardiac death. This patient had a history of obesity, obstructive sleep apnea, and hypertensive cardiovascular disease.

†≥5% in any treatment group.

‡Safety data are expressed as EAIR/100 PY to account for variable periods of exposure to treatment.

§EAIR ≥5/100 PY in any treatment group.

‖None of the herpes zoster cases was serious, disseminated, or resulted in treatment discontinuation.

above background rates (not shown). Reported cases of malignancy were lower than the background rates in psoriasis from Psoriasis Longitudinal Assessment and Registry and MarketScan (reference databases).[17,18] There were no meaningful changes during treatment with deucravacitinib in laboratory parameters known to change with JAK 1/2/3 inhibitors.[2,3,19-21] The results

of the present trial are consistent with phase 2 results[8,9] and the recently completed phase 3 POETYK PSO-2 trial.

This study was limited by the 1-year duration, which is short given the chronic nature of psoriasis; further long-term analyses are warranted to validate the maintenance of response and long-term safety profile of deucravacitinib. The POETYK PSO-LTE trial (NCT04036435) should provide additional insight into longer-term efficacy and safety of deucravacitinib. Racial diversity was limited in this study with >98% of patients self-reporting as White or Asian; applicability to other racial types or ethnicities needs to be confirmed in future studies.

CONCLUSIONS

In POETYK PSO-1, deucravacitinib was well tolerated and demonstrated efficacy that was superior to placebo and apremilast. As expected based on its TYK2 selectivity, deucravacitinib did not elicit any laboratory changes characteristic of JAK 1/2/3 inhibitors. These data highlight the potential for deucravacitinib, a once-daily oral drug, to reduce disease activity and improve symptoms and QoL among patients who require systemic therapy for psoriasis.

The authors thank the patients and their families, the study site staff, and study site investigators for their participation. This clinical trial was sponsored by Bristol Myers Squibb. Writing and editorial assistance was provided by Lisa Feder, PhD, of Peloton Advantage, LLC, an OPEN Health company, Parsippany, NJ, USA, funded by Bristol Myers Squibb. Richard B. Warren, MD, is supported by the NIHR Manchester Biomedical Research Centre. The authors acknowledge Jonghyeon Kim, PhD, who was employed by Bristol Myers Squibb at the time the study was conducted, for his statistical assistance, as well as Marianne Peluso, Phenique Blacks, and Laura Aubrey for their assistance in trial coordination.

Conflicts of interest

Dr Armstrong has received research grants and personal fees from Bristol Myers Squibb, Eli Lilly, Janssen, Leo Pharma, and Novartis; has received personal fees from Boehringer Ingelheim/Parexel, Celgene, Dermavant, Genentech, GlaxoSmithKline, Menlo Therapeutics, Merck, Modernizing Medicine, Ortho Dermatologics, Pfizer, Regeneron, Sanofi Genzyme, Science 37, Sun Pharma, and Valeant; and has received grants from Dermira, Kyowa Hakko Kirin, and UCB, outside the submitted work. Dr Gooderham has served on an advisory board and as a principal investigator for, and has received lecture fees from, AbbVie, Galderma, Leo Pharma, Pfizer, and Regeneron; has served on an advisory board for, and has received lecture fees from, Actelion; has served as a principal investigator for, and received consulting fees from, Akros Pharma; has served on an advisory board and as a principal investigator for, and received lecture and consulting fees from, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen, Novartis, Sanofi Genzyme, and Valeant; has served as a principal investigator for Arcutis, Bristol Myers Squibb, Dermira, GlaxoSmithKline, MedImmune, Merck, Roche Laboratories, and UCB; and has served as a principal investigator for, and received lecture fees from, Glenmark. Dr Warren has received research grants from AbbVie, Almirall, Amgen, Celgene, Eli Lilly, Janssen, Leo Pharma, Novartis, Pfizer, and UCB and has received consulting fees from AbbVie, Almirall, Amgen, Biogen, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen, Leo Pharma, Novartis, Pfizer, Sanofi, UCB, and UNION. Dr Papp has served on a speakers bureau for AbbVie, Amgen, Astellas, Celgene, Eli Lilly, Galderma, Janssen, Kyowa Hakko Kirin, Leo Pharma, Merck Sharp & Dohme, Novartis, Pfizer, and Valeant; has received grant/research support from AbbVie, Akros, Allergan, Amgen, Anacor, Arcutis, AstraZeneca, Baxalta, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Coherus, Dermira, Dow Pharma, Eli Lilly, Galderma, Genentech, GlaxoSmithKline, Janssen, Kyowa Hakko Kirin, Leo Pharma, MedImmune, Meiji Seika Pharma, Merck Serono, Novartis, Pfizer, Regeneron, Roche, Sanofi Genzyme, Takeda, UCB, and Valeant; has served as a consultant for AbbVie, Akros, Amgen, Arcutis, Astellas, AstraZeneca, Baxalta, Baxter, Boehringer Ingelheim, Bristol Myers Squibb, CanFite, Celgene, Coherus, Dermira, Dow Pharma, Eli Lilly, Forward Pharma, Galderma, Genentech, Janssen, Kyowa Hakko Kirin, Leo Pharma, Meiji Seika Pharma, Merck Serono, Merck Sharp & Dohme, Mitsubishi Pharma, Novartis, Pfizer, Regeneron, Roche, Sanofi Genzyme, Takeda, UCB, and Valeant; has received honoraria from AbbVie, Akros, Amgen, Baxter, Boehringer Ingelheim, Celgene, Coherus, Eli Lilly, Forward Pharma, Galderma, GlaxoSmithKline, Janssen, Kyowa Hakko Kirin, Merck Serono, Merck Sharp & Dohme, Novartis, Pfizer, Takeda, UCB, and Valeant; and has served as a scientific officer, on a steering committee, and on an advisory board for AbbVie, Akros, Amgen, Anacor, Astellas, Baxter, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Dow Pharma, Eli Lilly, Galderma, Janssen, Kyowa Hakko Kirin, Merck Serono, Merck Sharp & Dohme, Novartis, Pfizer, Regeneron, Sanofi Genzyme, and Valeant. Dr Strober has served as a consultant (honoraria) for AbbVie, Almirall, Amgen, Arcutis, Arena, Aristea, Asana, Boehringer Ingelheim, Bristol Myers Squibb, Connect Biopharma, Dermavant, Equillium, GlaxoSmithKline, Immunic Therapeutics, Janssen, Leo Pharma, Eli Lilly, Maruho, Meiji Seika Pharma, Mindera, Novartis, Ortho Dermatologics, Pfizer, Regeneron, Sanofi Genzyme, Sun Pharma, UCB, Ventyxbio, and vTv Therapeutics; has served as a speaker for AbbVie, Eli Lilly, Janssen, and Sanofi Genzyme; has served as coscientific director for, and received consulting fees from, CorEvitas' (Corrona) Psoriasis Registry; and has served as an investigator for AbbVie, Cara, CorEvitas' (Corrona) Psoriasis Registry, Dermavant, Dermira, and Novartis. Dr Thaçi has received grant/research support from, and served on a scientific advisory board member and a speaker's bureau for, AbbVie,

Almirall, Amgen, Biogen Idec, Boehringer Ingelheim, Eli Lilly, Galapagos, Galderma, Janssen-Cilag, Leo Pharma, Novartis, Pfizer, Regeneron, Roche, Sandoz-Hexal, Sanofi, Target-Solution, and UCB. Dr Morita has received honoraria as a meeting chair or lecturer from AbbVie, AYUMI, Boehringer Ingelheim Japan, Celgene K.K., Eisai, Eli Lilly Japan K.K., Inforward, Janssen Pharmaceutical K.K., Kyowa Kirin, Maruho Co., Mitsubishi Tanabe Pharma, Nippon Kayaku, Novartis Pharma K.K., Taiho Pharmaceutical, Torii Pharmaceutical, and Ushio; has received funding from AbbVie GK, Eisai, Eli Lilly Japan K.K., Kyowa Hakko Kirin, Leo Pharma K.K., Maruho, Mitsubishi Tanabe Pharma, Novartis Pharma K.K., Taiho Pharmaceutical, and Torii Pharmaceutical; has received consulting fees from AbbVie, Boehringer Ingelheim Japan, Bristol Myers Squibb, Celgene K.K., Eli Lilly Japan K.K., GlaxoSmithKline K.K., Janssen Pharmaceutical K.K., Kyowa Hakko Kirin, Maruho, Mitsubishi Tanabe Pharma, Nichi-Iko Pharmaceutical, Nippon Kayaku, Novartis Pharma K.K., NPO Health Institute Research of Skin, Pfizer Japan, Sun Pharma, Taiho Pharmaceutical, and UCB Japan. Dr Szepietowski has served as an advisory board member/consultant for AbbVie, Leo Pharma, Novartis, Pierre-Fabre, Sanofi Genzyme, and Trevi; has served as a speaker for AbbVie, Eli Lilly, Janssen-Cilag, Leo Pharma, Novartis, and Sanofi Genzyme; and has served as an investigator for AbbVie, Amgen, Bristol Myers Squibb, Galapagos, Galderma, Incyte, InfraRX, Janssen-Cilag, Menlo Therapeutics, Merck, Novartis, Pfizer, Regeneron, UCB, and Trevi. Dr Imafuku has received grants and personal fees from AbbVie, Eisai, Janssen, Kyowa Kirin, Leo Pharma, Maruho, Sun Pharma, Taiho Yakuhin, Tanabe Mitsubishi, and Torii Yakuhin and has received personal fees from Amgen (Celgene), Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Novartis, and UCB. Dr Colston, Ms Linaberry, and Dr Banerjee are employees of and shareholders in Bristol Myers Squibb. Dr Throup, Dr Kundu, and Dr Schoenfeld were employees of and shareholders in Bristol Myers Squibb at the time of study conduct. Dr Blauvelt has served as a speaker/received honoraria from AbbVie and UCB; served as a scientific adviser/received honoraria from AbbVie, Abcentra, Affibody, Aligos, Almirall, Alumis, Amgen, AnaptysBio, Arcutis, Arena, Aslan, Athenex, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, Dermavant, EcoR1, Eli Lilly and Company, Evelo, Evommune, Forte Biosciences, Galderma, HighlightII Pharma, Incyte, Janssen, Landos, Leo Pharma, Merck, Novartis, Pfizer, Rapt, Regeneron, Sanofi Genzyme, Spherix Global Insights, Sun Pharma, TLL Pharmaceutical, TrialSpark, UCB, Vibliome, and Xencor; and has acted as a clinical study investigator for (institution has received clinical study funds from) AbbVie, Acelyrin, Amgen, Arcutis, Athenex, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant, Eli Lilly and Company, Evelo, Galderma, Incyte, Janssen, Leo, Merck, Novartis, Pfizer, Regeneron, Sun Pharma, and UCB.

REFERENCES

1. Burke JR, Cheng L, Gillooly KM, et al. Autoimmune pathways in mice and humans are blocked by pharmacological stabilization of the TYK2 pseudokinase domain. *Sci Transl Med*. 2019;11:eaaw1736.
2. Nogueira M, Puig L, Torres T. JAK inhibitors for treatment of psoriasis: focus on selective TYK2 inhibitors. *Drugs*. 2020;80:341-351.
3. Schwartz DM, Kanno Y, Villarino A, Ward M, Gadina M, O'Shea JJ. JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. *Nat Rev Drug Discov*. 2017;16:843-862.
4. Krueger JG, McInnes IB, Blauvelt A. Tyrosine kinase 2 and Janus kinase–signal transducer and activator of transcription signaling and inhibition in plaque psoriasis. *J Am Acad Dermatol*. 2022;86:148-157.
5. Karaghiosoff M, Neubauer H, Lassnig C, et al. Partial impairment of cytokine responses in TYK2-deficient mice. *Immunity*. 2000;13:549-560.
6. Sohn SJ, Barrett K, Van Abbema A, et al. A restricted role for TYK2 catalytic activity in human cytokine responses revealed by novel TYK2-selective inhibitors. *J Immunol*. 2013;191:2205-2216.
7. Schurich A, Raine C, Morris V, Ciurtin C. The role of IL-12/23 in T cell-related chronic inflammation: implications of immunodeficiency and therapeutic blockade. *Rheumatology (Oxford)*. 2018;57:246-254.
8. Papp K, Gordon K, Thaçi D, et al. Phase 2 trial of selective tyrosine kinase 2 inhibition in psoriasis. *N Engl J Med*. 2018;379:1313-1321.
9. Mease PJ, Deodhar A, van der Heijde D, et al. Efficacy and safety of deucravacitinib (BMS-986165), an oral, selective tyrosine kinase 2 inhibitor, in patients with active psoriatic arthritis: results from a phase 2, randomized, double-blind, placebo-controlled trial. Presented at: the 2020 ACR Convergence; November 5-9, 2020 (virtual). Poster L03.
10. Feldman SR, Mathias SD, Schenkel B, et al. Development of a patient-reported outcome questionnaire for use in adults with moderate-to-severe plaque psoriasis: the Psoriasis Symptoms and Signs Diary. *J Dermatol Dermatol Surg*. 2016;20:19-26.
11. Mathias SD, Feldman SR, Crosby RD, Colwell HH, McQuarrie K, Han C. Measurement properties of a patient-reported outcome measure assessing psoriasis severity: the psoriasis symptoms and signs diary. *J Dermatolog Treat*. 2016;27:322-327.
12. Otezla (apremilast) [package insert]: Amgen Inc.; December 2021. Accessed June 21, 2022. https://www.pi.amgen.com/-/media/Project/Amgen/Repository/pi-amgen-com/Otezla/otezla_pi_english.pdf
13. US Food and Drug Administration. Conduct of clinical trials of medical products during the COVID-19 public health emergency. Guidance for industry, investigators, and institutional review boards. Accessed June 21, 2022. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency
14. Papp K, Reich K, Leonardi CL, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). *J Am Acad Dermatol*. 2015;73:37-49.
15. Paul C, Cather J, Gooderham M, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase III, randomized controlled trial (ESTEEM 2). *Br J Dermatol*. 2015;173:1387-1399.

16. Sunzini F, McInnes I, Siebert S. JAK inhibitors and infections risk: focus on herpes zoster. *Ther Adv Musculoskelet Dis*. 2020; 12:1759720x20936059.
17. Fiorentino D, Ho V, Lebwohl MG, et al. Risk of malignancy with systemic psoriasis treatment in the psoriasis Longitudinal Assessment Registry. *J Am Acad Dermatol*. 2017;77:845-854.e5.
18. Kimball AB, Schenfeld J, Accortt NA, Anthony MS, Rothman KJ, Pariser D. Cohort study of malignancies and hospitalized infectious events in treated and untreated patients with psoriasis and a general population in the United States. *Br J Dermatol*. 2015;173:1183-1190.
19. Baker KF, Isaacs JD. Novel therapies for immune-mediated inflammatory diseases: what can we learn from their use in rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus, psoriasis, Crohn's disease and ulcerative colitis? *Ann Rheum Dis*. 2018;77:175-187.
20. Gadina M, Le MT, Schwartz DM, et al. Janus kinases to jakinibs: from basic insights to clinical practice. *Rheumatology (Oxford)*. 2019;58:i4-i16.
21. Winthrop KL. The emerging safety profile of JAK inhibitors in rheumatic disease. *Nat Rev Rheumatol*. 2017; 13:234-243.