Results: At baseline, levels of IL-6, CXCL9, CXCL10, and CCL7 correlated significantly with baseline DAS28-ESR, consistent with effector roles for IL-6 and interferon (IFN) in intercurrent disease activity. Clustering of the differential protein fold change at Weeks 2 and 12 for UPA and PBO groups revealed four clusters enriched for proteins related to: 1) IL-6, IFN, leukocyte trafficking, and macrophage activation ($\uparrow\downarrow\downarrow$); 2) T helper cell differentiation ($\downarrow$); 3) T and B cell signaling ($\downarrow\downarrow$); and 4) hematopoiesis and myeloid cell differentiation ($\uparrow$). Pathway analysis based on the differential expression of 37 significantly modulated proteins suggests that treatment with UPA results in the normalization of key pathways associated with the pathobiology of RA including: 1) pathways associated with IL-1, IL-6, IL-12, IL-15, IL-18, IFN α , IFN β , IFN γ , CSF2, and TNF; and 2) pathways associated with behaviors of leukocytes (lymphocytes, myeloid cells, and granulocytes), including leukocyte migration, T cell response, and inflammatory response. In keeping with the latter, the changes in IL-6, CCL23, CCL7, MMP1, and S100A12 levels at Week 12 correlated significantly with the relative change in DAS28-ESR, suggesting a link between UPA MoA and macrophage activation.

Conclusion: In keeping with its selectivity for JAK1, UPA operates via inhibition of multiple JAK1-dependent upstream pathways that result in the normalization of key functional downstream effects associated with the pathobiology of RA, including T cell and myeloid cell-related pathways. Notably, non-JAK signaling pathways also normalize, suggesting functional integration of JAK1 with parallel pathogenic signaling in RA effector cells.

REFERENCES:

- [1] Burmester GR, et al. Lancet 2018;391:2503–12;
- [2] Genovese MC, et al. Lancet 2018;391:2513–24

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THU0182 PHARMACOKINETICS AND SAFETY OF A SINGLE ORAL DOSE OF PEFICITINIB (ASP015K) IN SUBJECTS WITH NORMAL AND IMPAIRED RENAL FUNCTION

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Background: Peficitinib (ASP015K), a novel oral Janus kinase inhibitor, was shown to be efficacious as once-daily therapy for moderate-to-severe rheumatoid arthritis (RA) in a phase 2b study (NCT01649999)¹ and in two phase 3 studies (NCT02308163² and NCT02305849).³ Mean urinary excretion of peficitinib accounted for 9–15% of the oral dose.⁴

Objectives: To assess the pharmacokinetics (PK) and safety of a single, oral dose of peficitinib 150 mg in subjects with normal and impaired renal function.

Methods: This was an open-label, single-dose, parallel-group study conducted at two centres in Japan. All subjects were aged 20–75 years with a body mass index ≥ 17.6 to <30.0 kg/m². Renal function was classified according to estimated glomerular filtration rate (eGFR) using a GFR predictive equation for Japanese subjects: normal ≥ 90 mL/min/1.73 m²; mild impairment ≥ 60 to <90 mL/min/1.73 m²; moderate impairment ≥ 30 to <60 mL/min/1.73 m²; and severe impairment ≥ 15 to <30 mL/min/1.73 m². Subjects with impaired renal function had unchanged renal impairment treatment (including diet) within 14 days prior to dosing. Subjects received a single, oral dose of peficitinib 150 mg tablet under fasting conditions in a hospital setting. The selected dose was based on the peficitinib daily dose in the phase 3 RA studies. Blood samples for peficitinib plasma PK analysis were collected before administration and up to 72 h post dose. Safety was assessed throughout the study.

Results: A total of 31 subjects (87.1% male; Table 1) were enrolled and received study drug according to study protocol. Subjects comprised 8 with normal renal function, and 8 with mild, 8 with moderate and 7 with

severe renal impairment. The peficitinib concentration–time profiles from dosing to 72 h (Fig. 1), extrapolated to infinity (AUC_{inf}) and maximum concentration (C_{max}) were similar between those with normal and impaired renal function (Table 2). Two subjects had mild/grade 1 (CTCAE v4.0 JCOG) treatment-emergent adverse events (TEAEs): 1/8 (12.5%) with normal renal function had a headache (considered to be drug-related) and 1/8 (12.5%) with mild renal impairment had increased alanine aminotransferase (ALT) (not considered to be drug-related). There were no serious TEAEs or deaths during the study. There were no clinically significant mean changes from baseline in other clinical laboratory parameters or vital sign measurements, except for grade 1 increased ALT in a subject with mild renal impairment.

Abstract THU0182 –Table 1.

Table 1 Demographic characteristics (PKAS)

Parameter	Renal function ¹				Total
	Normal (n=8)	Mild impairment (n=8)	Moderate impairment (n=8)	Severe impairment (n=7) ²	
Male, n (%)	6 (75.0)	7 (87.5)	7 (87.5)	7 (100.0)	27 (87.1)
Median (min, max) age, y	56.5 (23, 69)	59.5 (37, 70)	62.0 (46, 75)	67.0 (58, 71)	60.0 (23, 75)
Median (min, max) weight, kg	65.8 (55.5, 73.0)	66.8 (46.7, 72.6)	66.4 (56.5, 76.4)	69.4 (62.9, 77.5)	67.6 (46.7, 77.5)
Median (min, max) BMI, kg/m ²	23.4 (20.9, 28.3)	23.0 (18.6, 24.7)	23.6 (22.3, 28.0)	25.0 (23.2, 29.0)	23.6 (18.6, 29.0)
Median (min, max) eGFR, mL/min/1.73 m ²	94.4 (91.7, 104.4)	79.8 (66.7, 83.4)	48.2 (37.0, 58.8)	23.5 (18.0, 27.3)	66.7 (18.0, 104.4)

¹Classification of renal impairment was based on the predictive glomerular filtration rate equation: for males, eGFR_{crea} (mL/min/1.73 m²) = 194 × (serum creatinine [mg/dL])^{-1.094} × (age)^{-0.287}; and for females, (male eGFR) × 0.739. Definitions were: normal function ≥ 90 mL/min/1.73 m²; mild impairment ≥ 60 to <90 mL/min/1.73 m²; moderate impairment ≥ 30 to <60 mL/min/1.73 m²; and severe impairment ≥ 15 to <30 mL/min/1.73 m². BMI=body mass index (weight in kg ÷ height in m²); eGFR=estimated glomerular filtration rate.

Conclusion: Exposure after a single 150 mg oral dose of peficitinib under fasting conditions was similar between subjects with and without renal impairment. The peficitinib dose was generally well tolerated, with no differences in TEAE incidence by renal function.

Abstract THU0182 –Table 2.

Table 2 Plasma PK parameters of peficitinib (PKAS)

Parameter	Renal function ¹			
	Normal (n=8)	Mild impairment (n=8)	Moderate impairment (n=8)	Severe impairment (n=7) ²
Mean (SD) AUC _{inf} , ng·h/mL	1595 (360.2)	1419 (385.0)	1427 (562.7)	1933 (984.6)
GMR (90% CI) for AUC _{inf} vs normal renal function	-	0.87 (0.61, 1.25)	0.83 (0.58, 1.19)	1.09 (0.74, 1.60)
Mean (SD) C _{max} , ng/mL	426.4 (156.8)	376.7 (119.6)	342.1 (134.9)	387.2 (260.4)
GMR (90% CI) for C _{max} vs normal renal function	-	0.90 (0.60, 1.35)	0.78 (0.52, 1.18)	0.78 (0.51, 1.20)
Mean (SD) t _{1/2} , h	6.80 (4.34)	14.96 (8.33)	14.36 (14.33)	10.80 (5.13)

¹Classification of renal impairment was based on the predictive glomerular filtration rate equation: for males, eGFR_{crea} (mL/min/1.73 m²) = 194 × (serum creatinine [mg/dL])^{-1.094} × (age)^{-0.287}; and for females, (male eGFR) × 0.739. Definitions were: normal function ≥ 90 mL/min/1.73 m²; mild impairment ≥ 60 to <90 mL/min/1.73 m²; moderate impairment ≥ 30 to <60 mL/min/1.73 m²; and severe impairment ≥ 15 to <30 mL/min/1.73 m².

²Number of subjects available for AUC_{inf} and t_{1/2} was 6.

AUC_{inf}=area under the concentration–time curve from the time of dosing extrapolated to infinity; CI=confidence interval; C_{max}=maximum concentration; eGFR_{crea}=estimated glomerular filtration rate based on serum creatinine; GMR=geometric mean ratio; SD=standard deviation; t_{1/2}=terminal elimination half-life; t_{max}=time of C_{max}.

Figure 1 Mean (± standard deviation) plasma concentration–time profile of peficitinib by degree of renal impairment (semi-log scale, PKAS)

Abstract THU0182 – Figure 1

REFERENCES:

- [1] Takeuchi T, et al. Ann Rheum Dis 2016; 75: 1057–64; 2. Tanaka Y, et al. ACR/ARHP Annual Meeting 2018: Abstract 887; 3. Takeuchi T, et al. ACR/ARHP Annual Meeting 2018: Abstract 888; 4. Cao YJ, et al. Clin Pharmacol Drug Dev 2016;5:435–49

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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.

REFERENCES:

- [1] Mohamed, et al. Clin Pharmacol Drug Dev. 2018 Apr 24.
- [2] Genovese et al. Lancet. 2018;391(10139):2513-2524.
- [3] Burmester et al. Lancet. 2018;391(10139):2503-2512.

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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.

REFERENCES:

- [1] Niu Q, Cai B, Huang ZC, Shi YY, Wang LL. Disturbed Th17/Treg balance in patients with rheumatoid arthritis. Rheumatol Int, 2012, 32(9): 2731-2736.
- [2] Lai ZW, Kelly R, Winans T, et al. Sirolimus in patients with clinically active systemic lupus erythematosus resistant to, or intolerant of, conventional medications: a single-arm, open-label, phase 1/2 trial. Lancet, 2018, 391(10126): 1186-1196.
- [3] Wang J, Zhang SX, Hu FY, et al. Sirolimus treatment in patients with refractory rheumatoid arthritis: a double-arm, open-label, phase 1/2 trial.