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BMS-986326 is a novel IL-2/CD25 fusion protein that induces highly selective and durable expansion of regulatory T cells in vitro and following single doses in healthy volunteers

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Introduction & Objectives:

Low-dose interleukin (IL)-2 has shown signs of clinical efficacy in immune-mediated diseases via expansion of regulatory T cells (Tregs), which are essential in maintaining immune tolerance.1 BMS-986326 is an investigational IL-2/CD25 fusion protein designed for greater Treg selectivity and a longer half-life through slow dissociation from an inactive, non-covalent homodimer to active monomers. We report results from an in vitro study of BMS-986326 in whole blood from healthy volunteers (HVs) compared with patients with immune-mediated disease, and an ongoing first-in-human single-ascending dose (SAD) study to evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of BMS-986326.

Materials & Methods:

Treg IL-2 receptor (IL-2R) proximal signaling was evaluated by measuring phosphorylated STAT5 (pSTAT5) after 15 min stimulation of whole blood ex vivo with BMS-986326 from both HVs and patients with immune-mediated disease (eg, systemic lupus erythematosus [SLE], atopic dermatitis). Total CD25 staining and pSTAT5 induction potency (% positive cells) in Tregs were compared between HVs and patients with SLE.

In a phase 1 SAD study (NCT04736134), HVs were randomized to receive either a single dose of IV BMS-986326 or placebo (PBO; 6 treated and 2 PBO per dose). AEs were monitored over a 55-day follow-up. Blood samples were collected at prespecified times for PK/PD analyses (Treg, T conventional [Tcon], and CD8+ T-cell count [106/L], and pSTAT5 % in Tregs). A power model assessed dose-proportionality.

Results:

In vitro, mean (SD) Treg half maximal effective concentrations of BMS-986326 for the induction of pSTAT5 were 0.72 (0.37) nM for HVs (n = 12) and 1.4 (1.1) nM for patients with SLE (n = 11). More patients with SLE had a CD25-low Treg profile, indicating CD25 deficiency, than HVs (median [SD], 56% [16%] and 43% [10%], respectively). BMS-986326 induced pSTAT5 with a comparable maximal signal and an approximately 2-fold reduction in potency in Tregs from patients with SLE vs HVs.

In the SAD study, 32 male HVs aged 19–50 years were randomized to PBO or 1 of 4 ascending BMS-986326 doses (A, B, C, D). All AEs were mild/moderate; 13 (54%) and 5 (50%) HVs experienced AEs when treated with BMS-986326 across doses or PBO, respectively. Eosinophilia was seen in HVs receiving doses C or D. PK data showed linear dose-proportional increases in BMS-986326 exposure (half-life: 4–6 days). There were dose-dependent increases in Treg expansion; doses A, B, C, and D showed peak mean fold change (SE) vs baseline of 1.5 (0.3 [day 28]), 1.8 (0.3 [day 11]), 2.6 (0.3 [day 28]), and 5.4 (1.0 [day 15]), respectively. These increases were maintained by all HVs until the last time point (day 55): mean fold change (SE) of 1.1 (0.2), 1.5 (0.3), 1.4 (0.2), and 2.7 (0.1) for doses A, B, C, and D, respectively. All doses showed increases in pSTAT5 % in Tregs vs baseline following a single dose of BMS-986326. Minimal changes on Tcon and CD8+ T-cell populations were observed.

Conclusion:

In whole blood from patients with immune-mediated disease, BMS-986326 induced comparable maximal IL-2R signaling to that in blood from HVs.

In a SAD study in HVs, BMS-986326 was generally well-tolerated with robust, selective, durable, and dose-dependent Treg expansion. Further clinical studies are warranted to investigate how BMS-986326 may restore immune homeostasis by Treg expansion in patients with immune-mediated dermatologic diseases.

Reference:

1He J, et al. *Ann Rheum Dis* 2020;79:141–9.