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THU0183

UPADACITINIB PHARMACOKINETICS IN JAPANESE SUBJECTS WITH RHEUMATOID ARTHRITIS WITH THE EXTENDED-RELEASE FORMULATION AND COMPARABILITY TO NON-JAPANESE SUBJECTS

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Background: Upadacitinib (UPA), an oral selective JAK1 inhibitor, is being developed for treatment of patients with moderate to severely active rheumatoid arthritis (RA). UPA efficacy was demonstrated in subjects with moderate to severe RA in five global Phase 3 studies and a regional Phase 2b/3 study in Japanese subjects.

Objectives: To characterize the pharmacokinetics of UPA after administration of the extended-release formulation in Japanese subjects with RA and to compare UPA plasma exposures between Japanese and non-Japanese subjects.

Methods: Population pharmacokinetic analyses were conducted using UPA data across Phase 1 to 3 studies including Japanese and non-Japanese subjects. The population pharmacokinetic model was used to estimate UPA plasma exposures from the extended-release formulation regimens in non-Japanese and Japanese subjects with RA in Phase 3 trials. Additionally, a total of 29 Japanese subjects with RA who were enrolled in SELECT-SUNRISE Phase 2b/3 study participated in a pharmacokinetics substudy in which serial blood samples were collected from each subject over a 24 hour period after UPA dosing. UPA was administered in the study at doses of 7.5 mg, 15 mg, and 30 mg QD using the extended-release formulation. Pharmacokinetic parameters were calculated in the pharmacokinetic substudy using noncompartmental methods.

Results: UPA maximum plasma concentration was reached within 2 hours of dosing under fasting condition. UPA plasma exposures were approximately dose proportional over the evaluated dose range in Japanese subjects with RA. UPA model estimated plasma exposures (based on population pharmacokinetic analyses) were comparable (within 20%) between Japanese and non-Japanese subjects with RA (Table 1). Results from the pharmacokinetic substudy using noncompartmental methods were consistent with the population pharmacokinetic analyses.

Abstract THU0183 – Table 1. Upadacitinib Model Estimated Exposures in Japanese and Non-Japanese Subjects with RA for the Extended-Release Formulation

Median (5 th , 95 th Percentiles)				
Population	Treatment	C _{max} (ng/mL)	C _{avg} (ng/mL)	C _{trough} (ng/mL)
Japanese (N = 104)	7.5 mg QD	24.0 (18.0, 31.0)	8.8 (5.0, 15.2)	2.4 (0.7, 7.7)
Non-Japanese (N = 1495)	15 mg QD	40.9 (28.2, 54.7)	15.1 (8.9, 32.4)	3.8 (1.3, 21.3)
Japanese (N = 97)	30 mg QD	47.0 (36.7, 70.2)	16.5 (10.4, 33.6)	4.0 (1.3, 22.2)
Non-Japanese (N = 850)		81.0 (57.2, 113.9)	29.1 (17.9, 63.8)	7.5 (2.4, 40.5)
Japanese (N = 99)		97.7 (72.7, 124.3)	35.1 (21.7, 59.7)	9.5 (2.9, 27.8)

C_{max}: maximum plasma concentration; C_{avg}: average plasma concentration during a dosing interval; C_{trough}: trough plasma concentration

Conclusion: No clinically relevant difference was observed in UPA plasma exposures between Japanese and non-Japanese subjects with RA.

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THU0184

SIROLIMUS SELECTIVELY INCREASES CIRCULATING TREG CELL NUMBERS AND RESTORES THE TH17/TREG BALANCE IN RHEUMATOID ARTHRITIS PATIENTS WITH DAS28 ≤ 3.2 WHO PREVIOUSLY RECEIVED CONVENTIONAL DMARDS

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Background: Many immunosuppressants used to treat rheumatoid arthritis (RA) were designed to broadly suppress T cell function, including that of regulatory T cells (Tregs). Patients with inactive RA also show a reduced frequency of peripheral Tregs [1]. Tregs are essential for maintaining effective immune tolerance and a homeostatic balance of Th17/Treg. Accordingly, there has been increasing interest in developing Treg-friendly regimens to minimize or eliminate the immunosuppression of conventional medications for RA. mTOR signaling negatively controls the development and function of Tregs. Rapamycin, an mTOR inhibitor, could expand Tregs (CD4⁺CD25⁺FoxP3⁺) in patients with active systemic lupus erythematosus [2] and active RA [3]; however, the response of Tregs to rapamycin in RA patients with DAS28 ≤ 3.2 is still unclear.

Objectives: To investigate the effects of rapamycin, under the generic name sirolimus, on Tregs in RA patients with DAS28 ≤ 3.2 who previously received conventional DMARDs.

Methods: Fifty-five RA patients and 60 healthy controls were enrolled in this study. All patients had previously received conventional DMARDs and had a low DAS28 score (≤ 3.2). Peripheral blood samples and clinical information were obtained at baseline and following 6 and 12 weeks of sirolimus treatment, or after 12 weeks of conventional treatment. The circulating levels of lymphocyte subpopulations were assessed by flow cytometry.

Results: Thirty-five patients received sirolimus and 20 patients continued treatment with conventional DMARDs. None of the baseline clinical characteristics differed significantly between the two groups. The absolute counts and proportions of CD4⁺CD25⁺FoxP3⁺ Tregs were significantly lower in all RA patients with DAS28 ≤ 3.2 as compared with those in healthy controls. By contrast, the difference in circulating Th17 cell numbers was not significant. Sirolimus administration resulted in significant elevations in circulating Treg cell numbers and significant reductions in the Th17/Treg cell ratio, whereas the circulating level of Tregs and the Th17/Treg cell ratio in patients under conventional treatment both showed a tendency of reduction (Figure 1). Furthermore, a greater proportion of patients under sirolimus treatment achieved DAS28-based remission at 12 weeks.

Conclusion: Sirolimus can favorably expand Tregs in RA patients with DAS28 ≤ 3.2, consequently restoring a healthy balance of Th17/Treg cells, which might improve the likelihood of long-term and sustained clinical remission and reduce the probability of disease flare-ups in RA. These findings provide valuable insights that might potentially lead to changes in clinical practice for the routine treatment of RA.

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Abstract THU0184 – Figure 1. The numbers of Th17, Tregs, and the ratio of Th17/Treg in healthy controls and RA patients. **A:** Healthy controls and RA patients before and after sirolimus treatment. **B:** Healthy controls and RA patients before and after conventional treatment.

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THU0185

THE FIRST REPORT OF SIGNIFICANTLY IMPROVEMENT OF NT-PROBNP LEVEL IN RHEUMATOID ARTHRITIS PATIENTS TREATED WITH TOFACITINIB DURING 12-MONTH FOLLOW-UP

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Background: The amino-terminal fragment of the B-type natriuretic peptide prohormone (NT-proBNP) is a marker for functional cardiac impairment and is increased in heart disease with or without symptoms of congestive heart failure (CHF)¹.

Objectives: To prospectively investigate the effect of tofacitinib (TOFA) on the levels of NT-proBNP, as a predictor of CHF in patients (pt) with active rheumatoid arthritis (RA).

Methods: Twenty six RA pt (median age 54 [40;62] years, 81% female, disease duration 44[24;63.0] month (m), moderate to high activity (DAS28-5.1[4.6;6.1], SDAI-27(22;35)), positive for ACCP (73%)/RF (77%), who were non-responders to MTX at least 15 mg/week and/or other synthetic DMARDs and bDMARDs) free of clinical overt cardiovascular disease were treated with TOFA and followed for 12 m. TOFA therapy was started in all pt in dose 5 mg BID per os with dose escalation to 10 mg BID in 8 (31%) pt. TOFA used in combination with MTX in 24 (92%) pt, leflunomide in 1 (4%). Low-dose oral corticosteroids (<10 mg/day prednisone or equivalent) were received by 9 (35%) pt. Remission was achieved in 38,5% pt (DAS28), 38,5% (SDAI). Cardiovascular risk factors (CVRF) and the NT-proBNP levels were measured at baseline and after 12m. At baseline the most of pt had multiple CVRF and sub-clinical organ damage. Cardioprotective therapy received 16 (57%) pt (β-AB-7, ARA/ACE inhibitors-11, statins-11, dihydropyridine CCB-7). Twenty controls matched for CVRF were included for comparison of normal NT-proBNP levels with those of RA pt.

Results: The NT-proBNP level was significantly higher in RA pt than in the control group (median 62.2(26.9-101.7) pg/mL vs 44.0 (34.0-54.3) pg/mL, p<0.05). At baseline NT-proBNP level was higher in female than in male (p=0,019). Its concentration correlated with DAS28 (r=0,41,p=0,036). Three pt (11,5%) had NT-proBNP level over 125 pg/mL. All RA pt with a NT-proBNP level over 125 pg/mL were asymptomatic and exhibited normal echocardiography. Median DAS28 and SDAI were significantly

reduced following TOFA treatment (from 5.1 to 2.9, p < 0.001 and from 26.8 to 4.7, p < 0.001, respectively). During follow-up, no RA pt exhibited a cardiovascular event or CHF. NT-proBNP levels decreased by 63% over the 12-m of TOFA treatment (from 62.16 pg/mL to 14.8 pg/mL, p=0.011). The incidence rate of arterial hypertension (58%vs65%), overweight (62%vs62%), abdominal obesity (58%vs62%), smokers (27%vs27%), menopausal status (52%vs52%), DM type 2 (7%vs7%), mSCORE≥5% (23%vs27%), subclinical carotid atherosclerosis (58%vs58%) did not change significantly. An increase in body mass index (BMI) was observed from 26.5[22.9;29.0] to 26.9[24.0;30.1],p<0.001 and in HDL level from 1.37 [1.06;1.87] to 1.90[1.29;2.16],p<0.01. The percentage change in the NT-proBNP level significantly correlated with the percentage change in the BMI (r=0,6,p=0,007), DAS 28 (r = 0.41, p = 0.038) SDAI (r = 0.51, p = 0.009). Changes in NT-proBNP levels in RA pt with remission was greater than that observed in pt who didn't achieve remission (-87% vs -26%, p=0,005). The percentage change in the NT-proBNP level was not correlated with the percentage change in other CVRF.

Conclusion: TOFA decreased the NT-proBNP level in patients with RA without clinical overt cardiovascular disease and CHF. TOFA may have a cardioprotective effect in those with active RA.

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THU0186

SAFETY, TOLERABILITY AND PHARMACOKINETICS OF MBS2320, A SELECTIVE MODULATOR OF IMMUNE METABOLISM, IN HEALTHY VOLUNTEERS AND PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Despite the availability of several treatment options some patients with Rheumatoid Arthritis (RA) fail to benefit and for those who do response rates are similar across therapeutic classes. Thus there remains a need for new therapies with novel mechanisms of action. MBS2320 is a selective modulator of immune metabolism that shows anatomically appropriate osteoid layering and a broader spectrum of osteoprotective efficacy compared to TNFα inhibition in preclinical models.

Objectives: To investigate the safety, tolerability and pharmacokinetics of MBS2320 in healthy volunteers and patients with Rheumatoid Arthritis (RA) receiving a stable dose of methotrexate (MTX).

Methods: Cohorts of healthy volunteers (randomised 6:2 drug:placebo) received single or multiple oral doses of MBS2320 for 14 days. Single Ascending Dose (SAD) cohorts comprised 2, 10, 25, 50, 75, 125, 250, 375 mg (PO) and Multiple Ascending Dose (MAD) cohorts 75, 100, 160 mg/d. Patients with RA received 75 mg/d for 14 days in addition to their existing weekly MTX treatment. Safety and tolerability were assessed throughout. Plasma MBS2320 (SAD, MAD and patients with RA) and MTX (patients with RA only) were measured using LC-MS/MS. In patients with RA, C-reactive protein (CRP) and biomarkers of bone turnover were assessed on Day 14.

Results: A total of 96 healthy subjects and 9 patients with RA entered the study and were randomised to the drug or matching placebo.

MBS2320 was well tolerated by healthy subjects at single oral doses of 2 to 375 mg. There were no serious adverse events (SAEs). Nausea was the most commonly reported adverse event (AE) and occurred most frequently at the high doses but was mild and resolved without treatment. Daily doses of 75 to 160 mg QD MBS2320 for 14 days were generally well tolerated by healthy subjects. The most common drug-related treatment emergent adverse events (TEAEs) were gastrointestinal disorders,