Efficacy of Deucravacitinib, an Oral, Selective Tyrosine Kinase 2 Inhibitor, in Musculoskeletal Manifestations of Active Psoriatic Arthritis in a Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial

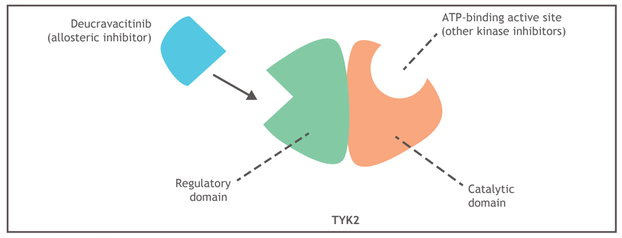
Philip J Mease,[1] Atul Deodhar,[2] Désirée van der Heijde,[3] Frank Behrens,[4] Alan J Kivitz,[5] Thomas Lehman,[6] Lan Wei,[6] Marleen Nys,[7] Subhashis Banerjee,[6] Miroslawa Nowak[6]

[1]Swedish Medical Center/Providence St. Joseph Health and University of Washington, Seattle, WA, USA; [2]Oregon Health & Science University, Portland, OR, USA; [3]Leiden University Medical Center, Leiden, The Netherlands; [4]CIRI/Rheumatology and Fraunhofer Institute, Translational Medicine and Pharmacology ITMP, Goethe University, Frankfurt, Germany; [5]Department of Rheumatology, Altoona Center for Clinical Research, Duncansville, PA, USA; [6]Bristol Myers Squibb, Princeton, NJ, USA; [7]Bristol Myers Squibb, Braine-l'Alleud, Belgium

Background

- Deucravacitinib
  - Novel, oral, selective tyrosine kinase 2 (TYK2) inhibitor with a unique mechanism of action distinct from Janus kinase (JAK) 1/2/3 inhibitors[1] (**Figure 1**)
  - Binds the TYK2 regulatory domain with high selectivity and inhibits TYK2 via an allosteric mechanism[1]
  - Inhibits key cytokines involved in psoriasis and psoriatic arthritis (PsA) (eg, interleukin [IL]-23)[1]
  - Does not inhibit cytokines and mediators involved in metabolic or hematopoietic pathways[1]
  - Showed superior efficacy in two Phase 3 trials in moderate to severe plaque psoriasis[2]
  - Showed superior efficacy in a Phase 2 trial in PsA[3]

Figure 1. Mechanism of action of deucravacitinib



ATP, adenosine 5'-triphosphate; TYK2, tyrosine kinase 2.

Objective

- To explore improvement in musculoskeletal disease domains from the Phase 2 trial in PsA

Methods

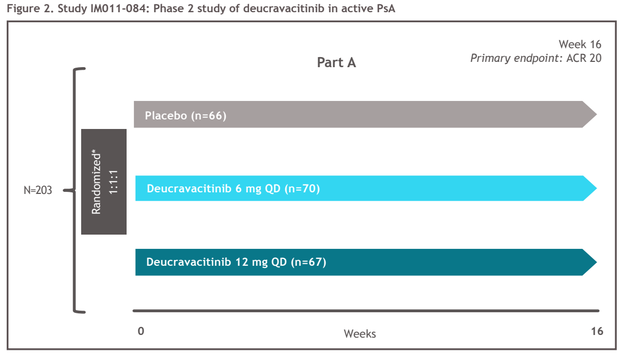
Study design

- This 1-year, randomized, double-blind, placebo-controlled (initial 16 weeks [Part A]), multicenter, Phase 2 trial in patients with active PsA (NCT03881059) randomized patients 1:1:1 to deucravacitinib 6 mg QD or 12 mg QD, or placebo (**Figure 2**)

Inclusion criteria

- PsA diagnosis for ≥6 months
- Meet Classification Criteria for Psoriatic Arthritis
- ≥1 confirmed psoriatic lesion (≥2 cm)
- ≥3 swollen joints and ≥3 tender joints
- C-reactive protein (CRP) ≥3 mg/L (upper limit of normal, 5 mg/L)
- Failed or intolerant to ≥1 conventional synthetic disease-modifying antirheumatic drug, nonsteroidal anti-inflammatory drug, and/or corticosteroid
- Failed up to 1 tumor necrosis factor inhibitor (TNFi)

Figure 2. Study IM011-084: Phase 2 study of deucravacitinib in active PsA



Patients who reached Week 16 were eligible for participation in an optional blinded long-term extension period until Week 52 (Part B).
*Patients were stratified based on prior exposure to TNF inhibitors (experienced vs naïve) and body weight (<90 kg vs ≥90 kg).
ACR, American College of Rheumatology; PsA, psoriatic arthritis; QD, once daily.

Results

Baseline demographics and clinical characteristics

- Baseline demographic and clinical characteristics were similar across the 3 groups (**Table 1**)

Table 1. Demographic and baseline disease characteristics

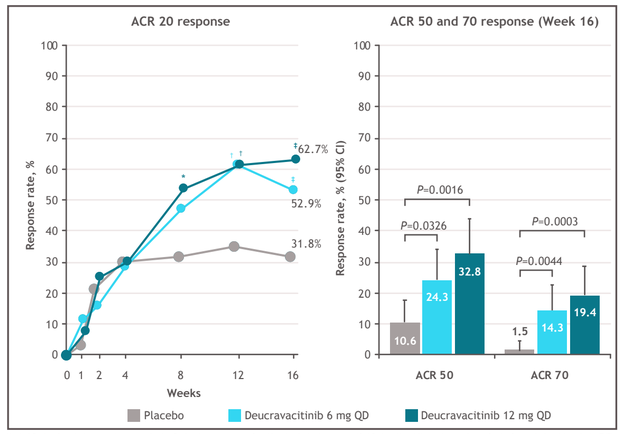
	Total N=203	Placebo n=66	Deucravacitinib 6 mg QD n=70	Deucravacitinib 12 mg QD n=67
Age, years, mean	49.8	48.5	50.5	50.5
Gender, female, n (%)	104 (51.2)	40 (60.6)	30 (42.9)	34 (50.7)
Baseline BMI, kg/m², mean	30.4	31.2	29.6	30.3
Disease duration since diagnosis, years, median (range)	4.5 (0.1-42.8)	4.5 (0.6-22.9)	5.3 (0.1-42.8)	3.8 (0.6-27.7)
Tender joint count, mean (SD)	**18.1 (10.68)**	**16.9 (9.79)**	**18.1 (10.33)**	**19.4 (11.84)**
Swollen joint count, mean (SD)	**11.3 (7.91)**	**10.5 (7.74)**	**11.9 (6.99)**	**11.3 (8.96)**
HAQ-DI, mean (SD)	**1.3 (0.57)**	**1.3 (0.56)**	**1.3 (0.59)**	**1.3 (0.59)**
Patients with SPARCC enthesitis score ≥1 at baseline, n (%)	**111 (54.7)**	**34 (51.5)**	**43 (61.4)**	**34 (50.7)**
Psoriasis body surface area ≥3% at baseline, n (%)	165 (81.3)	54 (81.8)	59 (84.3)	52 (77.6)
PASI score at baseline in subjects with ≥3% BSA at baseline, mean (range)	8.50 (1.2-33.8)	9.09 (1.2-31.4)	8.47 (1.6-33.8)	7.92 (1.4-31.8)
Oral steroid use at baseline, n (%)	25 (12.3)	12 (18.2)	7 (10.0)	6 (9.0)
Mean daily dose, mg	4.00	4.40	3.71	3.54
Use of csDMARDs at baseline, n (%)	132 (65.0)	44 (66.7)	45 (64.3)	43 (64.2)
Use of MTX at baseline, n (%)	111 (54.7)	39 (59.1)	35 (50.0)	37 (55.2)
Mean weekly dose, mg	16.5	16.7	16.4	16.5
Prior TNF-inhibitor use, n (%)	32 (15.8)	11 (16.7)	12 (17.1)	9 (13.4)

BMI, body mass index; BSA, body surface area; csDMARD, conventional synthetic disease-modifying antirheumatic drug; HAQ-DI, Health Assessment Questionnaire-Disability Index; MTX, methotrexate; PASI, Psoriasis Area and Severity Index; QD, once daily; SPARCC, Spondyloarthritis Research Consortium of Canada; TNF, tumor necrosis factor.

Efficacy

- The primary endpoint, achievement of ACR 20 response at Week 16, was met (**Figure 3**). Both deucravacitinib 6 mg QD and 12 mg QD demonstrated significantly greater ACR 20 responses versus placebo at Week 16. Achievement of ACR 50 and ACR 70 responses at Week 16 was also significantly higher with deucravacitinib versus placebo

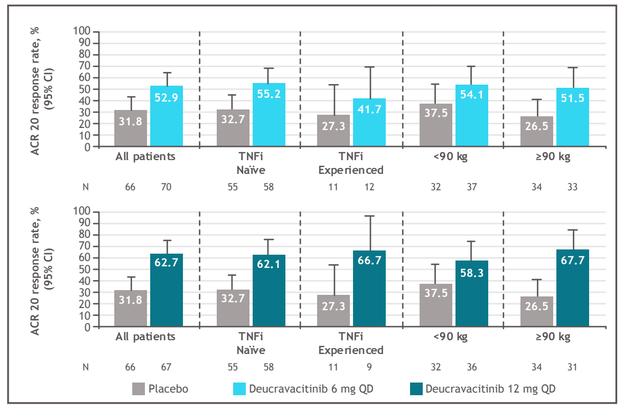
Figure 3. ACR 20, ACR 50, and ACR 70 responses (ITT, NRI)



Nominal *P* values for pairwise comparison versus placebo. *P* values in time course are for odds ratios obtained using a stratified Cochran-Mantel-Haenszel test with stratification factors (body weight and prior TNFi use) per randomization. ITT population.
*P<0.0108 (12 mg). †P<0.0021 (6 mg); P<0.0021 (12 mg). ‡P<0.0134 (6 mg); P<0.0004 (12 mg).
ACR, American College of Rheumatology; ITT, intent-to-treat; NRI, nonresponder imputation; QD, once daily; TNFi, tumor necrosis factor inhibitor.

- ACR 20 responses were generally similar in patients regardless of prior TNFi use and body weight <90 kg or ≥90 kg (**Figure 4**)

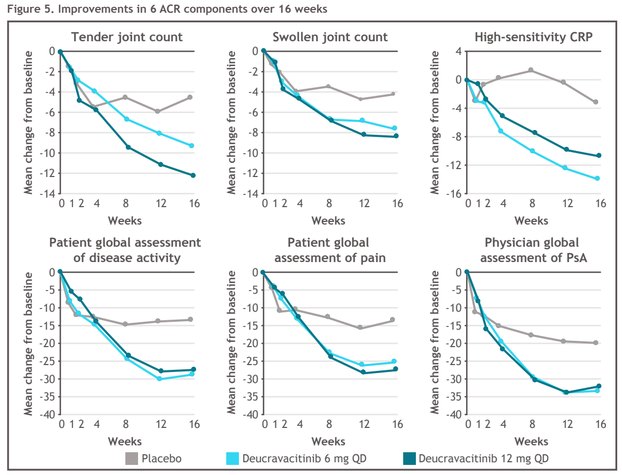
Figure 4. ACR 20 response at Week 16: Effects of TNFi experience and body weight



Comparative data for the TNFi-experienced groups should be interpreted with caution due to small sample sizes. Analyses were performed using NRI for patients with missing data.
ACR, American College of Rheumatology; CI, confidence interval; NRI, nonresponder imputation; QD, once daily; TNFi, tumor necrosis factor inhibitor.

- Mean improvements from baseline at Week 16 in individual ACR components were greater with both deucravacitinib doses versus placebo, including tender joint count, swollen joint count, high-sensitivity CRP, patient global assessment of disease activity, patient global assessment of pain, and physician global assessment of PsA (**Figure 5**)

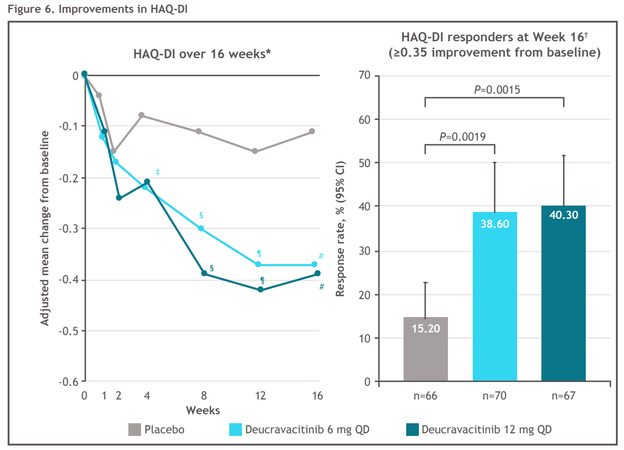
Figure 5. Improvements in 6 ACR components over 16 weeks



These analyses were done post hoc using data as observed.
Tender joint count baseline values [mean]: PBO [16.9], 6 mg [18.1], 12 mg [19.4]. Swollen joint count baseline values [mean]: PBO [10.5], 6 mg [11.9], 12 mg [11.3].
ACR, American College of Rheumatology; CRP, C-reactive protein; PBO, placebo; PsA, psoriatic arthritis; QD, once daily.

- Significant improvement in HAQ-DI score was evident by Week 4 with the 6 mg deucravacitinib dose, and by Week 8 with both deucravacitinib doses compared with placebo. Significant improvement was maintained with both doses through Week 16 (**Figure 6**)
- With both doses of deucravacitinib, a significantly greater proportion of patients achieved HAQ-DI response, defined as an improvement from baseline in HAQ-DI score of at least 0.35 (**Figure 6**)

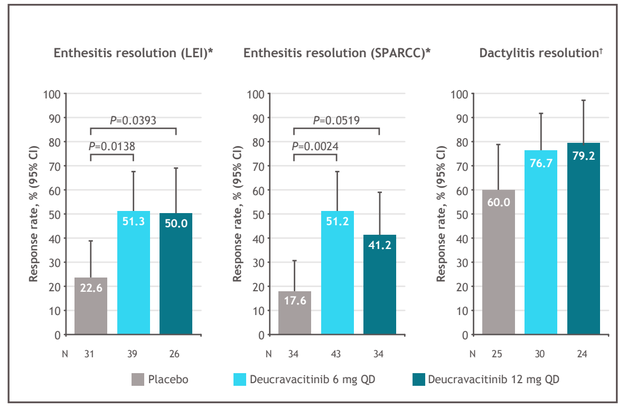
Figure 6. Improvements in HAQ-DI



*Modified baseline observation carried forward (mBOCF) was used to impute missing data. *P* values obtained from an analysis of covariance model with factors for body weight and TNFi use and the baseline value as covariate. †Nonresponder imputation method was used to impute missing data. *P* values obtained using stratified Cochran-Mantel-Haenszel test with stratification factors (body weight and prior TNFi use) per randomization. ‡P<0.0426 (6 mg). §P<0.0155 (6 mg); P<0.0005 (12 mg). ¶P<0.0073 (6 mg); P<0.0010 (12 mg). #P<0.0020 (6 mg); P<0.0008 (12 mg).
HAQ-DI, Health Assessment Questionnaire-Disability Index; QD, once daily; TNFi, tumor necrosis factor inhibitor.

- Greater proportions of patients in the deucravacitinib treatment groups achieved enthesitis resolution at Week 16 compared with placebo (**Figure 7**)
- At Week 16, dactylitis resolution was achieved by 76.7% and 79.2% of patients in the deucravacitinib 6 mg and 12 mg dose groups compared with 60% in the placebo group (**Figure 7**)

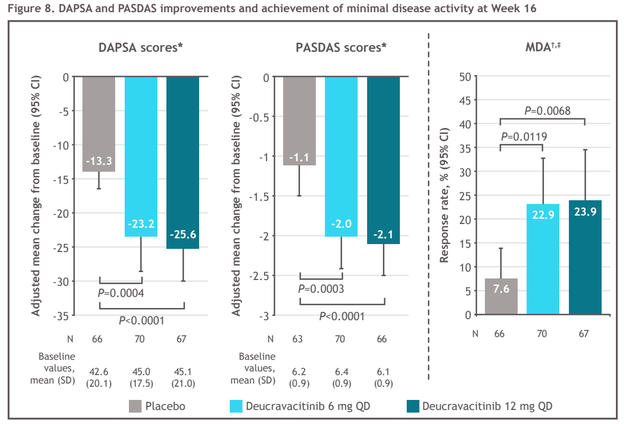
Figure 7. Enthesitis and dactylitis resolution at Week 16



Missing data are reported using nonresponder imputation.
*Enthesitis resolution defined as score of 0 in patients with score of ≥1 at baseline. †Dactylitis resolution defined as score of 0 in patients with ≥1 tender or swollen digit at baseline (based on LDI).
Proportion of patients with baseline score ≥1: [SPARCC, n (%): 34 (51.5) PBO, 43 (61.4) 6 mg, 34 (50.7) 12 mg]; [LEI, n (%): 31 (47.0) PBO, 39 (55.7) 6 mg, 26 (38.8) 12 mg].
LDI, Leeds Dactylitis Index; LEI, Leeds Enthesitis Index; PBO, placebo; QD, once daily; SPARCC, Spondyloarthritis Research Consortium of Canada.

- Achievement of minimal disease activity (MDA) and improvements in Disease Activity Index for Psoriatic Arthritis (DAPSA) and Psoriatic Arthritis Disease Activity Score (PASDAS) were significantly greater with both deucravacitinib doses versus placebo at Week 16 (**Figure 8**)

Figure 8. DAPSA and PASDAS improvements and achievement of minimal disease activity at Week 16



*Missing data are reported using modified baseline observation carried forward. *P* values from ANCOVA with factors for body weight and TNFi use and the baseline value as a covariate. †Missing data are reported using nonresponder imputation. *P* values obtained using Cochran-Mantel-Haenszel test with stratification factors (body weight and prior TNFi use) per randomization. ‡% of 7 of the following outcomes: tender joint count ≤1; swollen joint count ≤1; PASI ≤1 or body surface area ≤3%; Patient Global Assessment of pain ≤15; Patient Global Assessment of disease activity ≤20; HAQ-DI ≤0.5; tender entheseal points ≤1.
ANCOVA, analysis of covariance; DAPSA, Disease Activity Index for Psoriatic Arthritis; HAQ-DI, Health Assessment Questionnaire-Disability Index; MDA, minimal disease activity; PASDAS, Psoriatic Arthritis Disease Activity Score; PASI, Psoriasis Area and Severity Index; QD, once daily; TNFi, tumor necrosis factor inhibitor.

Safety

- Deucravacitinib was well tolerated; the most common adverse events (AEs) were nasopharyngitis, sinusitis, headache, rash, upper respiratory tract infection, bronchitis, and diarrhea (**Table 2**). Most AEs were mild to moderate in severity
- No serious AEs, including serious infections, were reported in deucravacitinib-treated patients. There were no thrombotic events in the deucravacitinib groups
- There were no occurrences of herpes zoster infections, opportunistic infections, or malignancies observed in any deucravacitinib treatment group

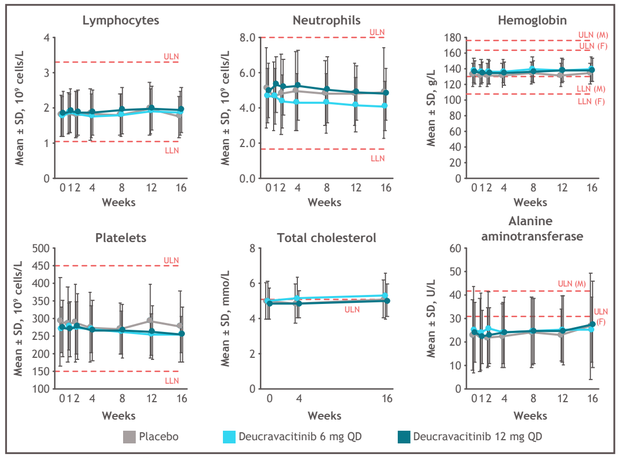
Table 2. Overall safety summary

Patients, n (%)	Placebo (n=66)	Deucravacitinib 6 mg QD (n=70)	Deucravacitinib 12 mg QD (n=67)
Deaths	0	0	0
Serious adverse events	1 (1.5)	0	0
Treatment-related adverse events	6 (9.1)	22 (31.4)	17 (25.4)
Discontinued treatment due to adverse events	1 (1.5)	3 (4.3)	4 (6.0)
Most frequent adverse events (≥5%)			
Nasopharyngitis	5 (7.6)	4 (5.7)	12 (17.9)
Sinusitis	0	0	5 (7.5)
Headache	3 (4.5)	5 (7.1)	1 (1.5)
Rash	0	3 (4.3)	4 (6.0)
Upper respiratory tract infection	0	4 (5.7)	1 (1.5)
Bronchitis	1 (1.5)	4 (5.7)	0
Diarrhea	0	4 (5.7)	0

Includes events with a start date between the first dose and the Week 16 visit date (inclusive) or between the first dose and 30 days after the last dose of study drug for patients who discontinued early.
QD, once daily.

- No clinically meaningful changes were observed over time in lymphocytes, neutrophils, hemoglobin, platelets, total cholesterol, or alanine aminotransferase during the trial for deucravacitinib versus placebo (**Figure 9**)

Figure 9. Laboratory parameters over 16 weeks



F, female; LLN, lower limit of normal; M, male; QD, once daily; ULN, upper limit of normal.

Conclusions

- Deucravacitinib treatment was efficacious versus placebo, with improvements observed across all ACR domains and enthesitis endpoints
- Efficacy of deucravacitinib versus PBO was observed across TNFi and body weight subgroups
- The safety profile of deucravacitinib was consistent with its selective mechanism of action and with that observed in Phase 3 trials in patients with psoriasis[2]

References

1. Burke JR et al. *Sci Transl Med*. 2019;11:1-16. **2.** Armstrong A et al. Presented at American Academy of Dermatology Virtual Meeting Experience 2021; April 23-25, 2021. **3.** Mease PJ et al. Presented at the 2020 ACR Convergence, American College of Rheumatology; Nov 5-9, 2020.

Acknowledgments

- This study was sponsored by Bristol Myers Squibb. Professional medical writing assistance from Julianne Hatfield, PhD, and editorial assistance were provided by Peloton Advantage, LLC, an OPEN Health company, and were funded by Bristol Myers Squibb.

Relationships and Activities

- **PJM:** Research grants: AbbVie, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Galapagos, Gilead, GlaxoSmithKline, Janssen, Novartis, Pfizer, SUN Pharma, UCB; Consulting and/or speaker fees: AbbVie, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Galapagos, Gilead, GlaxoSmithKline, Janssen, Novartis, Pfizer, SUN Pharma, UCB
- **AD:** Consulting and/or advisory boards: AbbVie, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Galapagos, GlaxoSmithKline, Janssen, Novartis, Pfizer, UCB; Research grants: AbbVie, Eli Lilly, GlaxoSmithKline, Novartis, Pfizer, UCB
- **DvdH:** Consulting fees: AbbVie, Amgen, Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Cyxone, Daiichi, Eisai, Eli Lilly, Galapagos, Gilead, GlaxoSmithKline, Janssen, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi, Takeda, UCB Pharma; Director, Imaging Rheumatology BV
- **FB:** Research grants: Pfizer, Janssen, Chugai, Celgene, Roche; Consultancies/speaker fees: Pfizer, AbbVie, Sanofi, Lilly, Novartis, Genzyme, Boehringer, Janssen, MSD, Celgene, Roche, Chugai, Bristol Myers Squibb, UCB Pharma
- **AJK:** Shareholder: Pfizer, Sanofi, GlaxoSmithKline, Gilead Sciences, Inc., Novartis; Paid consultant: AbbVie, Boehringer Ingelheim, Flexion, Janssen, Pfizer, Sanofi, Regeneron, SUN Pharma Advanced Research, Gilead Sciences, Inc.; Speakers bureau: Amgen, Horizon, Lilly, Novartis, Pfizer, Sanofi, Genzyme, Flexion, AbbVie
- **TL, LW, MN, SB, MN:** Employees and shareholders of Bristol Myers Squibb

Email (for Philip J Mease, MD): pmease@philipmease.com