BMS-986165, an Oral, Selective Tyrosine Kinase 2 (TYK2) Inhibitor: Evaluation of Changes in Laboratory Parameters in Response to Treatment in a Phase 2 Trial in Psoriasis Patients

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Introduction

- 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, that are involved in the pathogenesis of psoriasis and other immune-mediated disorders[1-5]
- BMS-986165, an oral, selective TYK2 inhibitor with a unique mode of binding to the pseudokinase domain of the enzyme rather than the ATP binding site of the active kinase domain targeted by other tyrosine kinase inhibitors, provides high functional selectivity for TYK2[2,6]
- In a 12-week, Phase 2 trial (NCT02931838) in adults with moderate to severe plaque psoriasis, BMS-986165 demonstrated a dose-dependent improvement in Psoriasis Area and Severity Index (PASI) 75 response and a favorable safety profile[7]
  - At Week 12, PASI 75 responses were highest (67-75%) at doses from 3 mg twice daily (BID) up to 12 mg once daily (QD) versus placebo (7%; $P<0.001$; primary endpoint)

Objective

- The objective of this post hoc analysis of the Phase 2 trial was to assess the effect of BMS-986165 on laboratory parameters

Methods

Patient population and study design

- The Phase 2 trial included adult patients with plaque psoriasis for >6 months and a body mass index of 18-40 kg/m^2, who were eligible for phototherapy or systemic therapy and had moderate to severe disease as defined by affected body surface area ≥10%, PASI score ≥12, and static Physician's Global Assessment score ≥3[7]
- Patients were randomized to 1 of 5 oral doses of BMS-986165 (3 mg every other day, 3 mg QD, 3 mg BID, 6 mg BID, 12 mg QD) or placebo[7]
- The treatment period was 12 weeks, with an additional 30-day off-treatment follow-up period for safety[7]

Laboratory assessments

- Assessments of clinical laboratory parameters included hematologic parameters, C-reactive protein, metabolic parameters (creatinine, creatine phosphokinase [CPK], glucose, total cholesterol, high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], and triglyceride levels), and immunoglobulin (Ig) levels. Other laboratory parameters were measured but are not presented here
- Mean (standard deviation [SD]), median (interquartile range), or median (range) absolute values for laboratory parameters are reported for the placebo group and the most clinically effective BMS-986165 doses (ie, doses ≥3 mg BID). For this ad hoc analysis on the intention-to-treat cohort, data are shown for the 12-week treatment period

Results

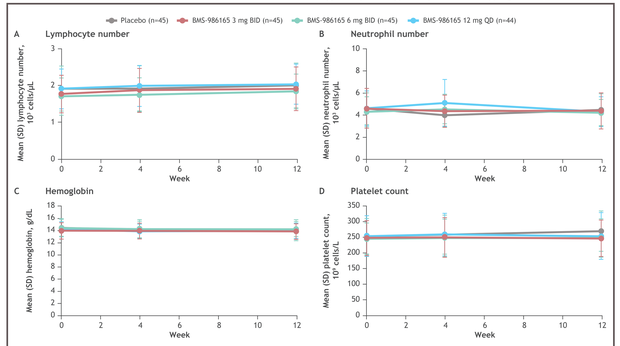
Patient population

- Of the 267 patients who were randomized and received treatment in the Phase 2 trial, 45 patients each received placebo, BMS-986165 3 mg BID, or BMS-986165 6 mg BID, and 44 received BMS-986165 12 mg QD and were included in this analysis
- Patient demographics and baseline disease characteristics were generally similar across treatment groups[7]

Laboratory parameters

- Hematologic parameters, including numbers of lymphocytes and neutrophils, platelet count, and hemoglobin levels, remained within normal ranges for placebo and BMS-986165-treated patients over 12 weeks of treatment (**Figure 1**)
- Other hematologic parameters assessed, including numbers of erythrocytes, leukocytes, and natural killer cells, were also within normal ranges (data not shown)

Figure 1. Hematologic parameters at baseline and on treatment for all randomized and treated patients who received BMS-986165 3 mg BID, 6 mg BID, or 12 mg QD or placebo



Data shown are for the 12-week treatment period.
BID=twice daily; QD=every day; SD=standard deviation.

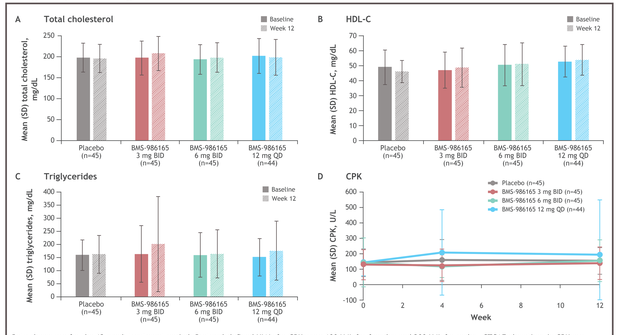
- Serum levels of C-reactive protein, creatinine, glucose, total cholesterol, HDL-C, and triglycerides remained within normal ranges during the 12-week trial period (**Table 1**; **Figure 2**). For patients with LDL-C values available, no increase was observed over 12 weeks of treatment (data not shown)
- Increases in CPK observed at 12 weeks in the placebo and BMS-986165 groups were asymptomatic, mostly Grade 1 or 2, and were observed in 12/44 (27%) patients who received placebo and 57/221 (26%) who received BMS-986165

Table 1. C-reactive protein, creatinine, and glucose levels at baseline and on treatment for all randomized and treated patients who received BMS-986165 3 mg BID, 6 mg BID, or 12 mg QD or placebo

Absolute values	Placebo (n=45)	BMS-986165		
		3 mg BID (n=45)	6 mg BID (n=45)	12 mg QD (n=44)
C-reactive protein, mg/L				
Baseline	3.863 (3.9629), n=45	4.344 (6.3423), n=45	3.397 (5.0866), n=44	3.159 (3.5864), n=41
Week 4	3.128 (2.8095), n=44	3.623 (5.1206), n=42	4.413 (6.2391), n=39	3.517 (3.8205), n=44
Week 12	4.046 (3.4668), n=31	4.910 (8.1941), n=43	2.638 (3.2964), n=39	3.426 (5.2116), n=41
Creatinine, mg/dL				
Baseline	0.846 (0.1535), n=45	0.849 (0.1957), n=45	0.797 (0.1400), n=45	0.778 (0.1503), n=44
Week 4	0.858 (0.1443), n=44	0.845 (0.1790), n=42	0.784 (0.1371), n=39	0.801 (0.1515), n=44
Week 12	0.808 (0.1210), n=32	0.843 (0.1788), n=43	0.794 (0.1382), n=39	0.788 (0.1553), n=41
Glucose, mg/dL				
Baseline	96.3 (21.03), n=45	99.3 (44.34), n=45	115.2 (79.93), n=45	98.3 (26.09), n=44
Week 12	96.5 (16.14), n=31	100.0 (38.47), n=43	109.1 (51.36), n=39	100.8 (27.12), n=41

Data are means (SD). Data shown are for the 12-week treatment period.
BID=twice daily; QD=every day; SD=standard deviation.

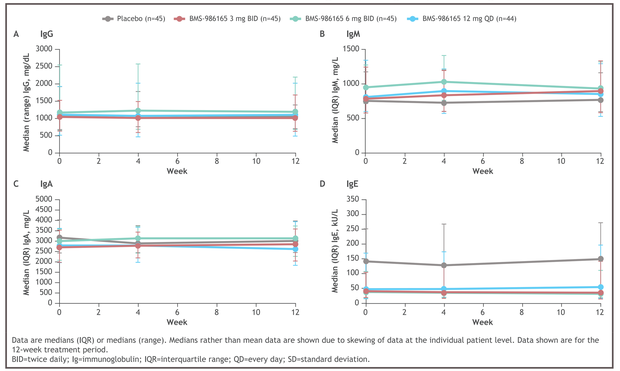
Figure 2. Total cholesterol, HDL-C, triglyceride, and CPK levels at baseline and on treatment for all randomized and treated patients who received BMS-986165 3 mg BID, 6 mg BID, or 12 mg QD or placebo



Data shown are for the 12-week treatment period. Protocol-defined ULNs for CPK were 180 U/L for females and 200 U/L for males. CTCAE elevations in CPK are defined as: Grade 1, >ULN to 2.5 x ULN; Grade 2, >2.5 x ULN to 5 x ULN; Grade 3, >5 x ULN to 10 x ULN; Grade 4, >10 x ULN.[8]
BID=twice daily; CPK=creatine phosphokinase; CTCAE=Common Terminology Criteria for Adverse Events; HDL-C=high-density lipoprotein cholesterol; QD=every day; SD=standard deviation; ULN=upper limit of normal.

- Changes in CPK levels were not dose-dependent and there were no events resulting in discontinuation from the trial
- Serum levels of IgE, IgA, IgM, and IgG also stayed within normal ranges (**Figure 3**)

Figure 3. Immunoglobulin levels at baseline and on treatment for all randomized and treated patients who received BMS-986165 3 mg BID, 6 mg BID, or 12 mg QD or placebo



Data are medians (IQR) or medians (range). Medians rather than mean data are shown due to skewing of data at the individual patient level. Data shown are for the 12-week treatment period.
BID=twice daily; Ig=immunoglobulin; IQR=interquartile range; QD=every day; SD=standard deviation.

Conclusions

- There were no consistent differences observed between placebo and BMS-986165 treatment groups in any hematologic parameters, serum chemistry (hepatic, renal, or lipid) parameters, or serum Ig isotype levels
- In addition, there were no clear dose-dependent changes observed with BMS-986165 for any of the laboratory parameters investigated
- Results of 4 large ongoing Phase 3 trials of BMS-986165 (NCT03624127 [POETYK-PSO-1], NCT03611751 [POETYK-PSO-2], NCT04167462 [POETYK-PSO-3], and NCT03924427) and the long-term extension study (NCT04036435) in patients with moderate to severe plaque psoriasis will provide long-term safety and laboratory data

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