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THU0190 THE SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF BMS-986166, A NOVEL, SELECTIVE, PARTIAL AGONIST OF THE SPHINGOSINE-1-PHOSPHATE (S1P) SUBTYPE 1 RECEPTOR IN HEALTHY PARTICIPANTS

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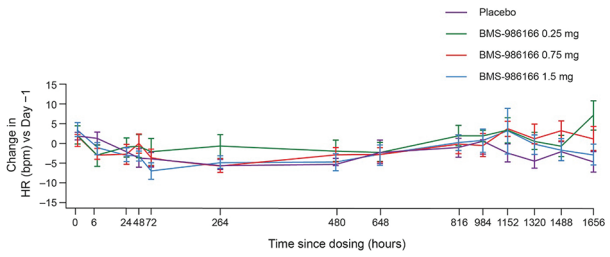
Background: S1P mediates a number of immune processes including the egress of lymphocytes from lymphoid organs via stimulation of the S1P subtype 1 receptor (S1P1R). S1P1R inhibition has the potential to suppress abnormal immune responses and modulate autoimmune inflammatory diseases.[1] BMS-986166, a novel, selective partial agonist of S1P1R, which is phosphorylated in vivo to its pharmacologically active form, BMT-121795, may have utility for the treatment of autoimmune and/or inflammatory diseases.
Objectives: To investigate safety, pharmacokinetics (PK), and pharmacodynamics (PD) of BMS-986166 in single- and multiple-ascending dose (SAD/MAD) placebo (PBO)-controlled studies in healthy participants.
Methods: SAD study (NCT02790125): BMS-986166 was administered as a single dose of 0.75, 2.0, or 5.0 mg (n=10/group; 4:1 ratio of BMS-986166:PBO); a series of upwardly titrated single daily doses of 0.25, 0.5, 0.75, 1.0, then 1.5 mg over 14 days (n=16; 3:1 ratio); or as a single 2.0-mg dose in participants who were fed, fasted, or administered famotidine prior to dosing (n=8/group). MAD study (NCT03038711): BMS-986166 was administered as once-daily doses of 0.25 (n=12; 2:1 ratio), and 0.75 or 1.5 mg (n=10/dose; 4:1 ratio), for 28 days. Safety, PK, and PD (absolute lymphocyte count [ALC]) were assessed. Cardiac safety was assessed by continuous cardiac monitoring and at intervals by 12-lead electrocardiogram.
Results: 70 (60 BMS-986166, 10 PBO; mean [standard deviation (SD)] age: 32.8 [8.5] years) and 32 (24 BMS-986166, 8 PBO; mean [SD] age: 35.8 [8.6] years) participants were randomised to dosing in the SAD and MAD studies, respectively. Participants were predominantly male. Mean (SD) body mass index was 26.8 (2.9) and 27.2 (2.5) kg/m^2, respectively. Multiple oral doses of BMS-986166 up to 1.5 mg daily for 28 days were generally well tolerated, and all treatment-related adverse events were mild (Grade 1). In the MAD (Figure 1) and SAD studies, a clinically insignificant, dose-related decrease in mean hourly heart rate (HR) was observed following administration of BMS-986166 compared with PBO, based on a time-matched analysis of nominal hourly HR data from continuous cardiac monitoring over 72 hours post dose. Compared with participants receiving PBO, a mean decrease from baseline in hourly HR was apparent for participants in the 2 higher dose panels (2.0 mg, 5.0 mg) in the SAD study. In the SAD study, the largest decreases in PBO-corrected, time-matched, nadir hourly HR were –0.29, –6.38, and –8.37 bpm for the 0.75, 2.0, and 5.0 mg dose panels, respectively. Similarly, in the MAD study, these numbers were –0.83, –3.46, and –5.54 bpm at the 0.25, 0.75, and 1.5 mg dose levels, respectively. Increases in systemic plasma exposure (maximum concentration and area under the curve from time 0–24 hours) of BMS-986166 and its active metabolite BMT-121795 were approximately proportional to dose increases over the range of 0.75–5 mg with single doses, and of 0.25–1.5 mg on Days 1, 14, and 28 with multiple doses. Decreases in percent change from baseline in ALC with multiple doses of BMS-986166 vs PBO were dose-related over the 28-day treatment period. Between Day 0 and 35, median (range) nadir in lymphocyte reductions were 53.7% (31.7–55.9%), 75.9% (63.3–85.8%), and 81.9% (37.9–92.2%) at 0.25, 0.75, and 1.5 mg BMS-986166 dose levels, respectively. Recovery of ALC levels began 14, 14–21, and 7 days after the last dose of 0.25, 0.75, and 1.5 mg, respectively, on Day 28.

Figure 1. Mean (SE) time-matched change from Day −1 in HR (bpm) following dosing in the MAD study



bpm=beats per minute; HR=heart rate; MAD=multiple-ascending dose; SE=standard error.

Abstract THU0190 – Figure 1

Conclusion: In healthy participants, multiple daily doses of BMS-986166 in the range of 0.25–1.5 mg were well tolerated, with no clinically relevant lowering of HR. PK were linear and decreases in ALC were dose related.

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THU0191 UPADACITINIB AS MONOTHERAPY IN PATIENTS WITH RHEUMATOID ARTHRITIS: RESULTS AT 48 WEEKS FROM THE SELECT-MONOTHERAPY STUDY

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Background: In the SELECT-MONOTHERAPY trial, upadacitinib (UPA), an oral JAK1-selective inhibitor, showed efficacy when used as monotherapy over 14 weeks (wks) in rheumatoid arthritis (RA) patients (pts) with an inadequate response to methotrexate (MTX).[1]
Objectives: Safety and efficacy of UPA monotherapy were assessed through 48 wks in an ongoing long-term extension period of SELECT-MONOTHERAPY.
Methods: At baseline (BL), pts on stable MTX were randomized to either continue MTX (cMTX, given as a blinded study drug) or switch to once-daily (QD) UPA at 15 (UPA15) or 30 mg (UPA30) monotherapy for 14 wks. From Wk14, the start of a long-term blinded extension, pts randomized to cMTX were switched to UPA15 or 30mg per pre-specified assignment at BL, pts randomized to UPA15 or 30 continued their initial treatment. No dose adjustments for UPA were allowed. Starting at Wk26, for pts who did not achieve CDAI ≤10, background csDMARDS could be initiated. Efficacy data up to the Wk48 visit are reported “As Observed”. Adverse events (AE) per 100 pt yrs (PYs) are summarized up to May 25 2018.
Results: Of 648 pts randomized at BL, 598 (92%) completed 14 wks and continued on to the extension period. By May 25 2018, 16% discontinued study drug; 5% due to AE, 0.5% due to lack of efficacy, 4% withdrew consent, 1% were lost to follow-up, and 6% due to other reasons. Cumulative exposures to UPA15 and UPA30 were 336.0 PYs and 337.1