pts. These data provide mechanistic insights into the efficacy of FEN in RA patients.

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Table 1. FEN Treatment Causes Changes in B and Myeloid Cell Biomarkers (median% of baseline at week 12)

	Cohort 1					Cohort 2	
	FEN 50 mg qD (n=37)	FEN 150 mg qD (n=99)	FEN 200 mg BID (n=99)	PBO (n=100)	ADA 40 mg q2w (n=103)	FEN 200 mg BID (n=45)	PBO (n=41)
RF	71	63*	58*	87	66*	56*	120
IgM	88*	86*	84*	100	103	78*	96
IgG	100	96*	91*	100	100	89*	99
CCL4	83*	88*	77*	96	64*	79*	112
IL6	63	63	60	76	43*	60*	83
CRP	66	64	59*	81	37*	42*	98

*significant versus PBO (p-value ≤ 0.05 FDR adjusted); Kruskal-Wallis test

Disclosure of Interests: Alyssa Morimoto Shareholder of: Stockholder of Genentech/Roche, Employee of: Employee of Genentech/Roche, Julie Rae Shareholder of: Stockholder of Genentech/Roche, Employee of: Employee of Genentech/Roche, Leslie Chinn Shareholder of: Stockholder of Genentech/Roche, Employee of: Employee of Genentech/Roche, Nandhini Ramamoorthi Shareholder of: Stockholder of Genentech/Roche, Employee of: Employee of Genentech/Roche, Olivia Hwang Shareholder of: Stockholder of Genentech/Roche, Employee of: Employee of Genentech/Roche, Alexandra Ward Shareholder of: Stockholder of Genentech/Roche, Employee of: Employee of Genentech/Roche, D. James Haddon Shareholder of: Stockholder of Genentech/Roche, Employee of: Employee of Genentech/Roche, Caroline Looney Shareholder of: Stockholder of Genentech/Roche, Employee of: Employee of Genentech/Roche, Rupal Desai Shareholder of: Stockholder of Genentech/Roche, Employee of: Employee of Genentech/Roche, Balazs Toth Shareholder of: Stockholder of Genentech/Roche, Employee of: Employee of Genentech/Roche, Katie Tuckwell Shareholder of: Genentech/Roche, Employee of: Genentech/Roche, Michael J. Townsend Shareholder of: Stockholder of Genentech/Roche, Employee of: Genentech/Roche

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FRI0130 RELATIONSHIP BETWEEN DEPRESSION AND DISEASE ACTIVITY IN US VETERANS WITH EARLY RHEUMATOID ARTHRITIS RECEIVING METHOTREXATE

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Background: Depression is common in rheumatoid arthritis (RA) patients and exacerbates disease activity and may reduce response to first-line disease-modifying antirheumatic drugs.

Objectives: To determine whether depression affects disease activity in patients with early RA treated with methotrexate (MTX).

Methods: Patients in the Veterans Affairs Rheumatoid Arthritis registry with early RA (onset <2 years) receiving MTX were selected (n=268). Depression was assessed at baseline using International Classification of Diseases codes (296.2-296.39, 300.4, 311). Disease activity was measured using the 28 joint count disease activity score (DAS-28), tender and swollen joint counts (TJC and SJC), patient and provider global assessment (PTGA and PRGA), patient-reported pain, multidimensional health assessment questionnaire (MDHAQ), and erythrocyte sedimentation rate (ESR). Baseline confounders included sociodemographics, anthropometrics, concomitant treatments, and other clinical characteristics. Propensity score weights were used to equate the depressed and non-depressed participants on baseline confounders. Generalized linear survey models were used to compare disease activity trajectories between depressed (n=48) and non-depressed (n=220) patients over two years. Standardized causal mean outcome differences were estimated at 6 months and 1- and 2-years follow-up.

Results: Depression was associated with significantly greater DAS-28 at 6 months (β=0.36; 95% CI: 0.03, 0.69) but not at 1- or 2-years follow-up (Table 1). Associations for DAS-28 component measures were smaller in magnitude, decreased over time, and not statistically significant. Depression was also associated with significantly greater pain at both 6 months (β=0.47; 95% CI: 0.11, 0.82) and 1-year (β=0.42; 95% CI: 0.03, 0.82) follow-up but not the PRGA or MDHAQ at any assessed time interval.

Table 1. Causal mean differences in standardized disease activity at 6 months and 1- and 2-years follow-up comparing those with depression to those without at baseline.

Measure	6 Months(β, 95% CI)	1 Year(β, 95% CI)	2 Years(β, 95% CI)
DAS-28	**0.36 (0.03, 0.69)**	0.11 (-0.29, 0.51)	-0.20 (-0.75, 0.35)
SJC	0.24 (-0.01, 0.50)	0.03 (-0.28, 0.34)	0.03 (-0.49, 0.54)
TJC	0.29 (-0.02, 0.61)	0.12 (-0.22, 0.47)	-0.16 (-0.75, 0.43)
PTGA	0.30 (-0.06, 0.66)	0.27 (-0.08, 0.61)	0.00 (-0.65, 0.65)
ESR	0.17 (-0.23, 0.57)	-0.07 (-0.47, 0.33)	-0.15 (-0.72, 0.41)
PRGA	0.14 (-0.16, 0.43)	0.15 (-0.20, 0.50)	-0.33 (-1.00, 0.34)
Pain	**0.47 (0.11, 0.82)**	**0.42 (0.03, 0.82)**	0.20 (-0.35, 0.75)
MDHAQ	0.18 (-0.15, 0.51)	0.11 (-0.27, 0.48)	0.06 (-0.46, 0.58)

DAS-28: 28 joint count disease activity score; SJC: Swollen joint count; TJC: Tender joint count; PTGA: Patient global assessment; ESR: erythrocyte sedimentation rate; PRGA: Provider global assessment; MDHAQ: Multidimensional health assessment questionnaire.

Conclusion: Findings demonstrate that depression is associated with less robust short-term response to MTX, and despite clinical RA treatment, more persistent and severe pain. Depression in RA patients may be a risk factor for primary non-response to MTX treatment, and interventions targeted at treating depression could result in better initial RA disease control and DMARD persistence.

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FRI0131 ELUCIDATING THE MECHANISM UNDERLYING CREATINE PHOSPHOKINASE UPREGULATION WITH UPADACITINIB

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Background: JAK inhibitors, including Upadacitinib (UPA), have been associated with increased serum levels of creatine phosphokinase (CPK) in patients with inflammatory disorders, but not in patients with myeloproliferative disease or in healthy subjects treated for a limited duration (1). While CPK increases can be indicative of muscle damage, there are no other indicators of muscle pathology observed with JAK inhibitors, suggesting that there may be another mechanism behind the increased CPK levels. Inflammatory diseases including rheumatoid arthritis are often associated with reduced muscle mass (sarcopenia), a process reversed with disease control (2).

Objectives: We hypothesized that one or more cytokines present in the inflammatory milieu may block differentiation of myoblasts into mature myocytes and that JAK inhibition restores differentiation and associated CPK expression. We focused on the gp130-mediated cytokines IL6, Oncostatin M (OSM), CNTF, and LIF as these have been shown to impact myoblast differentiation.

Methods: Human skeletal muscle myoblast (HSMM) cells were cultured in 10% fetal bovine serum, or were serum starved (2% horse serum) to induce differentiation into myocytes, with and without stimulation with OSM (1—100 ng/ml) and/or UPA (0.0007—1 μM) for up to 5 days. RNA was purified and expression of CPK (M-type) was determined by QPCR using GAPDH as a reference. CPK expression was also measured following stimulation of HSMM cells with other JAK inhibitors (Baricitinib and Tofacitinib).

Results: We have demonstrated that the gp130-mediated cytokine oncostatin M blocks myoblast differentiation into myotubules 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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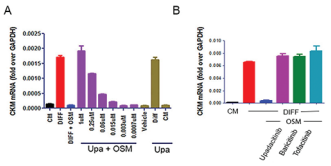

Figure 1. JAK inhibitors result in increased CPK expression in the presence of OSM. (A) M-type CPK mRNA expression in HSMM cells stimulated with OSM (100 ng/mL) and/or UPA (0.0007—1 μM) for 24 hours. (B) M-type CPK mRNA expression in HSMM cells stimulated with OSM (100 ng/mL) and UPA, Baricitinib, or 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. HSMM, human skeletal muscle myoblasts.
Disclosure of Interests: Kara Queeney Shareholder of: Kara Queeney is an employee of AbbVie and may hold stock or options, Employee of: Kara Queeney is an employee of AbbVie and may hold stock or options, William Housley Shareholder of: Will Housley is an employee of AbbVie and may hold stock or options, Employee of: Will Housley is an employee of AbbVie and may hold stock or options, Jeremy Sokolov Shareholder of: Jeremy Sokolov is an employee of AbbVie and may hold stock or options, Employee of: Jeremy Sokolov is an employee of AbbVie and may hold stock or options, Andrew Long Shareholder of: Andrew Long is an employee of AbbVie and may hold stock or options, Employee of: Andrew Long is an employee of AbbVie and may hold stock or options
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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 prespecified 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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Table 1. Efficacy Endpoints at Week 60 (as observed); n/N (%)

	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)
ACR50	64/92 (70)	55/84 (65)	122/168 (73)	120/169 (71)
ACR70	46/95 (48)	43/84 (51)	88/171 (51)	77/168 (46)
DAS28-CRP LDA (≤3.2)	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 LDA (≤10)	72/93 (77)	56/83 (67)	129/171 (75)	123/169 (73)
CDAI REM (≤2.8)	28/93 (30)	29/83 (35)	59/171 (35)	54/169 (32)
Change from BL in HAQ-DI	-0.79	-0.68	-0.83	-0.73

Table 2. Treatment- emergent Adverse events; E/100PYs

	UPA 15 mg, N=324 PYs=393.3 E/100PYs	UPA 30 mg, N=321 PYs=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[1]	2.3	7.5
Herpes Zoster[2]	3.1	7.5
Hepatic disorder[3]	14.2	13.7
Malignancy (excl. NMSC)	1.0	2.7
MACE (adjudicated)[4]	0.8	0.8
VTE[5] (adjudicated)	0.3	0.3
Deaths[6]	0	0.8

E, events; PYs, patient-years; E/100PY, 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)
[1]Most frequently reported serious infection were pneumonia, sepsis, staphylococcal wound infection and bronchitis.
[2]Herpes zoster: most involved 1 or 2 dermatomes. No meningoencephalopathic/ noncutaneous involvement, except one primary varicella zoster pneumonia (chicken pox). Two HZ events were reported as ophthalmic.
[3]Hepatic disorders: Most were asymptomatic lab abnormalities.
[4]MACE: 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
[5]VTE: UPA15: 1 pt with DVT and PE; UPA30:1 pt with DVT
[6]Deaths: UPA30: 1 CV death in pt prior history of diabetes, hypertension, hyperlipidemia, non-fatal MI with coronary bypasses; 1 due to colon adenocarcinoma; 1 due to lymphangiosis carcinomatosa

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