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FRI0133 **FILGOTINIB, A SELECTIVE JANUS KINASE 1 (JAK1) INHIBITOR, MODULATES DISEASE-ASSOCIATED CYTOKINES IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS**

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Background: Filgotinib (FIL), an oral selective JAK1 inhibitor, was safe and effective in FINCH2, a randomized, double-blind, placebo-controlled, phase 3 study in patients with active rheumatoid arthritis (RA) who had an inadequate response to biologic disease-modifying anti-rheumatic drugs (bDMARDs).¹

Objectives: A longitudinal study of cytokines from patients in FINCH2 was conducted to identify RA-associated biomarkers related to bone biology, immune cell migration, and inflammation that are altered by FIL therapy; and FIL-associated biomarkers that correlated with clinical response (DAS28 [CRP], swollen and tender joint counts, pain, and fatigue).

Methods: Plasma, serum, and urine samples from RA patients (n=449) who received FIL (100 mg, 200 mg) or placebo (PBO) once daily plus methotrexate were analyzed at baseline (BL) and week 12 for 42 disease-relevant cytokines using validated, commercially available single or multiplex assays. PBO-corrected on-treatment changes in cytokine levels from BL to week 12 were compared between treatment arms (Wilcoxon rank sum test). Spearman rank correlation was used to compare changes in cytokine level from BL to week 12 and clinical response. P-values <0.05 were considered significant.

Results: At week 12, 18 of 42 cytokines significantly decreased with FIL 100 mg treatment relative to PBO; FIL 200 mg decreased these cytokines to a similar or greater degree. An additional 6 cytokines were significantly decreased by FIL 200 mg. Conversely, 2 cytokines increased relative to PBO with FIL 100 mg, and 5 cytokines increased with FIL 200 mg (sIL-6R, IL-10, IL-2, leptin, and IL-17A). Biomarkers most significantly modulated by FIL 200 mg (p<0.0001) included markers related to bone biology (MMP1 [-22.8%], MMP3 [-24.7%], CTX1 [-27.4%], and NTX [-16.4%]), immune cell migration (VCAM1 [-20.0%], ICAM1 [-14.2%], CXCL13 [-45.0%], and CXCL10 [-32.3%]), and inflammation (TNFRI [-20.7%], CRP [-77.4%], SAA [-61.8%], IL-6 [-13.6%], and resistin [-20.2%]).

Hierarchical clustering of BL biomarker levels revealed distinct groups of cytokines that were strongly correlated with each other. Among them, SAA, IL-6, and CXCL10 were significantly positively correlated with each other (rho >0.6) and with RA disease activity (DAS28[CRP]) at BL (rho >0.3). Biomarkers, including CRP (IL-6, SAA), PainVAS (CRP, SAA), and SJC28 (CRP, IL-6, CXCL10), were also significantly correlated with individual components of DAS28[CRP]. Several biomarkers associated with RA disease activity at BL were decreased with FIL at week 12 relative to PBO (FIL 100 mg: CRP [-48.7%], SAA [-36.9%], and IL-6 [-2.6%]; and FIL 200 mg: CRP [-77.4%], SAA [-61.8%], IL-6 [-13.6%], and CXCL10 [-32.3%]), suggesting FIL impacts these disease activities at a molecular level.

Conclusion: Twelve weeks of FIL treatment significantly reduced 24 disease-relevant cytokines associated with bone biology, immune cell migration, and inflammation in patients with active RA. These effects were dose-dependent and suggest a shift toward a restored immune homeostasis. These findings are consistent with the clinical efficacy of FIL in FINCH2.

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FRI0134

A PHASE 3 STUDY OF THE EFFICACY AND SAFETY OF PEFICITINIB (ASP015K) IN PATIENTS WITH RHEUMATOID ARTHRITIS WHO HAD AN INADEQUATE RESPONSE TO DMARDS

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Background: Peficitinib (ASP015K), a novel oral JAK inhibitor, demonstrated efficacy as once-daily monotherapy in patients with moderate to severe rheumatoid arthritis (RA) in a phase 2b study (NCT01649999).

Objectives: To evaluate the efficacy and safety of peficitinib alone or in combination with disease-modifying antirheumatic drugs (DMARDs) in patients with RA who had an inadequate response to DMARDs.

Table 1 Primary and selected secondary efficacy endpoints at week 12/ET

Result at week 12/ET	PBO	Peficitinib 100 mg/day	Peficitinib 150 mg/day	Etanercept 50 mg/week (open-label arm)
ACR20 ^a , n/N (%)	31/101 (30.7)	60/104 (57.7)***	76/102 (74.5)***	167/200 (83.5)
ACR50 ^a , n/N (%)	9/101 (8.9)	32/104 (30.8)***	43/102 (42.2)***	105/200 (52.5)
ACR70 ^a , n/N (%)	1/101 (1.0)	14/104 (13.5) ^{b,c}	28/102 (27.5)***	61/200 (30.5)
Mean (SD) CRP change from baseline, mg/dL	0.022 (1.498)	-1.056 (1.908)***	-1.734 (1.906)***	-1.207 (2.694)
Mean (SD) ESR change from baseline, mm/h	-1.96 (17.82)	-12.96 (21.51)***	-23.92 (21.26)***	-20.92 (21.66)
DAS28-CRP <2.6 ^a , n/N (%)	5/100 (5.0)	25/102 (24.5)***	35/101 (34.7)***	91/200 (45.5)
Mean (SD) DAS28-CRP change from baseline	-0.64 (1.20)	-1.62 (1.41)***	-2.17 (1.14)***	-2.42 (1.11)
Mean (SD) change from baseline in patient's assessment of pain, 100 mm VAS	-6.64 (24.61)	-23.78 (30.75)***	-30.65 (27.91)***	-30.82 (27.68)
SDAI remission (SDAI score ≤3.3) ^a , n/N (%)	0/100 (0.0)	9/102 (8.8) ^b	9/101 (8.9) ^b	37/200 (18.5)

Last Observation Carried Forward imputation method was used. Statistical testing was performed for ASP015K 100 mg and 150 mg, compared with PBO. ***p<0.001 vs PBO according to Wald's Chi-square test for ACR20, ACR50, ACR70, DAS28-CRP <2.6, and SDAI remission, and analysis of covariance for CRP, ESR, DAS28-CRP and patient's assessment of pain. Closed testing procedure was used for multiplicity adjustment in the primary analysis.

^aBased on logistic regression model: Response (responder, non-responder) = treatment + the prior biologic-DMARD-IR (no, yes) + concomitant DMARD use (no, yes) + study region (Japan, Korea, and Taiwan).

^bNot estimable owing to the small number of responders.

^cIn a post-hoc analysis, based on the logistic regression model in which the only independent variable was treatment, the odds ratio between PBO and peficitinib 100 mg for ACR70 was estimated and p=0.009.

SD=standard deviation; SDAI=simplified disease activity index; VAS=visual analog scale.

Table 2 Treatment-emergent adverse events

	PBO (N=101)	Peficitinib 100 mg/day (N=104)	Peficitinib 150 mg/day (N=102)	Peficitinib 100 mg/day + 150 mg/day (N=206)	Etanercept 50 mg/week (open-label arm) (N=200)
Event, n (%), week 0-12					
Any AE	54 (53.5)	59 (56.7)	55 (53.9)	114 (55.3)	119 (59.5)
Drug-related AE ^a	29 (28.7)	33 (31.7)	38 (37.3)	71 (34.5)	75 (37.5)
Death	0	0	0	0	0
SAE	4 (4.0)	3 (2.9)	2 (2.0)	5 (2.4)	4 (2.0)
Drug-related SAE ^a	3 (3.0)	2 (1.9)	1 (1.0)	3 (1.5)	4 (2.0)
Grade ≥3 AE ^a	8 (7.9)	6 (5.8)	3 (2.9)	9 (4.4)	6 (3.0)
AE leading to permanent discontinuation of study drug or reference drug	4 (4.0)	6 (5.8)	3 (2.9)	9 (4.4)	5 (2.5)
Serious infection	0	0	1 (1.0)	1 (0.5)	1 (0.5)
Herpes zoster-related disease	0	1 (1.0)	0	1 (0.5)	2 (1.0)
Malignancy	0	0	0	0	0
Incidence rate per 100 patient-years (95% confidence interval), overall study period^b					
Serious infection ^c	0.0	1.1 (0.2, 8.1)	2.2 (0.5, 8.7)	2.0 (0.8, 4.9)	2.0 (0.8, 5.5)
Herpes zoster-related disease	0.0	5.8 (2.4, 13.8)	4.4 (1.7, 11.7)	5.8 (3.4, 9.8)	2.6 (1.1, 6.2)
Malignancy	0.0	2.3 (0.6, 9.1)	0.0	1.2 (0.4, 3.8)	0.5 (0.1, 3.6)

^aPossibly or probably related to study drug, as assessed by the investigator, or records where relationship is missing.

^bBased on NCI-CTCAE grade: grade 3-severe or medically significant, grade 4-life threatening, grade 5-death related to AE.

^cPatient-years covers from initial dose up to first incidence of AE for patients who had at least one event; otherwise, the duration of the patients are summed as from initial dose through follow-up. Incidence rate was calculated as (100 × number of patients who had at least one incidence) / total patient-years.

^dIncludes AEs that occurred after initial peficitinib dosing, and after switching from PBO to peficitinib 100 mg/day or 150 mg/day.

^eDefined as an AE belonging to the system organ class of 'Infections and infestations' and regarded as serious.

AE=adverse event; SAE=serious adverse event.