Results: We have demonstrated that the gp130-mediated cytokine oncostatin M blocks myoblast differentiation into myotubes resulting in a decrease in CPK expression. Jak inhibition restores muscle differentiation and increased CPK expression (Figure 1A). Oncostatin M is highly expressed in RA synovium and other inflammatory milieu and may be one mechanism driving sarcopenia in RA. In addition to Upadacitinib, both Baricitinib and Tofacitinib restore myoblast differentiation suggesting that this is a class effect for JAK inhibitors (Figure 1B).

Conclusion: Our studies suggest that the increase in serum CPK upon treatment with JAK inhibitors may represent recovery of muscle development via reversal of inflammation-associated inhibition of myoblast differentiation

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Figure 1. JAK inhibitors result in increased CPK expression in the presence of OSM. (A) M-type CPK mRNA expression in HSM cells stimulated with OSM (100 ng/mL) and/or UPA (0.0007–1 μM) for 24 hours. (B) M-type CPK mRNA expression in HSM cells stimulated with OSM (100 ng/mL) and UPA, Baricitinib, or Tofacitinib for 24 hours. Data is represented as a mean +/- Standard deviation. One representative is shown of 3 from two donors. CM, 10% FBS media; Diff, 2% Horse serum differentiation media; OSM, oncostatin M; UPA, Upadacitinib; CKM, creatine kinase M-type. HSM, human skeletal muscle myoblasts.

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FRI0132

LONG-TERM SAFETY AND EFFICACY OF UPADACITINIB IN PATIENTS WITH RHEUMATOID ARTHRITIS AND AN INADEQUATE RESPONSE TO CSDMARDS: RESULTS AT 60 WEEKS FROM THE SELECT-NEXT STUDY

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Background: Upadacitinib (UPA), an oral, JAK1-selective inhibitor showed efficacy over 12 weeks (wks) in patients (pts) with moderately to severely active rheumatoid arthritis (RA) and inadequate response to csDMARDs (SELECT-NEXT).¹

Objectives: We assessed safety and efficacy of UPA through Wk60 in an ongoing extension of the phase 3 SELECT-NEXT study.

Methods: Pts received once-daily (QD) UPA at 15 mg (UPA15), 30 mg (UPA30) or placebo (PBO) for 12 wks on stable background csDMARDs. From Wk12, the start of a long-term blinded extension, pts initially randomized to PBO at BL were switched to UPA15mg or 30mg per pre-specified assignment at BL. Pts randomized to UPA continued their assigned dose. No dose adjustments of UPA were allowed; however, starting at Wk24, adjustments to background RA medications were permitted. Sites/subjects remain blinded to UPA dose throughout the extension period. Efficacy data up to Wk60 are reported "As Observed". Adverse events (AE) per 100 pt yrs (PY) are summarized based on a cut-off date of Mar 22 2018.

Results: 611/661 (92%) pts completed Wk12 and continued on to the extension. By the safety data cut-off date, 125/611 (20%) had

discontinued study drug, 50 (8.2%) discontinued due to an AE, and 10 (1.6%) due to lack of efficacy. Cumulative exposure was 393.3 PYs and 372.4 PYs for UPA15 and UPA30 respectively. Based on As Observed analysis, for pts who continued on UPA15 (262/310 [85%]) and UPA30 (243/301 [81%]), clinical and functional outcomes continued to improve or were maintained through Wk60, with 59% and 56% of pts achieving DAS28-CRP <2.6 and 35% and 32% achieving CDAI remission (≤2.8) with UPA 15 and 30 mg, respectively. Pts who switched from PBO to UPA15 or UPA30 showed comparable efficacy to those initially randomized to UPA (Table 1). The most frequently reported AEs were nasopharyngitis, urinary tract infection, upper respiratory tract infection, bronchitis, blood creatine phosphokinase increased, alanine aminotransferase increased, herpes zoster (HZ) and nausea. Most frequent AEs (≥0.8/100PYs) leading to premature study drug discontinuation were pneumonia, transaminase elevations, HZ and pyrexia. Event rates (E/100PYs) were numerically higher in UPA30 vs UPA15 for serious AE, AE leading to discontinuation, serious infections, HZ and malignancies, and were similar in UPA15 and UPA30 for adjudicated major adverse cardiovascular events and venous thromboembolic events (Table 2).

Conclusion: UPA15mg and 30mg on background csDMARD therapy demonstrated consistent efficacy and safety over 60 weeks in RA patients with inadequate response to csDMARDs. Both doses of UPA showed a similar efficacy profile at Wk 60, with numerically higher rates for certain safety events noted in the UPA30 group. An integrated safety analysis of upadacitinib across the phase 3 program is required to fully characterize the benefit:risk of UPA in RA.

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	PBO→UPA 15 MG	PBO→UPA 30 MG	UPA 15 MG	UPA 30 MG
ACR20	84/93 (90)	71/82 (87)	147/173 (85)	148/170 (87)
ACR30	64/82 (78)	55/64 (86)	122/168 (73)	120/169 (71)
ACR70	46/95 (48)	43/84 (51)	88/171 (51)	77/168 (46)
DAS28-CRP (LS, 2)	74/95 (78)	56/82 (68)	129/173 (75)	125/167 (75)
DAS28-CRP <2.6	60/95 (63)	46/82 (56)	102/173 (59)	93/167 (56)
CDAI (LS, 10)	72/93 (77)	56/83 (67)	129/171 (75)	123/169 (73)
CDAI REM (LS, 8)	28/93 (30)	29/83 (35)	59/171 (35)	54/169 (32)
Change from BL in HAQ-DI	0.79	-0.68	-0.81	-0.79

	UPA 15 mg N=310 P=393.3 E/100PYs	UPA 30 mg N=301 P=372.4 E/100PYs
Any Adverse Event (AE)	334.6	371.9
Serious AE	16.3	24.2
AE Leading To D/C of Study Drug	8.4	17.2
Serious Infection ^a	2.3	7.5
Herpes Zoster ^a	3.1	7.5
Hepatic disorders ^a	14.2	13.7
Malignancy (incl. NMSC)	1.0	2.7
MACE ^a (adjudicated) ^b	0.8	0.8
VTE ^a (adjudicated)	0.3	0.3
Deaths ^c	0	0.8

T, events; PYs, patient-years; E/100PYs, events per 100 patient-years; NMSC, non-melanoma skin cancer; MACE, major adverse cardiovascular event (cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke); VTE, venous thromboembolism (DVT, deep vein thrombosis; PE, pulmonary embolism)
^aMost frequently reported serious infection were pneumonia, sepsis, staphylococcal wound infection and bronchitis.
^bHerpes zoster, most involved 1 or 2 dermatomes. No meningococcal/septicemia/non-invasive involvement, except one primary varicella zoster pneumonia (chicken pox).
^cTwo IE events were reported as septal embolism.
^dHepatic disorders: Must have asymptomatic lab abnormalities.
^eMACE: UPA15: 1 pt with non-fatal MI, 2 pts with non-fatal stroke; UPA30: 1 cardiovascular death, 1 non-fatal MI, 1 non-fatal stroke
^fVTE: UPA15: 1 pt with DVT and PE; UPA30: 1 pt with DVT
^gDeaths: UPA30: 1 CV death in pt prior history of diabetes, hypertension, hyperlipidemia, non-fatal MI with coronary bypass; 1 due to colon adenocarcinoma; 1 due to lymphangioleiomyomatosis

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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.