PSORIASIS

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

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Introduction: Psoriasis, a chronic immune-mediated 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, a novel tyrosine kinase 2 (TYK2) inhibitor, blocks signal transduction of IL-23, IL-12, and type I interferons. BMS-986165 selectivity for TYK2, compared with Janus kinases (JAKs) 1–3, is driven by its binding to the TYK2 regulatory pseudokinase domain, rather than the conserved kinase domain.

Objective: Evaluate BMS-986165 in a randomized, placebo-controlled, dose-ranging trial in 267 patients with moderate-to-severe psoriasis.

Materials and Methods: Dose- and time-dependent effects on laboratory parameters indicative of non-selective inhibition of JAKs 1–3 were assessed. In an optional substudy, 37 patients provided biopsies, which were assessed from healthy-appearing skin (Day 1) and lesional skin (Days 1, 15, and 85) for changes in IL-23, IL-12, and type I interferon pathways by QRTPCR, RNA sequencing, and immunohistochemistry.

Results: All BMS-986165 treatment groups, except 3mg every other day (QOD), achieved superiority versus placebo in proportion of patients achieving PASI 75 at Week 12 (primary endpoint): 3mg QOD, 9.1%; 3mg daily (QD), 38.6%; 3mg twice daily (BID), 68.9%; 6mg BID, 66.7%; 12mg QD, 75.0% versus placebo, 6.7%. BMS-986165 did not affect mean levels of parameters impacted with JAK 1–3 inhibition, including haemoglobin, total cholesterol, neutrophils, platelets, total lymphocytes, natural killer, and B cells. IL-23 pathway markers, including IL-17(A/F), S100A8/9, IL-22, and β-defensin, returned to non-lesion levels dose-dependently. Interferon and IL-12 pathway genes were normalized;

keratinocyte dysregulation markers 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 biomarkers of JAK 1–3 inhibition. BMS-986165 has promising efficacy in psoriasis and a distinct selectivity profile that warrants further investigation.