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. 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 (NCT03039871): 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/m², 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. Increases in percent change from baseline in ALC in MAD with multiple doses of BMS-986166 vs PBO were dose-related over the 28-day treatment period. Between Day 0 and 30, 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.

Disclosure of Interests: None declared


THU0190

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 (OD) 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 had to 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, 595 (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...
Abstract THU0191 – Table 1.

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Abstract THU0191 – Table 2.

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Conclusion: UPA 15 or 30 monotherapy resulted in similar improvements in signs and symptoms and physical function through 48 wks. The overall benefit-risk profile of both doses of UPA was favorable based on safety and efficacy data through Wk48 but will be confirmed through an integrated safety analysis across all the ph 3 trials.

Abstract THU0192

UPADACITINIB MONOTHERAPY IMPROVES PATIENTS' REPORTED OUTCOMES IN METHOTREXATE-NAÏVE PATIENTS WITH MODERATELY TO SEVERELY ACTIVE RHEUMATOID ARTHRITIS: RESULTS FROM SELECT-EARLY

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Background: Monotherapy use of upadacitinib (UPA), a selective JAK1 inhibitor, demonstrated clinically meaningful improvement in the signs and symptoms of rheumatoid arthritis (RA) compared with methotrexate (MTX). To better understand the impact of UPA treatment in RA from the patient's perspective, we examined the effect of UPA on patient-reported outcomes (PROs).

Objectives: To evaluate the effect of UPA monotherapy vs MTX at week 12 on PROs in SELECT-EARLY (NCT02706873), a randomised controlled trial in MTX-naïve patients with moderate to severe RA.

Methods: Patients were randomised 1:1:1 to receive once daily UPA (15 mg or 30 mg) or weekly MTX (titrated by Week 8). PROs assessed included Patient Global Assessment of Disease Activity (PtGA) by visual analogue scale (VAS), pain by VAS, physical function by Health Assessment Questionnaire Disability Index (HAQ-DI), fatigue by Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), duration and severity of morning (AM) stiffness, HRQoL by Short Form 36 (SF-36), and Work Productivity and Activity Impairment (WPAI) measure. Least square mean (LSM) changes from baseline (BL) to Week 12 were based on analysis of covariance. Percentages of patients reporting changes in PRO scores from BL to Week 12 ≥ minimum clinically important differences (MCIDs) or scores ≥ normative values (age- and gender-matched for SF-36 only) were determined for UPA and MTX groups; comparisons used chi-square tests. For each PRO, the incremental number needed to treat (NNT) to achieve clinically meaningful improvement from BL was calculated.

Results: Data from 945 patients (MTX: 314; UPA 15 mg: 317; UPA 30 mg: 314) were analysed. Mean age was 53 years; 76% were female; 49% had RA for <6 months. Statistically significant LSM changes from BL to Week 12 were reported for both doses of UPA vs MTX for all PROs (Table). At Week 2, both UPA doses had significantly higher proportions of patients reporting improvements ≥ MCID or MTX in HAQ-DI duration and severity of AM stiffness, pain, and PtGA. Compared with MTX at Week 12, a significantly greater proportion of patients receiving UPA at either dose reported improvements ≥ MCID in all PROs. A significantly greater proportion of patients receiving UPA also reported scores ≥ normative values for all PROs except SF-36 Mental Health (MTX 15 mg) and SF-36 General Health (both UPA doses) domains. For most PROs, NNTs with UPA ranged from 4 to 8 patients at Week 12.

REFERENCE:

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