An Oral, Selective Tyrosine Kinase 2 Inhibitor, Deucravacitinib (BMS-986165), Reduced Absolute Psoriasis Area and Severity Index in a Phase 2 Trial in Psoriasis

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Introduction

- Plaque psoriasis is a debilitating, chronic, immune-mediated skin disorder that impairs patients' health-related quality of life (HRQoL) and productivity[1]
- Treatment outcomes for plaque psoriasis based on the absolute Psoriasis Area and Severity Index (PASI) are indicative of an individual patient's disease severity at the time of analysis[2]
  - Absolute PASI may be more clinically meaningful than percentage change in PASI from baseline captured by scores such as PASI 75 (≥75% reduction from baseline PASI)[2]
  - Although a consensus therapeutic target has yet to be defined, a recent analysis reported that attainment of an absolute PASI of ≤2 translates to meaningful improvements in clinical and HRQoL outcomes[2]
    - Previous studies have demonstrated that an absolute PASI ≤2 correlates with PASI 90 (≥90% improvement from baseline PASI), static Physician's Global Assessment (sPGA) score of 0/1 (range, 0-5; higher scores indicate greater disease severity), and Dermatology Life Quality Index (DLQI) of 0/1 (range, 0-30; higher scores indicate worse HRQoL)[2]
- Deucravacitinib (BMS-986165) is an oral, selective, allosteric inhibitor of tyrosine kinase 2 (TYK2), an intracellular enzyme involved in key cytokine signaling pathways in plaque psoriasis pathogenesis[3]
  - In a Phase 2, double-blind, randomized trial in patients with moderate to severe plaque psoriasis (NCT02931838), 67%–75% of patients treated with deucravacitinib at doses of 3 or 6 mg twice daily (BID) or 12 mg once daily (QD) achieved PASI 75 at Week 12 (primary endpoint) vs 7% with placebo (P<0.001)[3]
  - Deucravacitinib had a favorable safety and tolerability profile, and was associated with low rates of treatment discontinuation[3]

Objective

- This post hoc analysis of the Phase 2 trial compared the efficacy of deucravacitinib vs placebo based on absolute PASI over time up to Week 12

Materials and Methods

Inclusion criteria

- Adults with body mass index of 18-40 kg/m^2
- Moderate to severe plaque psoriasis for ≥6 months affecting ≥10% of body surface area
  - PASI ≥12 (range, 0-72; higher scores indicate greater disease severity)
  - sPGA ≥3
- Eligible for phototherapy or systemic therapy

Exclusion criteria

- Diagnosis of nonplaque psoriasis or other immune-mediated condition requiring concomitant systemic immunosuppressant therapy
- History or evidence of specific infections (eg, HIV or hepatitis B or C infection) or risk of tuberculosis
- Previous lack of response to any therapeutic agent targeting the TYK2 pathway (eg, interleukin-12/-23 pathways)

Treatment

- Patients were randomized equally to 1 of 5 oral doses of deucravacitinib (3 mg every other day, 3 mg QD, 3 mg BID, 6 mg BID, or 12 mg QD) or matching oral placebo for 12 weeks

Study endpoints

- This post hoc analysis assessed the following efficacy endpoints in the 3 most effective deucravacitinib dose groups (3 mg BID, 6 mg BID, 12 mg QD) vs placebo
  - Mean absolute PASI over time
  - Mean percentage change from baseline in absolute PASI over time
  - Percentage of patients at Week 12 who achieved an absolute PASI of ≤1, ≤2, ≤3, and ≤5

Statistical analysis

- This post hoc efficacy analysis was performed in the efficacy analysis population
- Absolute PASI over time and within predefined categories are expressed as patient numbers and percentages
- Patients who discontinued the treatment regimen early or who had a missing value at any time point had outcomes imputed as a nonresponse at that time point, regardless of response status at time of discontinuation

Results

Baseline demographics and disease characteristics

- 179 patients were included in this post hoc analysis (deucravacitinib groups, n=134; placebo, n=45)
- Baseline demographics and disease characteristics of patients in each dose group are presented in **Table 1**
  - Most patients were male (58%-82% across treatment groups), mean patient age was 43-47 years, and mean body mass index was 27-30 kg/m^2
  - Baseline mean PASI was similar across treatment groups (18-19)
  - Median disease duration was 13-20 years and 41%-44% of patients had received prior biologic therapy

Table 1. Baseline demographics and disease characteristics[3]

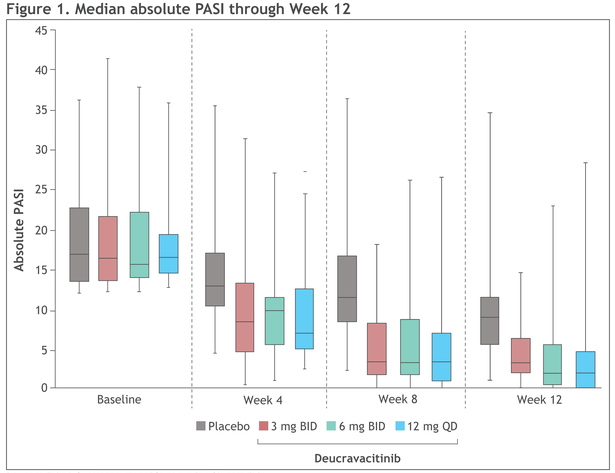
		Deucravacitinib		
Characteristic*	Placebo (n=45)	3 mg BID (n=45)	6 mg BID (n=45)	12 mg QD (n=44)
Demographic characteristics				
Mean age, y	46 ± 12	46 ± 15	43 ± 13	47 ± 12
Male sex, n (%)	37 (82)	26 (58)	35 (78)	30 (68)
Race, n (%)				
White	40 (89)	39 (87)	35 (78)	37 (84)
Asian	5 (11)	5 (11)	9 (20)	6 (14)
Other	0	1 (2)	1 (2)	1 (2)
Body weight, kg	96 ± 21	84 ± 18	84 ± 19	88 ± 24
Body mass index, kg/m^2	30 ± 6	28 ± 5	27 ± 5	29 ± 5
Clinical characteristics				
Median (range) disease duration, y	18 (2-48)	13 (1-61)	15 (1-55)	20 (1-47)
Prior use of biologic therapy, n (%)	20 (44)	19 (42)	20 (44)	18 (41)
PASI†	19 ± 6	19 ± 8	18 ± 6	18 ± 5
DLQI‡	13 ± 7	13 ± 5	11 ± 6	13 ± 7
Body surface area, %	24 ± 13	24 ± 15	25 ± 13	21 ± 12

From *N Engl J Med*, Papp K, Gordon K, Thaçi D, et al, Phase 2 trial of selective tyrosine kinase 2 inhibition in psoriasis, 379(14):1313-1321. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission.
BID, twice daily; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; QD, once daily.
*Values are means ± SD unless otherwise noted. Data have been rounded to the nearest integer. Percentages may not total 100 because of rounding.
†PASI ranges from 0-72, with higher scores indicating greater severity of psoriasis.
‡DLQI scores range from 0-30, with higher scores indicating worse quality of life.

Absolute PASI

- Deucravacitinib was associated with lower absolute PASI compared with placebo up to Week 12 (**Figure 1**)
  - Each of the 3 deucravacitinib doses evaluated resulted in similar levels of improvement in median absolute PASI over time

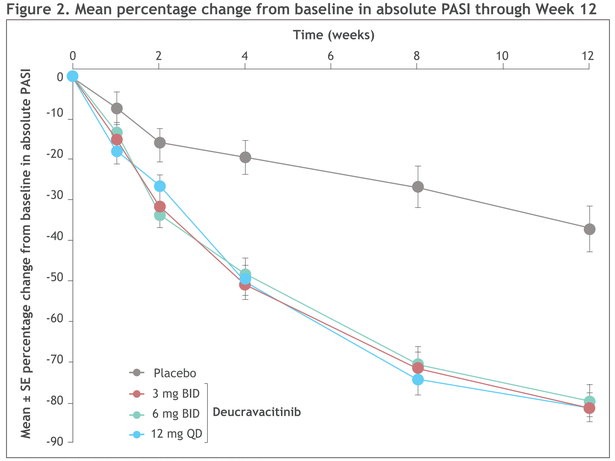
Figure 1. Median absolute PASI through Week 12



BID, twice daily; PASI, Psoriasis Area and Severity Index; QD, once daily.

- Deucravacitinib was also associated with greater reductions in mean percentage change from baseline in absolute PASI than placebo from Week 1 to Week 12 (**Figure 2**)

Figure 2. Mean percentage change from baseline in absolute PASI through Week 12



BID, twice daily; PASI, Psoriasis Area and Severity Index; QD, once daily.

- The percentages of patients achieving absolute PASI values of ≤1, ≤2, ≤3, and ≤5 at Week 12 were higher in the deucravacitinib groups than in the placebo group (**Table 2**)

Table 2. Absolute PASI at Week 12

	Patients achieving PASI threshold, % (intent-to-treat population)				
Absolute PASI	Placebo (n=45)	Deucravacitinib 3 mg BID (n=45)	Deucravacitinib 6 mg BID (n=45)	Deucravacitinib 12 mg QD (n=44)	Deucravacitinib combined (n=134)
≤1	0	24.4	33.3	34.1	30.6
≤2	0	46.7	44.4	50.0	47.0
≤3	2.2	57.8	53.3	63.6	58.2
≤5	8.9	73.3	64.4	77.3	71.6

BID, twice daily; PASI, Psoriasis Area and Severity Index; QD, once daily.
Patients who discontinued the treatment regimen early or who had a missing value at any time point had outcomes imputed as a nonresponse at that time point, regardless of response status at time of discontinuation.

Conclusions

- This analysis suggests that deucravacitinib elicits a rapid response and is efficacious in achieving an absolute PASI of ≤2 in approximately 50% of patients and an absolute PASI ≤1 in approximately 30% of patients with moderate to severe plaque psoriasis
  - As mentioned earlier, an absolute PASI of ≤2 has been shown to be clinically meaningful for clinical and HRQoL outcomes[2]
  - Mean percentage change from baseline in absolute PASI at Week 12 was approximately 80% in deucravacitinib-treated patients
- Five ongoing Phase 3 trials in plaque psoriasis (NCT03624127, NCT03611751, NCT04167462, NCT03924427, and NCT04036435) involving deucravacitinib treatment will evaluate this further over a longer duration and in larger patient cohorts
- PASI ≤2 has the potential to be an alternative therapeutic goal to percent PASI improvements and sPGA scores for patients with moderate to severe plaque psoriasis

References

1. Weigle N, McBane S. *Am Fam Physician*. 2013;87(9):626-633. **2.** Puig L et al. *Acta Derm Venereol*. 2019;99(11):971-977. **3.** Papp K et al. *N Engl J Med*. 2018;379(14):1313-1321.

Acknowledgments

- This work was sponsored by Bristol Myers Squibb. Professional medical writing from Ann Marie Fitzmaurice, PhD and editorial assistance were provided by Peloton Advantage, LLC, an OPEN Health company, Parsippany, NJ, and were funded by Bristol Myers Squibb.

Relationships and Activities

- **BS:** Honoraria or consultation fees: AbbVie, Almirall, Amgen, Arena, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Dermavant, Dermira, Eli Lilly, GSK, Janssen, Kyowa Hakko Kirin, Leo Pharma, Medac, Meiji Seika Pharma, Novartis, Ortho Dermatologics, Pfizer, Regeneron, Sanofi-Genzyme, Sun Pharma, UCB; Speaker: AbbVie, Janssen, Lilly, Ortho Dermatologics; Scientific Director (consulting fee): Corrona Psoriasis Registry; Investigator: AbbVie, Corrona Psoriasis Registry, Dermavant, Dermira
- **ABG:** Grant/research funding (paid to institution): Boehringer Ingelheim, Incyte, Janssen-Ortho, Novartis, UCB, XBiotech; Honoraria or consultation fees (paid to ABG): Abbott (AbbVie), Amgen, Bristol Myers Squibb, Celgene, Eli Lilly, Incyte, Janssen Biotech, Janssen-Ortho, Leo Pharma, Lilly ICOS, Novartis, Sun Pharma, UCB, XBiotech, and Avotres (no direct compensation received from Avotres); Stock options: XBiotech
- **DT:** Research support/principal investigator (clinical trials): AbbVie, Almirall, Amgen, Biogen Idec, Boehringer Ingelheim, Celgene, Chugai, Dermira, DS-Pharma, Eli Lilly, Galderma, GSK, Janssen-Cilag, Leo Pharma, MSD, Novartis, Pfizer, Regeneron, Roche, Sandoz-Hexal, Sanofi, UCB; Consultant: AbbVie, Almirall, Celgene, Dignity, Galapagos, Leo Pharma, Maruho, Mitsubishi, Novartis, Pfizer, Xenoport; Lectures: AbbVie, Almirall, Amgen, DS-Pharma, Janssen, Leo Pharma, MSD, Novartis, Pfizer, La Roche-Posay, Sandoz-Hexal, Sanofi, Target-Solution, UCB; Scientific advisory board: AbbVie, Amgen, Celgene, DS-Pharma, Eli Lilly, Galapagos, Janssen-Cilag, Leo Pharma, Morphosis, MSD, Novartis, Pfizer, Sandoz, Sanofi, UCB
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- **MJC, SK, RK, and SB:** Employees and shareholders of Bristol Myers Squibb

Presented at the 2020 Fall Clinical Dermatology Conference: October 29–November 1, 2020; virtual meeting and at Las Vegas, Nevada

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