An oral, selective TYK2 inhibitor, BMS-986165, in patients with moderate to severe plaque psoriasis and baseline PASI ≤15 versus >15

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Introduction

- Psoriasis is a chronic immune-mediated disease characterized by symptoms that negatively affect health-related quality of life and work productivity[1]
- Tyrosine kinase 2 (TYK2) activates intracellular signal transducer and activator of transcription (STAT)-dependent signaling pathways of specific cytokines, including interleukin (IL)-23, IL-12, and Type I interferons, which are involved in the pathogenesis of psoriasis and other immune-mediated disorders[2,3]
- BMS-986165 is an oral, selective TYK2 inhibitor with a unique mode of binding to the regulatory pseudokinase domain of the enzyme (allosteric inhibition) rather than to the active kinase domain targeted by other tyrosine kinase inhibitors (competitive inhibition), which provides high functional selectivity for TYK2[4]
- In a 12-week, Phase 2 trial (NCT02931838) in adults with moderate to severe plaque psoriasis, BMS-986165 demonstrated a dose-dependent improvement in clinical efficacy (**Table 1**) and a favorable safety profile[5]
  - At Week 12, Psoriasis Area and Severity Index (PASI) 75 responses were highest (67%–75%) at BMS-986165 dosages ranging from 3 mg twice daily (BID) up to 12 mg once daily (QD) vs placebo (7%; *P*<0.001; primary endpoint)

Table 1. Efficacy of BMS-986165 at Week 12 (nonresponder imputation)[5]

		BMS-986165				
	Placebo (n=45)	3 mg QOD (n=44)	3 mg QD (n=44)	3 mg BID (n=45)	6 mg BID (n=45)	12 mg QD (n=44)
Primary endpoint: PASI 75						
Patients, n (%)	3 (7)	4 (9)	17 (39)	31 (69)	30 (67)	33 (75)
P value vs placebo	—	0.49	<0.001	<0.001	<0.001	<0.001
Secondary endpoints						
PASI 90						
Patients, n (%)	1 (2)	3 (7)	7 (16)	20 (44)	20 (44)	19 (43)
Difference vs placebo, % (95% CI)	—	5 (−16 to 25)	14 (−7 to 33)	42 (21–60)	42 (21–60)	41 (20–58)
PASI 100						
Patients, n (%)	0 (0)	1 (2)	0 (0)	4 (9)	8 (18)	11 (25)
Difference vs placebo, % (95% CI)	—	2 (−18 to 23)	—	9 (−13 to 30)	18 (−4 to 38)	25 (4–44)
sPGA 0/1						
Patients, n (%)	3 (7)	9 (20)	17 (39)	34 (76)	29 (64)	33 (75)
Difference vs placebo, % (95% CI)	—	14 (−7 to 33)	32 (11–50)	69 (51–83)	58 (38–74)	68 (50–82)

Data have been rounded to the nearest integer. For patients who discontinued early or had a missing value at any time point, data were imputed as a nonresponse at that time point, regardless of the status of response at the time of discontinuation. The numbers of patients with nonresponder imputation in each group were as follows: For PASI endpoints: placebo, n=11; 3 mg QOD, n=6; 3 mg QD, n=3; 3 mg BID, n=1; 6 mg BID, n=5; and 12 mg QD, n=1. For sPGA 0/1: placebo, n=11; 3 mg QOD, n=6; 3 mg QD, n=6; 3 mg BID, n=1; 6 mg BID, n=6; and 12 mg QD, n=1. *P* values for endpoints other than the primary endpoint are not reported because these values have not been adjusted for multiple comparisons; 95% CIs are unadjusted.

BID, twice daily; PASI 75, ≥75% improvement from baseline in Psoriasis Area and Severity Index; PASI 90, ≥90% improvement from baseline in Psoriasis Area and Severity Index; PASI 100, 100% improvement from baseline in Psoriasis Area and Severity Index; QD, once daily; QOD, every other day; sPGA 0/1, static Physician's Global Assessment score of 0 or 1 (scores on the sPGA range from 0 to 5, with higher scores indicating greater disease severity).

- There is an unmet need for an oral medication that is safe and efficacious in patients with moderate to severe plaque psoriasis regardless of baseline disease severity

Objective

- This post hoc analysis of the Phase 2 trial evaluated improvements in PASI and static Physician's Global Assessment (sPGA) response rates stratified by baseline PASI (≤15 or >15)

Methods

Patient population and study design

- Adults with moderate to severe plaque psoriasis (affected body surface area ≥10%, PASI ≥12, and sPGA score ≥3) were recruited into the Phase 2 trial[5]
- Patients were randomized equally to BMS-986165 (3 mg every other day, 3 mg QD, 3 mg BID, 6 mg BID, or 12 mg QD) or placebo for 12 weeks[5]

Subgroup analyses

- Patients were grouped by baseline PASI (≤15 or >15); randomization was not stratified by baseline PASI
- Efficacy outcomes included:
  - Proportion of patients achieving ≥75% or ≥90% improvement from baseline in PASI (PASI 75 or PASI 90)
  - Proportion of patients with an sPGA score of 0 or 1 (sPGA 0/1; range, 0–5, where higher scores indicate greater disease severity)

Statistical analysis

- Missing data were imputed using nonresponder imputation: patients who discontinued early or who had a missing value at any time point had data imputed as a nonresponse at that time point, regardless of the status of response at the time of discontinuation

Results

Patient population

- In total, 267 patients were randomized and treated[5]
  - Patient demographics and clinical characteristics were similar across treatment groups (**Table 2**)

Table 2. Demographic and clinical characteristics of patients at baseline[5]

			BMS-986165				
	Total (N=267)	Placebo (n=45)	3 mg QOD (n=44)	3 mg QD (n=44)	3 mg BID (n=45)	6 mg BID (n=45)	12 mg QD (n=44)
Demographic characteristics							
Age, y	45 ± 13	46 ± 12	41 ± 12	45 ± 14	46 ± 15	43 ± 13	47 ± 12
Sex, male, n (%)	194 (73)	37 (82)	36 (82)	30 (68)	26 (58)	35 (78)	30 (68)
Race, n (%)*							
White	225 (84)	40 (89)	35 (80)	39 (89)	39 (87)	35 (78)	37 (84)
Asian	36 (13)	5 (11)	6 (14)	5 (11)	5 (11)	9 (20)	6 (14)
Other	6 (2)	0 (0)	3 (7)	0 (0)	1 (2)	1 (2)	1 (2)
Body weight, kg	88 ± 20	96 ± 21	90 ± 18	87 ± 22	84 ± 18	84 ± 19	88 ± 24
BMI, kg/m^2	29 ± 5	30 ± 6	29 ± 6	29 ± 5	28 ± 5	27 ± 5	29 ± 5
Clinical characteristics							
Median (range) duration of disease, y	15 (1–61)	18 (2–48)	18 (1–52)	13 (2–60)	13 (1–61)	15 (1–55)	20 (1–47)
Previous use of biologic agent, n (%)	115 (43)	20 (44)	19 (43)	19 (43)	19 (42)	20 (44)	18 (41)
PASI†	18 ± 6	19 ± 6	17 ± 4	18 ± 6	19 ± 8	18 ± 6	18 ± 5
PASI ≥20, n	71	14	9	10	16	12	10
DLQI‡	12 ± 7	13 ± 7	12 ± 8	12 ± 7	13 ± 5	11 ± 6	13 ± 7
BSA, %§	23 ± 13	24 ± 13	20 ± 8	23 ± 17	24 ± 15	25 ± 13	21 ± 12

Plus-minus (±) values are means ± SD. Formal statistical analysis was not performed to evaluate between-group differences. Data have been rounded to the nearest integer. Percentages may not total 100 because of rounding.
*Race was reported by the patients on a questionnaire at screening or baseline.
†PASI scores range from 0 to 72, with higher scores indicating greater severity of psoriasis.
‡DLQI scores range from 0 to 30, with higher scores indicating worse quality of life.
§Percentage of BSA affected by psoriasis.

BID, twice daily; BMI, body mass index; BSA, body surface area; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; QD, once daily; QOD, every other day.

- Among randomized and treated patients, 240 had PASI data available at Week 12 and were included in the current post hoc analysis: baseline PASI ≤15, n=94; baseline PASI >15, n=146 (**Table 3**)
  - Lack of stratification by baseline PASI at randomization led to an imbalance in the number of patients in each treatment group

Table 3. Number of patients with PASI ≤15 or >15 at baseline

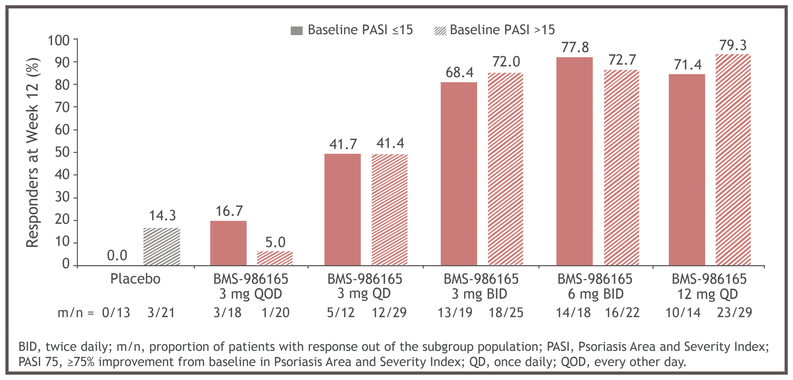
	PASI ≤15	PASI >15
Placebo	13	21
BMS-986165		
3 mg QOD	18	20
3 mg QD	12	29
3 mg BID	19	25
6 mg BID	18	22
12 mg QD	14	29

BID, twice daily; PASI, Psoriasis Area and Severity Index; QD, once daily; QOD, every other day.

Efficacy outcomes by baseline PASI ≤15 vs >15

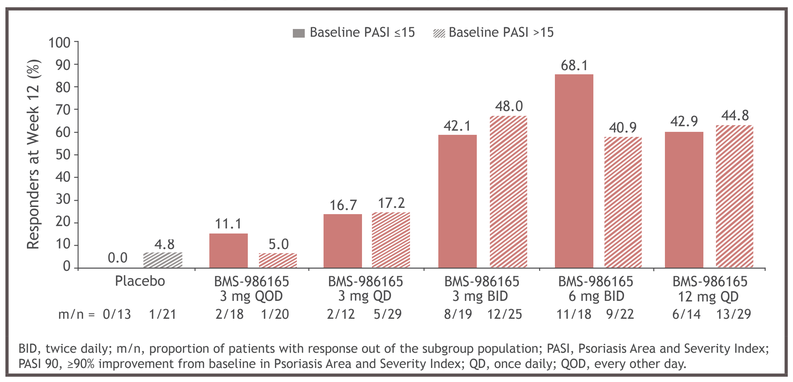
- Among patients receiving placebo or any dose of BMS-986165, the proportion achieving PASI 75 (**Figure 1**), PASI 90 (**Figure 2**), or sPGA 0/1 responses (**Figure 3**) were similar overall regardless of baseline PASI subgroup (≤15 vs >15), with some variability in responses due to low patient numbers

Figure 1. PASI 75 response rates at Week 12 by baseline PASI ≤15 vs >15



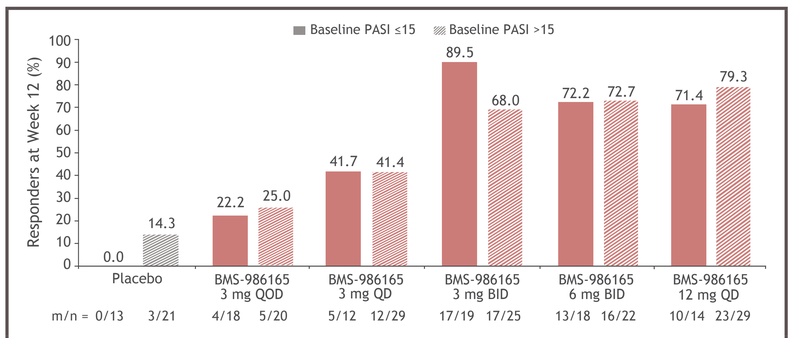
BID, twice daily; m/n, proportion of patients with response out of the subgroup population; PASI, Psoriasis Area and Severity Index; PASI 75, ≥75% improvement from baseline in Psoriasis Area and Severity Index; QD, once daily; QOD, every other day.

Figure 2. PASI 90 response rates at Week 12 by baseline PASI ≤15 vs >15



BID, twice daily; m/n, proportion of patients with response out of the subgroup population; PASI, Psoriasis Area and Severity Index; PASI 90, ≥90% improvement from baseline in Psoriasis Area and Severity Index; QD, once daily; QOD, every other day.

Figure 3. sPGA 0/1 response rates at Week 12 by baseline PASI ≤15 vs >15



BID, twice daily; m/n, proportion of patients with response out of the subgroup population; PASI, Psoriasis Area and Severity Index; QD, once daily; QOD, every other day; sPGA 0/1, static Physician's Global Assessment score of 0 or 1 (scores on the sPGA range from 0 to 5, with higher scores indicating greater disease severity).

Conclusion

- In this post hoc analysis of a Phase 2 study of patients with moderate to severe plaque psoriasis, BMS-986165 treatment for 12 weeks achieved similar PASI 75, PASI 90, and sPGA 0/1 response rates regardless of whether baseline PASI was ≤15 or >15
  - Interpretation of the results from this post hoc analysis is limited by the low patient numbers
- The efficacy of BMS-986165 in moderate to severe plaque psoriasis thus appears to be independent of baseline disease severity as measured by PASI

References

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