AN ORAL, SELECTIVE INHIBITOR OF TYROSINE KINASE 2, BMS-986165, IMPROVES MOLECULAR, CELLULAR, AND CLINICAL BIOMARKERS ASSOCIATED WITH EFFICACY IN MODERATE TO SEVERE PSORIASIS

Background Psoriasis, a chronic immune-mediated inflammatory disease dependent upon the interleukin (IL)–23/TH17 pathway, is thought to be initiated through plasmacytoid dendritic cell activation and induction of type I interferons. BMS-986165 is a novel tyrosine kinase 2 (TYK2) inhibitor that blocks signal transduction of IL-23, IL-12, and type I interferons. BMS-986165 selectivity for TYK2, compared with Janus kinases (JAKs) 13, is driven by binding to its pseudokinase domain, rather than the conserved kinase domain.

Methods BMS-986165 was evaluated in a randomized, placebo-controlled, dose-ranging trial in 267 patients with moderate-to-severe psoriasis. Dose- and time-dependent effects on laboratory parameters indicative of non-selective inhibition of JAKs 13 were assessed. In an optional sub-study, 37 patients provided biopsies, which were assessed from healthy-appearing skin on Day 1 and from lesional skin on Days 1, 15, and 85 for changes in the IL-23, IL-12, and type I interferon pathways by QRTPCR, RNA sequencing, and immunohistochemistry.

Results All BMS-986165 treatment groups, except 3 mg every other day (QOD), achieved superiority versus placebo in the proportion of patients achieving Psoriasis Area and Severity Index 75 after 12 weeks of treatment (primary endpoint): 3 mg QOD, 9.1%; 3 mg daily (QD), 38.6%; 3 mg twice daily (BID), 68.9%; 6 mg BID, 66.7%; and 12 mg QD, 75.0% vs 6.7% with placebo. Mean levels of factors impacted with JAK 13 inhibition, including hemoglobin, total cholesterol, neutrophils, platelets, total lymphocytes, natural killer, and B cells, were not affected by BMS-986165. Markers of the IL-23 pathway including IL-17(A/F), S100A8/9, IL-22, and -defensin returned to non-lesion levels dose-dependently. Interferon and IL-12 pathway genes were normalized; keratinocyte dysregulation markers keratin-16 and 10, and late cornified envelope genes, returned toward non-lesion levels with effective doses.

Conclusions Clinical efficacy with BMS-986165 was associated with decreases in IL-23/TH17 and interferon pathway markers. TYK2 selectivity was confirmed by lack of effect on clinical biomarkers of JAK 13 inhibition. BMS-986165 has promising efficacy in psoriasis, and a distinct selectivity profile that warrants further investigation.

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