An Oral, Selective Tyrosine Kinase 2 Inhibitor, 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]
- 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 BMS-986165 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]
  - BMS-986165 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 BMS-986165 vs placebo based on absolute PASI over time up to Week 12

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 BMS-986165 (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 BMS-986165 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 (BMS-986165 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]

Characteristic[a]	Placebo (n=45)	BMS-986165 3 mg BID (n=45)	BMS-986165 6 mg BID (n=45)	BMS-986165 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[b]	19 ± 6	19 ± 8	18 ± 6	18 ± 5
DLQI[c]	13 ± 7	13 ± 5	11 ± 6	13 ± 7
Body surface area, %	24 ± 13	24 ± 15	25 ± 13	21 ± 12

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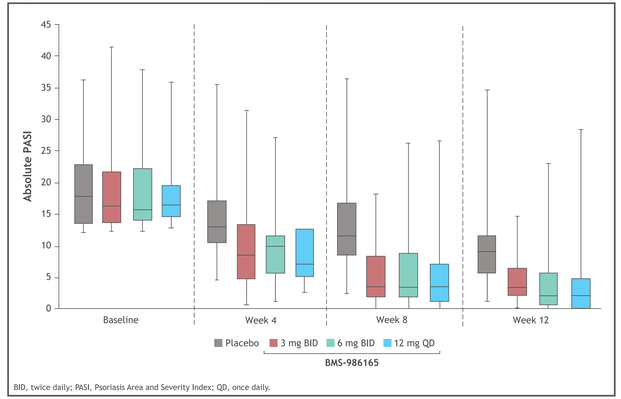
BID, twice daily; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; QD, once daily.
[a]Values are means ± SD unless otherwise noted. Data have been rounded to the nearest integer. Percentages may not total 100 because of rounding.
[b]PASI ranges from 0-72, with higher scores indicating greater severity of psoriasis.
[c]DLQI scores range from 0-30, with higher scores indicating worse quality of life.

Absolute PASI

- BMS-986165 was associated with lower absolute PASI compared with placebo up to Week 12 (**Figure 1**)
  - Each of the 3 BMS-986165 doses evaluated resulted in similar levels of improvement in median absolute PASI over time

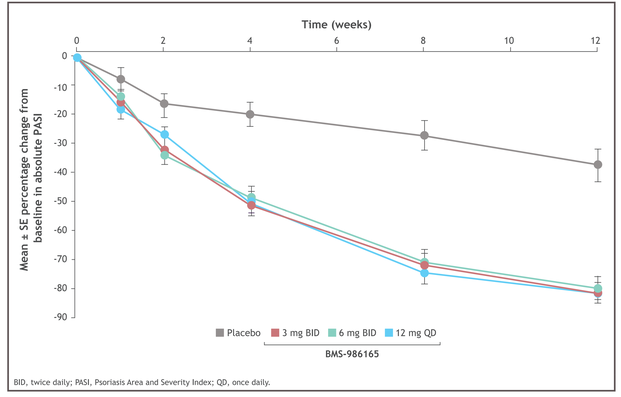
Figure 1. Median absolute PASI through Week 12



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

- BMS-986165 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 BMS-986165 groups than in the placebo group (**Table 2**)

Table 2. Absolute PASI at Week 12

Absolute PASI	Patients achieving PASI threshold, % (intent-to-treat population)				
	Placebo (n=45)	BMS-986165 3 mg BID (n=45)	BMS-986165 6 mg BID (n=45)	BMS-986165 12 mg QD (n=44)	BMS-986165 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 BMS-986165 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 BMS-986165-treated patients
- Five ongoing Phase 3 trials in plaque psoriasis (NCT03624127, NCT03611751, NCT04167462, NCT03924427, and NCT04036435) involving BMS-986165 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

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