OP0141 (2021)

EFFECTS OF FILGOTINIB ON SPINAL LESIONS IN ANKYLOSING SPONDYLITIS: MAGNETIC RESONANCE IMAGING DATA FROM THE TORTUGA TRIAL

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Background: The oral Janus kinase 1 preferential inhibitor filgotinib (FIL) significantly improved Spondyloarthritis Research Consortium of Canada (SPARCC) magnetic resonance imaging (MRI) inflammation scores (bone marrow oedema) in the spine and sacroiliac joints vs placebo (PBO) in the Phase 2 TORTUGA trial (NCT03117270) in patients with active ankylosing spondylitis (AS). [1]

Objectives: This post-hoc analysis evaluated the effects of FIL on Canada-Denmark (CANDEN) MRI measures of spinal inflammation and structural lesions in patients from the TORTUGA trial.

Methods: TORTUGA was a PBO-controlled, multicentre, double-blind, randomised trial. Patients with active AS (as per modified New York classification criteria, with sacroiliitis confirmed by central reading) were treated with FIL 200 mg (n=58) or PBO (n=58) once daily for 12 weeks. MRI of the total spine was conducted at baseline and at treatment end. Scans were re-evaluated post-hoc by 2 independent experts (blinded to time point and assigned treatment) using the CANDEN method; [2] inter-reader discrepancies were resolved by an independent adjudicator. Observed changes from baseline were evaluated using analysis of covariance, with factors for treatment, baseline value, and randomisation stratification by prior tumour necrosis factor inhibitor use. Least-squares (LS) mean changes from baseline and between-group differences with 95% confidence intervals (CI) were calculated; P values are nominal.

Results: MRI scans from 88 patients (47 FIL, 41 PBO) with an evaluable scan at baseline and Week 12 (or early termination) were re-evaluated. Baseline characteristics were generally similar between patients with/without an MRI scan. Of those with MRI scans, mean total spine inflammation score (which ranges from 0–614) was higher, and mean ankylosis score (which ranges from 0–460) was lower, in the FIL vs PBO group at baseline. Total spine inflammation scores decreased from baseline with FIL but not with PBO (Figure and Table ; P=0.0003 for between-group difference). Cumulative probability plots favoured FIL over PBO for change from baseline in subregion inflammation scores, including posterolateral elements (i.e. sum of lesions in ribs, transverse processes, spinous processes, soft tissue inflammation, and postero-lateral vertebral body), facet joint, and vertebral body. Total spine fat lesion scores numerically increased from baseline in the FIL but not PBO group (P=0.0878 for between-group difference; Table). There were no significant differences between groups for changes in erosion (P=0.1956) or ankylosis (P=0.3888) scores (Table).

Table 1.
Change from baseline at Week 12 in CANDEN total spine inflammation, total spine fat, total spine bone erosion, and ankylosis scores

	Treatment group	n	Sample mean (SE)	LS mean (SE)	95% CI of treatment mean	LS mean of group difference (SE)	95% CI of group difference	Between-group P value
Total spine inflammation score	Filgotinib	47	–4.98 (0.96)	–4.40 (1.13)	–6.65, –2.15	–4.49 (1.21)	–6.85, –2.12	0.0003
	Placebo	41	0.29 (0.78)	0.09 (1.13)	–2.17, 2.34			
Total spine fat score	Filgotinib	47	1.01 (0.62)	1.09 (0.66)	–0.22, 2.40	1.18 (0.69)	–0.18, 2.55	0.0878
	Placebo	41	–0.25 (0.19)	–0.09 (0.66)	–1.40, 1.21			
Total spine bone erosion score	Filgotinib	47	0.01 (0.02)	0.07 (0.03)	0.00, 0.14	0.05 (0.04)	–0.02, 0.12	0.1956
	Placebo	41	–0.02 (0.03)	0.02 (0.03)	–0.04, 0.09			
Total ankylosis score	Filgotinib	47	0.30 (0.29)	0.23 (0.31)	–0.40, 0.85	0.28 (0.34)	–0.37, 0.94	0.3888
	Placebo	41	–0.01 (0.08)	–0.06 (0.31)	–0.68, 0.56			

SE, standard error

Conclusion: This is the first PBO-controlled trial to demonstrate a decrease in inflammatory activity with FIL, not only in the spinal vertebrae but also in the postero-lateral elements of the spine and facet joints. As expected in a 12-week study period, no changes in erosion or ankylosis were seen, while fat lesions showed a tendency to increase with FIL. Larger trials are needed to confirm these results.

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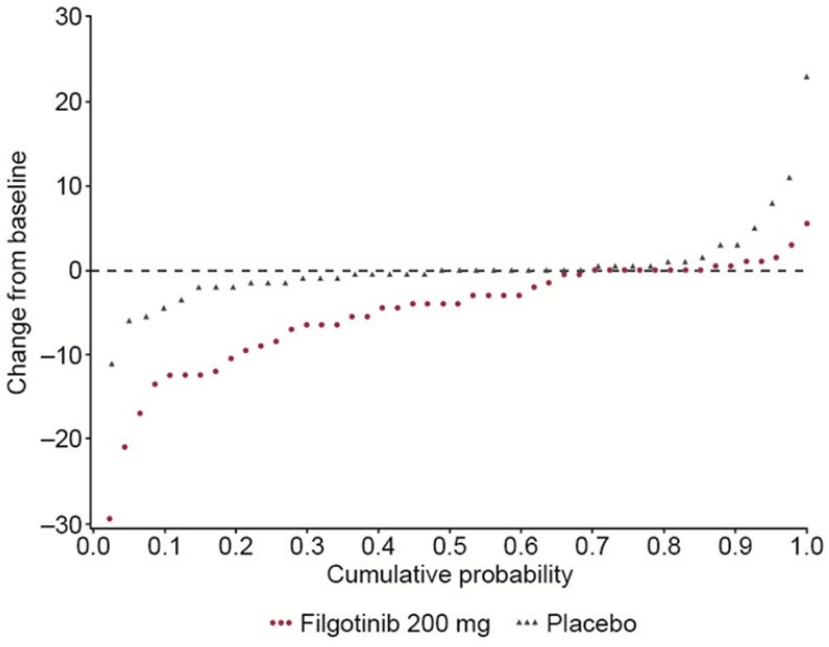
Figure. Change from baseline in total CANDEN spine inflammation score



CANDEN, Canada-Denmark

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Session: Spondyloarthritis - treatment *(Oral Presentations)*

AB0259 (2021)

EVALUATION OF THE EFFECT OF FILGOTINIB ON THE PHARMACOKINETICS OF ROSUVASTATIN, ATORVASTATIN, AND PRAVASTATIN

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Background: Filgotinib is an orally administered small molecule that preferentially inhibits Janus kinase 1 and is approved for use in Europe and Japan in adult patients with rheumatoid arthritis (RA) who have had an inadequate response to conventional therapies. Patients with RA are at a higher risk of cardiovascular morbidity and mortality relative to the general population [1]. Thus, it is important to understand potential drug-drug interactions of filgotinib with lipid-lowering agents such as statins. Based on in vitro studies, filgotinib is not expected to significantly increase exposure of statins via inhibition of the organic anion transporting peptide (OATP) at clinically relevant exposures. Hence, in Phase 2 and Phase 3 clinical studies, statins were allowed for use with filgotinib. A post-hoc analysis showed no increase in statin-induced AEs such as muscle or liver toxicities when statins were coadministered with filgotinib ("Concomitant Use of Statins in Filgotinib-Treated Patients with Rheumatoid Arthritis: A Post Hoc Analysis", submitted to EULAR 2021).

Objectives: The objectives of this study (NCT04608344) were to evaluate the effect of filgotinib on the pharmacokinetics of atorvastatin, pravastatin, and rosuvastatin, which are sensitive substrates for the OATP-1B1/1B3, and the short-term safety of administering filgotinib with or without statins.

Methods: This was an open-label, randomized, two-way, crossover study in healthy adult volunteers (n = 27). Study participants received a single dose of atorvastatin (ATV 40 mg) and a single dose of a cocktail of pravastatin (PRA 40 mg)/rosuvastatin (ROS 10 mg), on two different occasions with washout in between, alone or in combination with filgotinib (200 mg QD for 11 days). Serial pharmacokinetic sampling was performed and pharmacokinetic parameters for each statin were calculated. Safety was assessed throughout the study. An analysis of variance using a mixed-effects model was applied to the natural logarithmic transformation of pharmacokinetic parameters (C_{max} and AUC_{inf}) for ATV, 2-OH-ATV (active metabolite of ATV), PRA, and ROS.

Geometric-least squares means (GLSM) ratios and 90% confidence intervals (90% CI) of pharmacokinetic parameters were estimated for each analyte and were compared against pre-specified lack of pharmacokinetic alteration boundaries of 70 to 143%.

Results: Of the 27 enrolled participants, 25 participants completed all study treatments. Most AEs and laboratory abnormalities were Grade 1 or 2 in severity; 1 participant discontinued due to a Grade 3 increase in creatine kinase and 1 participant discontinued due to difficulty in blood draws. Following coadministration of filgotinib with ATV, relative to ATV alone, ATV AUC_{inf} was unaffected (GLSM ratio (90% CI): 0.91 (0.84, 0.99)), but ATV C_{max} was slightly reduced (GLSM ratio (90% CI): 0.82 (0.69, 0.98)). 2-OH-ATV exposure (C_{max} and AUC_{inf}) were unaffected (GLSM ratio (90% CI): 0.98 (0.81, 1.18) for C_{max} and 1.12 (1.02, 1.22) for AUC_{inf}), and were within the pre-specified lack-of-effect bounds. Following coadministration with filgotinib, PRA AUC_{inf} was unaffected (GLSM ratio (90% CI): 1.22 (1.06, 1.42)), but PRA C_{max} was slightly higher (1.25 (1.01, 1.54)). ROS exposure (C_{max} and AUC_{inf}) were moderately higher upon coadministration with filgotinib (GLSM ratio (90% CI): 1.68 (1.43, 1.97) for C_{max} and 1.42 (1.30, 1.56) for AUC_{inf}), and these changes in rosuvastatin exposure are not considered to be clinically relevant.

Conclusion: All study treatments were generally well tolerated. Co-administration with filgotinib did not have a clinically meaningful impact on the exposure of ATV, PRA, and ROS. These data support concomitant use of filgotinib with OATP substrates such as statins.

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Session: Rheumatoid arthritis - non biologic treatment and small molecules *(Publication Only)*

POS0536 (2021)

FILGOTINIB DEMONSTRATES CLINICAL EFFICACY IN RHEUMATOID ARTHRITIS INDEPENDENT OF SMOKING STATUS: A POST-HOC SUBGROUP ANALYSIS OF THREE PHASE 3 CLINICAL TRIALS

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Background: Filgotinib (FIL), an oral janus kinase 1 (JAK1) inhibitor, has been evaluated in three phase 3 clinical studies (FINCH 1-3) in adults with moderately-to-severely active rheumatoid arthritis (RA). Patients with RA who currently smoke (a predisposing factor for RA) have been reported to be less likely to respond to anti-TNFα treatment and more likely to discontinue or switch treatment. [1,2,3] However, the impact of smoking on JAKi efficacy in RA patients is unknown.

Objectives: A post-hoc sub-group analysis of FINCH patient (pt) data was performed in order to identify associations with smoking status.

Methods: Data from 3452 RA pts participating in the FINCH3 (MTX-naïve; NCT02886728), FINCH1 (MTX-IR; NCT02889796), or FINCH2 (bDMARD-IR; NCT02873936) clinical trials were included for analysis of clinical response at weeks 12 and 24. Logistic regression models were fitted to assess the effects of smoking status on categorical clinical endpoints (ACR20/50/70, CDAI ≤ 10, DAS28(CRP) ≤3.2 or < 2.6). Adjustments were made for covariates selected based on previously published work [1] and listed in the Figure 1 caption. No adjustments of p-values were made for multiple testing.

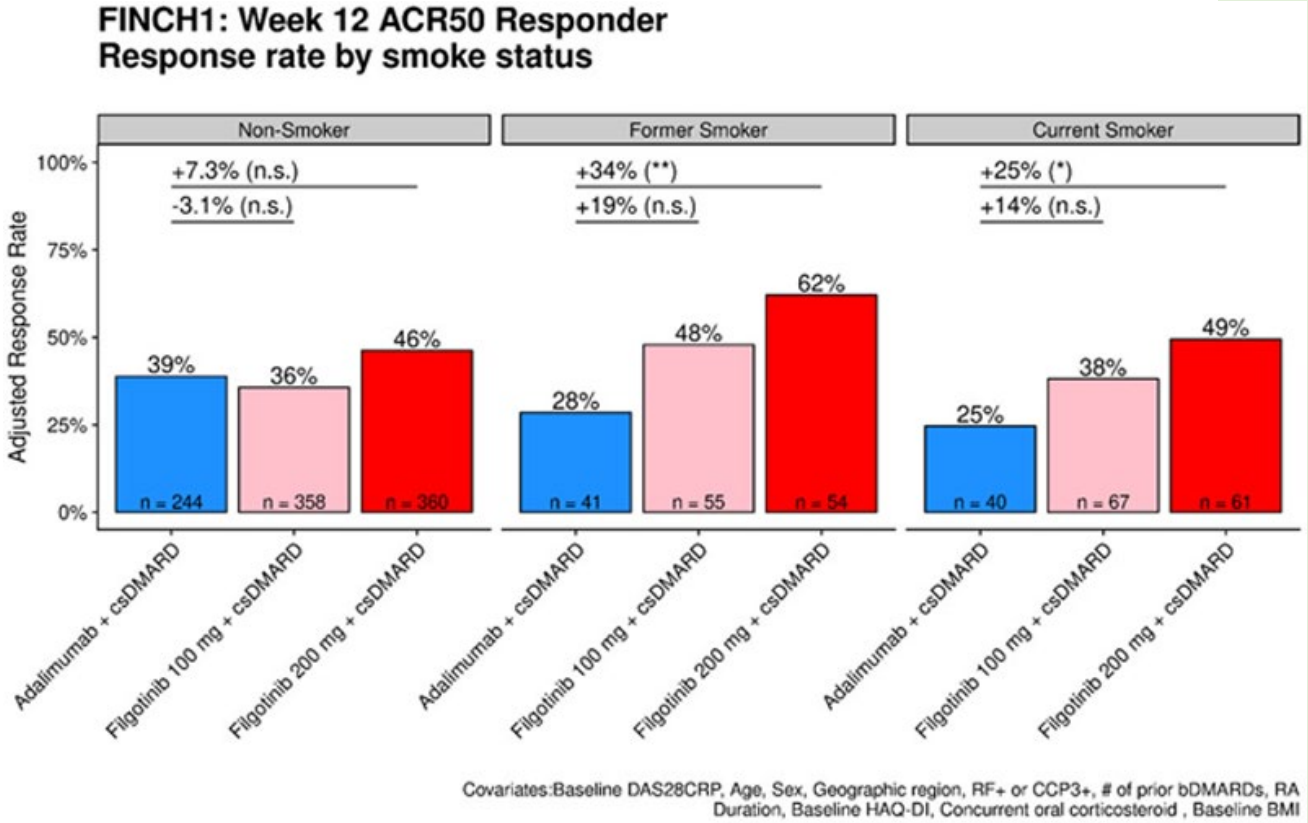
Results: In the MTX-IR population (FINCH1), current (12% of enrolled patients) and former (13%) smokers treated with ADA+MTX had a lower week 12 ACR50 response rate compared to non-smokers (25% and 28% vs. 39%, nominal p = 0.095 and p=0.21, respectively). In contrast, the ACR 50 response at week 12 in FIL+MTX treated pts showed no association with smoking status. Former smokers had higher response rates than non-smokers in the MTX-IR (FINCH1) and MTX naïve (FINCH3) populations (Table 1). Direct comparison between non-smoking pts in the MTX-IR FIL200+MTX-arm and ADA+MTX-arm showed no significant difference in ACR50 response rate (46% vs. 39%, p=0.08). In contrast, former and current smokers showed significantly better week 12 ACR50 response rates under FIL200+MTX treatment compared to ADA+MTX patients (former smoker: 62% vs. 28%, p=0.0017, current smoker: 50% vs. 25%, p=0.016, Figure 1 . Similar observations were made at both weeks 12 and 24 for other clinical endpoints, including ACR20/50/70, DAS28(CRP) < 2.6 or ≤3.2, and CDAI ≤ 10 response criteria.

Table 1.
Difference in adjusted ACR50 response rate compared to non-smokers for FINCH1/2/3.

		PBO+MTX [‡]	FIL100+MTX	FIL200+MTX
FINCH1	Current	-1%	+2.4%	+3.3%
	Former	-6%	+12%	+16% (*)
FINCH2 [†]	Current	0%	+13%	-9%
	Former	+9%	-7%	+4%
FINCH3	Current	0%	+1%	+4%
	Former	+4%	+20% (*)	+17% (*)

ACR50 response rate based on fully adjusted logistic regression model. [†]: FINCH2 patients received either MTX or csDMARD. [‡]FINCH3 had active comparator arm of MTX together with PBO to maintain blind. *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$

Figure 1.
FINCH1 adjusted Week 12 ACR50 response rate stratified by smoking status. ACR50 response rate based on fully adjusted logistic regression model. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$. Former and current smokers that received FIL200mg + MTX showed a higher response rate compared to similar ADA+MTX patients.



Conclusion: This exploratory analysis showed that current and former smokers with RA who received ADA+MTX trended toward a lower response rate compared to non-smokers. In contrast, FIL+MTX was found to be similarly efficacious independent of smoking status within both the MTX-IR and MTX-naïve RA populations. Current or former smokers were more likely to respond to FIL200mg + MTX compared to ADA+MTX across a range of endpoints. Given the small number of current and former smokers enrolled in these studies, further studies of the efficacy of JAK inhibitors and the mechanism of reduced response to anti-TNFs in patients with a history of smoking are warranted.

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Session: Rheumatoid arthritis - comorbidity and clinical aspects *(POSTERS only)*

POS0446 (2021)

FILGOTINIB-TREATED RHEUMATOID ARTHRITIS PATIENTS WITH HIGH BASELINE NEUTROPHIL-TO-LYMPHOCYTE RATIO SHOW BETTER CLINICAL RESPONSE RATES AND PATIENT-REPORTED OUTCOMES

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Background: Rheumatoid arthritis (RA) is a systemic inflammatory disease which includes increased innate and myeloid immune cell activation. Filgotinib (FIL), an oral JAK1 inhibitor, has shown safety and efficacy in three phase 3 studies (FINCH1-3) in adults with moderately-to-severely active RA. The baseline (BL) neutrophil-to-lymphocyte ratio (NLR) in RA has been associated with a positive response to anti-tumor necrosis factor (TNF) therapy [1] and a negative response to DMARD triple therapy [2]. We previously reported a BL signature of clinical response in the FINCH2 (bDMARD-IR) population which included a neutrophil component [3].

Objectives: We conducted a post-hoc analysis to explore whether the BL NLR was associated with response to treatment in the FINCH studies.

Methods: Clinical data of 3273 RA patients (pts) enrolled in the FINCH clinical trials (FINCH3, methotrexate (MTX)-naïve: NCT02886728; FINCH1, MTX-Inadequate Responder (IR): NCT02889796; FINCH2, bDMARD-IR: NCT02873936) were retrospectively analyzed for a relationship between the BL NLR and composite clinical endpoints (ACR-N, DAS28CRP, or CDAI) or PROs (Pain VAS, FACIT Fatigue, HAQ-DI) through week 24. Pts were classified as High or Low BL NLR using a cutpoint (2.7) identified as an independent predictor of treatment failure in a published RA study [2]. Adjusted clinical outcomes were estimated based on mixed effects linear regression models including geographic region and demographics covariates.

Results: 57% of pts enrolled in the FINCH trials were classified as BL NLR-High (Table 1) and FINCH3 NLR-High pts showed higher BL DAS28(CRP). FINCH1 and FINCH3 FIL+MTX-arm NLR-High pts demonstrated significantly better DAS28(CRP) response compared to NLR-Low pts (Figure 1). DAS28(CRP) differences between NLR-High and NLR-Low were detectable as early as Week 2 for FIL200mg + MTX and were sustained through Week 24. FINCH1 and FINCH3 FIL200mg + MTX NLR-High pts also demonstrated sustained clinical and PRO improvements over NLR-Low, including CDAI, ACR-N, Pain VAS, FACIT Fatigue, and HAQ-DI. The strength of these associations was dose-dependent; pts that received FIL100mg + MTX demonstrated weaker but directionally consistent trends in both populations. No significant association between NLR subgroup and clinical efficacy was observed in FINCH2 FIL+MTX-arm pts, FIL-monotherapy (FINCH3) pts, or adalimumab+MTX (FINCH1) pts.

Conclusion: In FINCH1 (MTX-IR) and FINCH3 (MTX-naïve), FIL200mg + MTX -arm NLR-High pts demonstrate better sustained clinical response and PRO scores compared to NLR-Low pts. These data are the first to report an association between the BL NLR and therapeutic response in large randomized RA clinical trials. Future studies on pathobiologies reflected by the NLR biomarker may clarify its potential to guide RA disease management.

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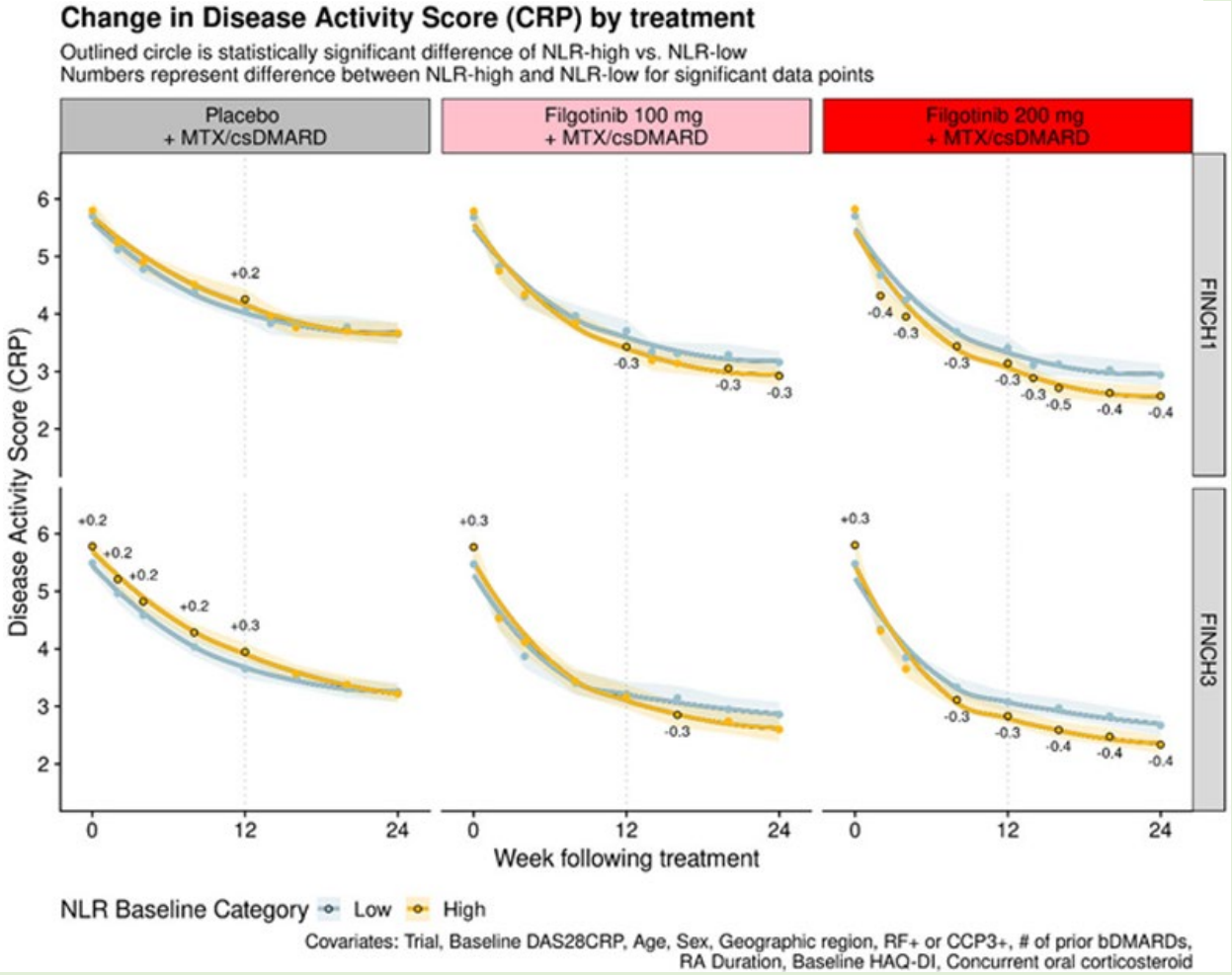
Table 1.

Demographics of patients enrolled in FINCH clinical trials by baseline NLR category.

	NLR-Low (NLR < 2.7) (N=1407, 43%)	**NLR-High (NLR > 2.7**) (N=1866, 57%)	**Total** (N=3273, 100%)	P-value
Age at enrollment				0.668 [2]
Mean (SD)	53.00 (12.74)	53.19 (13.24)	53.11 (13.02)	
Female	1,157 (82.2%)	1,448 (77.6%)	2,605 (79.6%)	0.001 [1]
Seropositivity	1,073 (76.3%)	1,575 (84.4%)	2,648 (80.9%)	< 0.001 [1]
Prior bDMARD #				
Mean (SD)	0.23 (0.73)	0.28 (0.82)	0.26 (0.78)	0.037 [2]
Duration of RA				
Mean (SD)	5.93 (7.39)	6.61 (8.07)	6.32 (7.79)	0.013 [2]
Baseline oral corticosteroid	537 (38.2%)	895 (48.0%)	1,432 (43.8%)	< 0.001 [1]
Baseline DAS28(CRP)	5.55 (0.90)	5.89 (0.97)	5.74 (0.95)	0.001 [2]
Baseline HAQ-DI	1.53 (0.60)	1.62 (0.65)	1.58 (0.63)	0.001 [2]

[1] Pearson's Chi-squared test. [2] Linear Model ANOVA.

Figure 1.
Association of BL NLR with DAS28(CRP). Dots represent DAS28(CRP) estimate from a fully adjusted mixed-effects model, shaded area shows the 95% confidence interval. Outlined circles and proximal text show significantly different values between NLR-High and NLR-Low.



Disclosure of Interests: Peter C. Taylor Consultant of: AbbVie, Biogen, Galapagos, Gilead, GlaxoSmithKline, Janssen, Lilly, BMS, Pfizer, Roche, Celltrion, Sanofi, Nordic Pharma, Fresenius and UCB, Grant/research support from: Celgene, Galapagos, Gilead, Lilly., Bryan Downie Shareholder of: Gilead Sciences, Inc., Employee of: Gilead Sciences, Inc., Sam Kim Shareholder of: Gilead Science, Employee of: Gilead Sciences, Rachael Hawtin Shareholder of: Gilead Sciences, Employee of: Gilead Sciences, Robert Moots Speakers bureau: Amgen, Chugai, Gilead, Libbs, Pfizer, Roche, Consultant of: Amgen, Chugai, Novartis, Pfizer, Roche, Grant/research support from: AKL, Novartis, UCB Pharma, Tsutomu Takeuchi Speakers bureau: AbbVie, Eisai Co. Gilead

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Session: Rheumatoid arthritis - prognosis, predictors and outcome *(POSTERS only)*

POS0092 (2021)

HERPES ZOSTER IN THE FILGOTINIB RHEUMATOID ARTHRITIS PROGRAM

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Background: The once daily, oral Janus kinase (JAK)-1 preferential inhibitor filgotinib (FIL) improved signs and symptoms of rheumatoid arthritis (RA) in phase (P)3 trials. [1-3] Patients (pts) with RA have increased herpes zoster (HZ) reactivation risk vs the general population. JAK inhibition is associated with increased infection incidence, including HZ. [4]

Objectives: To assess long-term safety of FIL across the global clinical program with respect to HZ.

Methods: Pts meeting 2010 ACR/EULAR RA criteria in a pooled analysis of P2 DARWIN 1–2 (D1–2), P3 FINCH 1–3 (F1–3), and long-term extension studies (D3, F4) were included. Placebo (PBO)-controlled as-randomised analysis included pts receiving FIL 100 mg (FIL100), FIL 200 mg (FIL200), or PBO up to week (W)12 (D1–2, F1–2); active-controlled as-randomised analysis included pts receiving FIL100, FIL200, adalimumab (ADA), or methotrexate (MTX) up to W52 (F1, F3). Long-term as-treated analysis included pts in all 7 studies receiving

FIL100, FIL200, ADA, MTX, or PBO; data after re-randomisation were included and contributed to treatment received. Exposure-adjusted incidence rates (EAIR)/100 patient-years, calculated up to the last follow-up time or day, and differences with 95% confidence intervals (CIs) were calculated from the Poisson model. Logistic regression model was used for treatment-emergent (TE) HZ risk factor analysis and odds ratio (95% CI) and *P* value were provided.

Results: Table 1 shows TE HZ EAIRs in a pooled analysis. Rates of HZ were lower for FIL200 vs PBO during the 12W PBO-controlled period. At 52W, HZ rates were higher for FIL200/100 vs active control. Long-term HZ rates increased for FIL200 vs FIL100.

Table 1.
EAIR of treatment-emergent herpes zoster

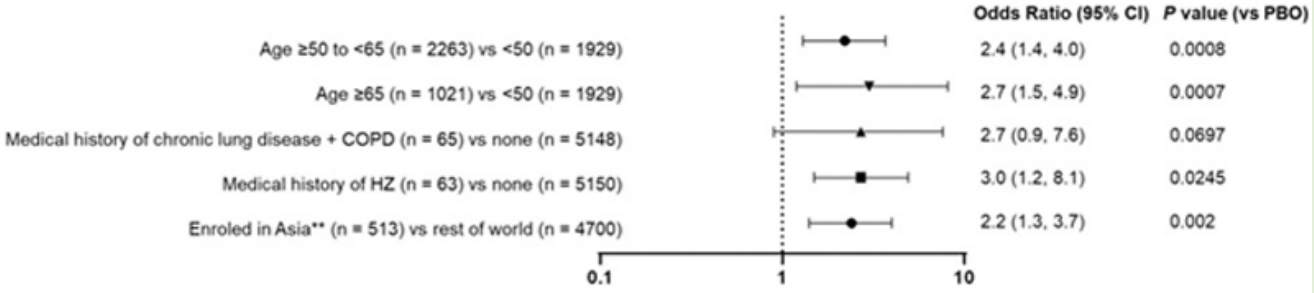
	N	Patient-years exposure	EAIR (95% CI)	EAIR diff (95% CI vs PBO/active control)
12W PBO-controlled				
FIL200	777	179.8	0.6 (0.1, 3.9)	−0.56 (−2.5, 1.3)
FIL100	788	181.6	1.1 (0.3, 4.4)	−0.02 (−2.2, 2.2)
PBO	781	178.4	1.1 (0.3, 4.5)	
Active-controlled, as-randomised [a]				
FIL200	475	439.7	1.4 (0.6, 3.0)	0.69 (−0.7, 2.1)
FIL100	480	443.4	0.9 (0.3, 2.4)	0.23 (−1.1, 1.5)
ADA	325	297.6	0.7 (0.2, 2.7)	
Active-controlled, as-randomised [a]				
FIL200	626	578.0	1.7 (0.9, 3.2)	0.65 (−0.8, 2.2)
FIL100	207	195.0	1.5 (0.5, 4.8)	0.46 (−1.6, 2.5)
MTX	416	372.2	1.1 (0.4, 2.9)	
Long-term as-treated [b]				
FIL200	2267	4047.7	1.8 (1.4, 2.3)	NC
FIL100	1647	2032.9	1.1 (0.8, 1.7)	NC

[a] up to W52. [b] data cut for LTE FINCH 4, Sept 19, 2019; DARWIN 3, April 26 2019.

ADA, adalimumab; CI, confidence interval; EAIR, exposure-adjusted incidence rate; FIL, filgotinib; MTX, methotrexate; NC, not calculated; PBO, placebo; W week.

Figure 1 shows multivariate logistic regression model of TE risk factors.

Figure: TE HZ risk factors analysis of multivariate logistic regression model* using long-term as-treated analysis set



*Model included treatment groups and risk factors that were significant in univariate analysis; patients could contribute to more than 1 group. Corticosteroid use was a risk factor (data not shown).
**Korea, Taiwan, Hong Kong, and Japan
CI, confidence interval; COPD, chronic obstructive pulmonary disease; HZ, herpes zoster; PBO, placebo; TE, treatment-emergent.

Of 104 pts with TE HZ in long-term as-treated analysis set, 5 receiving FIL200 had history of HZ; EAIR (95% CI) was 8.7 (3.6–21.0). Of 8 pts with multiple events, 3 had events of differing severity for the same HZ episode.

EAIRs (95% CI) of TE HZ in Asia were: 3.7 (1.7–8.1) FIL200, n=197; 2.8 (1.3–6.3) FIL100, n=158; 0 ADA, n=40; 2.8 (0.4–19.6) MTX, n=43; and 3.4 (0.5–23.8) PBO, n=77 in long-term as-treated population. EAIRs (95% CI) in rest of the world were: 1.6 (1.2–2.1) FIL200, n=2070; 0.9 (0.6–1.5) FIL100, n=1489; 0.8 (0.2–3.1) ADA, n=285; 0.9 (0.3–2.9) MTX, n=373; and 0.7 (0.2–2.9) PBO, n=704 for all pts as-treated.

Most TE HZ infections were mild to moderate and non-serious; 6 were serious; 2 were recurrences. No visceral TE HZ occurred across the FIL RA program; there was 1 case each of genital, disseminated, and ophthalmic HZ. The disseminated HZ occurred in a pt with prior HZ history. Lymphopenia was not associated with HZ during the PBO-controlled W12 period.

Conclusion: HZ was more common in both FIL groups vs ADA or MTX up to 52 weeks but comparable vs PBO during the 12-week placebo-controlled period. In multivariate analyses, prior history of HZ, Asian region, and age ≥50 years were associated with increased HZ risk.

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Session: Rheumatoid arthritis - non biologic treatment and small molecules - PART 1 *(Poster Tours)*

OP0126 (2021)

INFECTIONS AND SERIOUS INFECTIONS IN THE FILGOTINIB RHEUMATOID ARTHRITIS PROGRAM

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Background: The Janus kinase (JAK)-1 preferential inhibitor filgotinib (FIL) improved rheumatoid arthritis (RA) signs and symptoms in 3 phase (P)3 trials. [1–3] Like other RA therapies, JAK inhibition is associated with increased infection rates. [4]

Objectives: To assess long-term safety across the FIL program regarding infections, including serious infections (SI).

Methods: Patients (pts) meeting 2010 ACR/EULAR RA criteria in pooled analysis of P2 DARWIN 1–2 (D1–2), P3 FINCH 1–3 (F1–3), and long-term extension studies (DARWIN 3, FINCH 4) were included. The placebo (PBO)-controlled as-randomised data set included pts receiving FIL 100 mg (FIL100), FIL 200 mg (FIL200), or PBO up to week (W)12 (D1–2, F1–2). The active-controlled as-randomised data set included pts receiving FIL100, FIL200, adalimumab (ADA), or methotrexate (MTX) up to W52 (F1, F3). The long-term as-treated data set included pts in all 7 studies receiving FIL100 or FIL200; data after rerandomisation were included and contributed to treatment received.

Exposure-adjusted incidence rates (EAIRs) per 100 patient-years exposure (PYE) and differences with 95% confidence intervals (CIs) were calculated using Poisson regression; EAIRs for tuberculosis (TB) in active controlled sets were calculated using an Exact Poisson method. Kaplan-Meier (KM) event probabilities with 95% CIs were provided for SI. If pts had multiple events within the same treatment period, only the first event was counted in EAIR calculation; PYE were calculated up to the last follow-up time or day before next treatment, including after first event. For KM analysis, time to event was calculated until the first event.

Results: Of 2267/1647 pts in as-treated set receiving FIL200/FIL100, 1697 had treatment-emergent infection; 118 were SI. Baseline potential risk factors for pts with SI are in Table .

Table 1.
Baseline characteristics of pts with/without treatment emergent SI [a]

Parameter, n (%)	SI N = 92	No SI N = 2491
Medical history		
Chronic lung disease	13 (14.1)	125 (5.0)
Chronic renal disease	3 (3.3)	23 (0.9)
Infections and infestations	29 (31.5)	499 (20.0)
Baseline body mass index, kg/m ^{2}		
<30	64 (69.6)	1749 (70.2)
≥30	28 (30.4)	742 (29.8)
Age, years		
<65	67 (72.8)	2006 (80.5)
≥65	25 (27.2)	485 (19.5)
Former/current smoker	30 (32.6)	677 (27.2)
Oral corticosteroids, mg		
<7.5	28 (56.0)	731 (66.1)
≥7.5	22 (44.0)	375 (33.9)
Missing data	42	1385

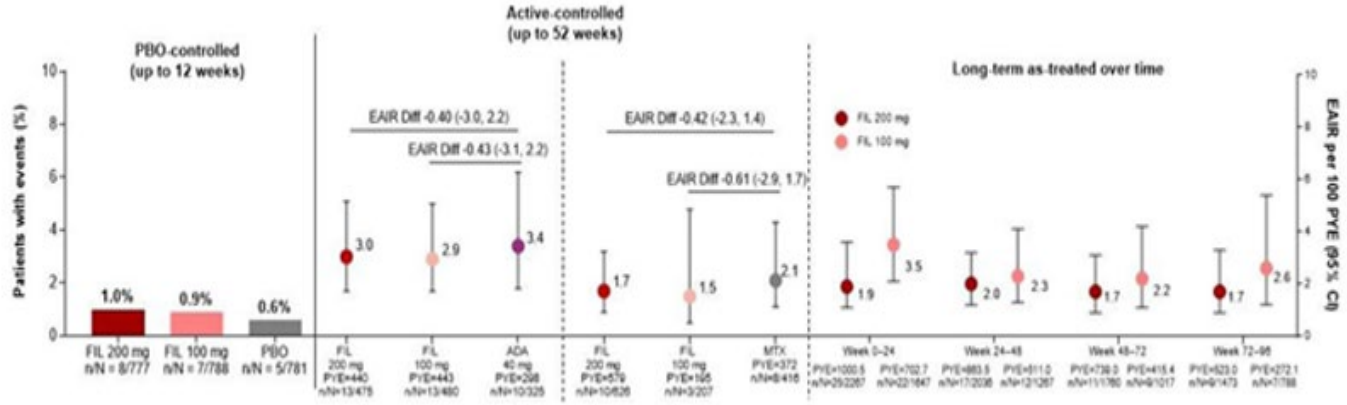
[a] Phase 3 (FINCH 1-4) studies, as randomised.

SI, serious infection.

In 12W PBO-controlled period, infection rates were 17.9%/15.6%/13.3% for FIL200/FIL100/PBO. In 52W ADA-controlled period, infection EAIRs (95% CIs)/100 PYE were 46.9 (40.9, 53.7)/43.7 (38.0, 50.4)/43.4 (36.5, 51.5), FIL200/FIL100/ADA; and 38.5 (33.8, 43.9)/39.0 (31.1, 48.8)/42.2 (36.1, 49.3), FIL200/FIL100/MTX in 52W MTX-controlled period; 24.8 (23.1, 26.5)/34.4 (30.4, 38.8), FIL200/FIL100 in long-term analysis. In 12W PBO-controlled period, there was no active TB for FIL200/FIL100/PBO. In 52W ADA-controlled period, active TB EAIRs (95% CIs)/100 PYE were: 0 (0.0, 0.8)/0 (0.0, 0.8)/0.3 (0.0, 1.9), FIL200/FIL100/ADA and 0 (0.0, 0.6)/0 (0.0, 1.9)/0 (0.0, 1.0), FIL200/FIL100/MTX in 52W MTX-controlled period; 0/0.1 (0.0, 0.5), FIL200/FIL100 in long-term analysis.

SI rate or EAIRs are in Figure . Most common infections were upper respiratory tract infection and nasopharyngitis; majority were low grade. Pneumonia was most common SI (<1%). In long-term population, event probability (95% CI) of SI was 2.2% (1.6, 2.9)/2.5% (1.8, 3.4) for FIL200/FIL100 at 52W. In F1–3 (excluding data after rerandomisation), there were no significant changes in mean neutrophil and lymphocyte counts; values remained within normal limits up to W52 for all arms.

Figure. Rate or EAIR of serious infections



ADA, adalimumab; CI, confidence interval; EAIR, exposure-adjusted incidence rate/100 PYE; FIL, filgotinib; MTX, methotrexate; PBO, placebo; PYE, patient-years of exposure.

Conclusion: EAIRs of infections and SI for FIL were similar to PBO, ADA, and MTX. At 52W, incidence rates of SI were comparable for FIL100 and FIL200. Long-term SI EAIR for FIL100 was slightly higher than for FIL200.

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Session: Rheumatoid arthritis - non biologic treatment and small molecules *(Oral Presentations)*

AB0565 (2021)

JAK INHIBITORS AND PSORIATIC ARTHRITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Despite the therapeutic armamentarium for the treatment of psoriatic arthritis (PsA) has considerably expanded over the last thirty years, there is a huge necessity of finding effective drugs for this disease. JAK inhibitors (JAKi) are small molecules able to interfere with the JAK/STAT pathway, involved in the pathogenesis of PsA (1). Up to now Tofacitinib is the only JAKi approved by the European Medicines Agency (EMA) for the treatment of PsA but in the next few years the number of approved JAKi is expected to rise significantly.

Objectives: To assess the efficacy and safety of different JAKi for the treatment of PsA.

Methods: A systematic review of the literature was performed to identify randomized controlled trials (RCTs), by electronic search of MEDLINE and EMBASE database until October 2020. Studies were considered eligible if they met the following criteria: I) study was a RCT; II) only patients with PsA were included; III) JAKi was compared to placebo in addition to the standard of care. Two reviewers (FC and AZ) performed study selection, with disagreements solved by the opinion of an expert reviewer (AS). The outcomes were expressed as odds ratio (OR) and 95% confidence intervals (95% CI). Statistical heterogeneity was assessed with the I^2 statistic.

Results: We identified 557 potentially relevant studies. A total of 554 studies were excluded based on title and/or abstract screening. Three RCTs for a total of 947 PsA patients treated with JAKi were included (2,3,4). Two were phase III studies on the efficacy and safety of Tofacitinib (OPAL Beyond and OPAL Broaden) and one was a phase II study on Filgotinib (Equator). All three studies were judged at low risk of bias according to Cochrane criteria (5). The primary efficacy outcome in all the studies was the number of patients who achieved the response rate of the American College of Rheumatology 20 score (ACR20). The outcomes evaluation was performed at 12 week for the Filgotinib trial and at 16 week for the Tofacitinib trials. We used for the main analyses the group of patients randomized to Tofacitinib 5 mg because this is the only dosage approved by the EMA for the treatment of PsA. JAKi showed a significantly higher ACR20 response rate compared to placebo (OR 3.54, 95% CI 1.76 - 7.09, I^2 = 74%). JAKi also showed a significantly higher ACR50 response rate (OR 3.36, 95% CI 2.22 - 5.09, I^2 = 0%), ACR70 response rate (OR 2.82, 95% CI 1.67 - 4.76, I^2 = 20%), PsARC response rate (OR 2.67, 95% CI 1.26 - 5.65, I^2 = 79%), PASI75 response rate (OR 3.15, 95% CI 1.61 - 6.15, I^2 = 45%) compared to placebo. JAKi were also associated with significantly better HAQ-DI (mean difference -0.23 95% CI -0.31 - -0.14) and fatigue, measured with FACIT-F (mean difference 3.54 95% CI 2.13 - 4.94). JAKi compared to placebo were associated with a non-statistically significant different risk of serious adverse events (OR 0.56, 95% CI 0.11 - 2.91, I^2 = 38%).

Conclusion: This is the first published systematic review that performed a comprehensive and simultaneous evaluation of the efficacy and safety of JAKi for PsA in RCTs. Our analysis suggests a statistically significant benefit of JAKi, that appears to be effective and safe over placebo. The impact of these data on international clinical guidelines needs further investigation.

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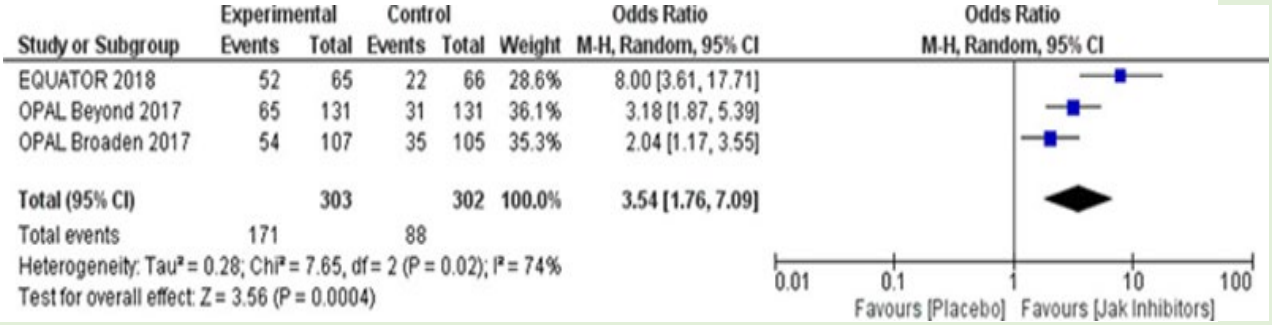
Figure 1.
ACR20 response rate of Jaki over Placebo



Disclosure of Interests: None declared.

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Session: Psoriatic arthritis – treatment *(Publication Only)*

POS0224 (2021)

SELECTIVITY OF CLINICAL JAK INHIBITORS AND THE IMPACT ON NATURAL KILLER (NK) CELL FUNCTIONAL RESPONSES

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Background: Janus kinase (JAK) inhibitors (JAKinibs) show similar efficacy in rheumatoid arthritis (RA). However, in vitro studies have shown differences in JAK selectivity profiles for baricitinib (BARI), tofacitinib (TOFA), upadacitinib (UPA) and filgotinib (FIL). [1,2] These lead to distinct pharmacologic profiles in cellular signaling assays that may impact clinical efficacy or safety [1]. NK cells are innate lymphocytes important in anti-pathogen responses and immune surveillance, which function via production of cytokines and cell killing [3]. NK cell proliferation and IFNγ production are JAK-dependent pathways and may be modulated by JAKinibs. Clinical findings show transient decreases in NK cell numbers in patients treated with JAKinibs, but the link to safety is unclear [4]

Objectives: To extend upon findings in proximal cell signaling assays, we compared the selectivity and potency of clinical JAKinibs on NK cell function by assessing proliferation mediated by IL-15 (JAK1/3) and IFN-γ production driven by IL-12 (JAK2/TYK2)+IL-18.

Methods: NK cells were isolated from healthy donor PBMC, incubated in vitro with 8 concentrations of each evaluated JAKinib (TOFA, BARI, FIL, FIL metabolite, UPA) and stimulated with IL-15 for proliferation or IL-12/18 for IFNγ production. Proliferation was assessed by Cell Trace dye dilution after 6 days and IFNγ production by

intracellular flow cytometry 4hrs post-stimulation. Half maximal inhibitory concentration (IC_{50}) values were calculated for $CD56^{bright}$, $CD56^{dim}$, and total NK cells. Steady-state pharmacologic profile over a clinical dosing interval was modeled using concentration-time profiles from JAKinib population pharmacokinetic data in RA subjects under the therapeutic dose [5-7]. For each JAKinib, the time above IC_{50} and average daily inhibition of IFNγ or proliferation were calculated for each NK cell population in each donor.

Results: Cellular assays in purified NK cells showed dose-dependent inhibition of IL-15-induced proliferation by all JAKinibs with TOFA showing the highest average inhibition and time above IC_{50} (35-60% inhibition for 8-15 hrs; TOFA>UPA>BARI≈FIL). The differences between JAKinibs are in line with differences in pSTAT inhibition downstream of IL-15 [1]. Interestingly, IL-12/18-induced production of IFNγ, which is mediated via JAK2/TYK2 (IL-12) and non-JAK dependent pathways (IL-18), showed weaker inhibition for all compounds. Moreover, all JAKinibs showed <25% average inhibition of IFNγ production over 24hrs and did not show any time above IC_{50} for IFNγ production or pSTAT4 inhibition at clinical doses. $CD56^{dim}$ and $CD56^{bright}$ sub-populations of NK cells are proposed to have distinct functions and unique expression of surface receptors. Analysis of the IC_{50} for pSTAT4 and IFNγ production showed ~2-10-fold weaker inhibition by JAKinibs in $CD56^{bright}$ NK cells, suggesting less dependence on JAK-dependent signals in $CD56^{bright}$ NK cells than $CD56^{dim}$ NK cells.

Conclusion: NK cell proliferation depends on JAK1 and JAK3-mediated signaling and is differentially inhibited at clinical doses of distinct JAKinibs. In contrast, functional responses downstream of JAK2/TYK2-dependent IL-12/18 were not substantially inhibited by any of the JAKinibs studied. Inhibition of functional and proliferative responses in purified NK cells aligned well with proximal pSTAT inhibition. JAKinib modulation of NK cell proliferation, but not response to IL-12, reflects unique pharmacologic profiles of the drugs studied and could be one component underlying clinical safety observations, including increased risk of viral infections or malignancy [4].

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Session: Rheumatoid arthritis - non biologic treatment and small molecules - PART 2 *(Poster Tours)*

POS0526 (2021)

SEXUAL FUNCTION IN MALE AND FEMALE PATIENTS WITH RHEUMATOID ARTHRITIS: A POST-HOC ANALYSIS OF THE FINCH STUDIES

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Background: While sexual function is impaired in a high proportion of patients with rheumatoid arthritis (RA), it is often neglected in patient care. [1] FINCH 1 (NCT02889796), FINCH 2 (NCT02873936) and FINCH 3 (NCT02886728) were Phase 3 studies to assess the safety and efficacy of filgotinib (FIL) for moderate-to-severe RA; patient-reported sexual function was also evaluated.

Objectives: To analyse disease characteristics associated with sexual function and explore the effect of FIL and adalimumab (ADA) on sexual function in males and females in the FINCH studies.

Methods: Post-hoc analyses included data from patients who were randomised and received ≥1 dose of study drug in the FINCH studies. Male and female subgroup analyses were performed to describe the correlation between baseline disease characteristics and baseline visual analogue scale (VAS) sexual function score (using Pearson correlation coefficient) and to assess the treatment effect on the change from baseline in VAS sexual function (mm) up to Week 52 (FINCH 1 and 3) or Week 24 (FINCH 2). Patients indicated how RA affected their ability to have sex during the last week using an exploratory 0–100 VAS (0: no effect; 100: complete inhibition). Changes from baseline were analysed with a mixed-effects model for repeated measures. All P values are nominal for exploratory purposes.

Results: Baseline characteristics are shown in the Table 1 . Univariate analyses revealed significant positive correlations ($P<0.05$) between disease duration and baseline VAS sexual function score in male and female subgroups in FINCH 1; no significant correlations were seen in male and female subgroups of FINCH 2 and 3. In all studies, significant correlations ($P<0.05$) were observed between baseline VAS sexual function score and baseline disease characteristics (swollen/tender joint count 28, Disease Activity Score-28, Health Assessment Questionnaire Disability Index, 36-Item Short Form Survey, patient global VAS, pain VAS or fatigue) in males or females. In all studies, analysis of least-squares mean changes from baseline in VAS sexual function revealed improvements in both males and females on FIL as early as Week 2, until Week 52 (Week 24 in FINCH 2). Figure 1 shows data for FINCH 1.

Conclusion: Sexual function should be considered as an important patient outcome in RA treatment. At baseline in the FINCH studies, disease activity negatively impacted sexual function in both male and female patients. Active treatment with FIL or ADA resulted in early and sustained improvements from baseline in sexual function.

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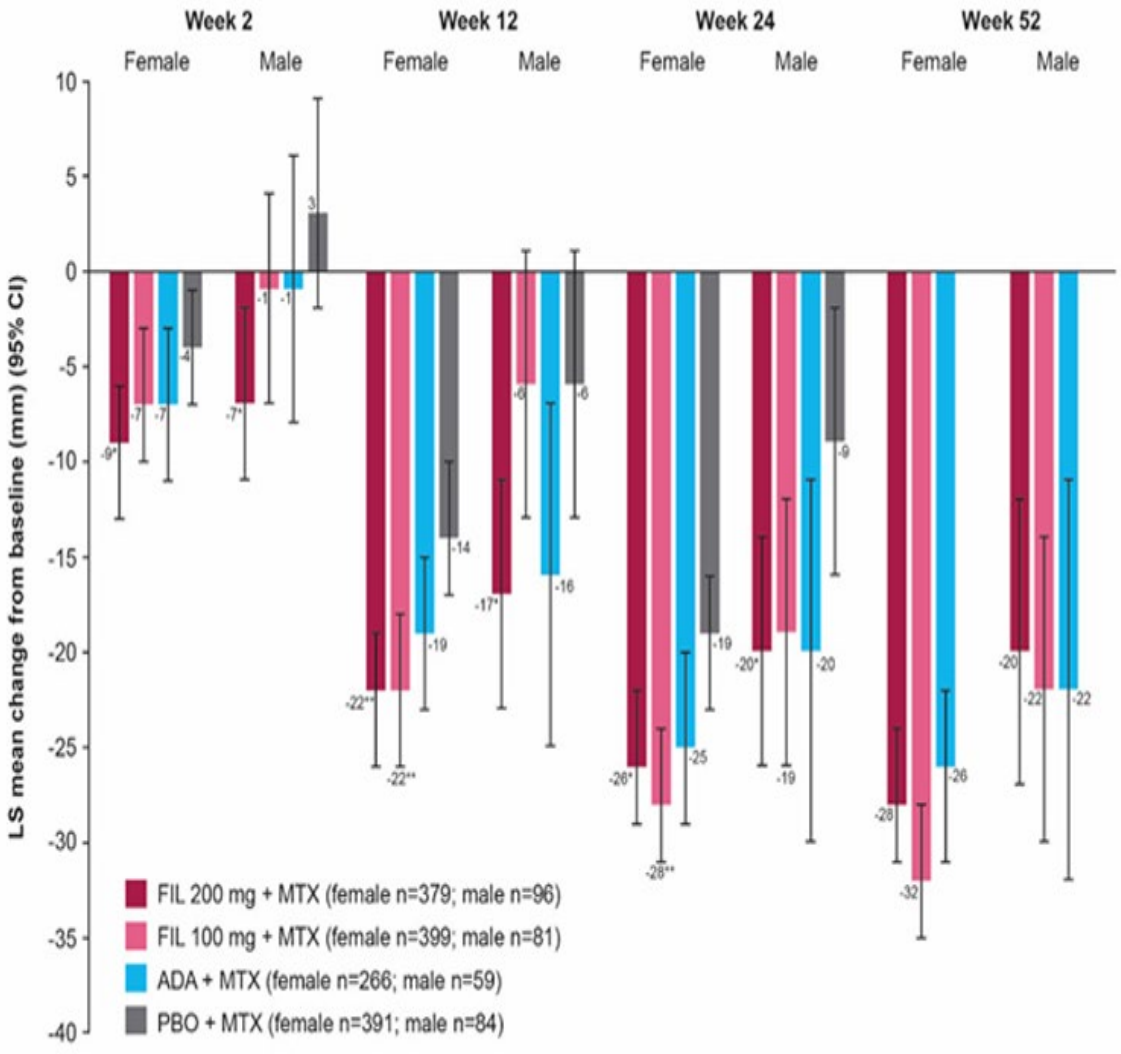
Table 1.
Mean (standard deviation) baseline characteristics

	FINCH 1		FINCH 2		FINCH 3	
	Male n=258	Female n=990	Male n=79	Female n=270	Male n=233	Female n=691
Duration of RA, yr	**6.8 (7.38)**	**8.0 (7.63)**	11.3 (8.53)	12.7 (9.35)	2.1 (5.35)	2.2 (4.85)
SJC28	**11 (5.0)**	**11 (5.1)**	**13 (6.2)**	**12 (6.1)**	**11 (5.4)**	**11 (5.7)**
TJC28	**14 (6.5)**	**15 (6.4)**	**15 (7.5)**	**16 (7.0)**	**14 (6.6)**	**15 (6.7)**
HAQ-DI	**1.35 (0.614)**	**1.64 (0.601)**	**1.41 (0.689)**	**1.73 (0.634)**	**1.37 (0.651)**	**1.62 (0.617)**
DAS28 (CRP)	**5.6 (0.95)**	**5.8 (0.90)**	**5.8 (1.08)**	**5.9 (0.92)**	**5.7 (1.00)**	**5.7 (0.99)**
SF-36 PCS	**34.3 (7.72)**	**33.0 (7.34)**	**31.7 (8.48)**	**30.9 (7.75)**	**34.4 (7.72)**	**33.4 (7.47)**
SF-36 MCS	**45.9 (10.15)**	**43.6 (10.65)**	**43.7 (11.20)**	**44.5 (11.71)**	**46.2 (11.75)**	**43.0 (10.89)**
FACIT-fatigue	**30.0 (10.00)**	**26.8 (10.49)**	**26.3 (11.15)**	**24.0 (11.64)**	**30.7 (10.93)**	**26.6 (10.89)**
Patient global VAS (mm)	**64 (19.8)**	**67 (19.0)**	**66 (20.0)**	**70 (19.5)**	**65 (22.4)**	**66 (20.3)**
Pain VAS (mm)	**61 (20.6)**	**66 (19.5)**	**62 (22.3)**	**68 (20.6)**	**64 (22.3)**	**66 (20.9)**
VAS sexual function score	44 (30.2)	49 (32.3)	48 (34.6)	49 (36.8)	42 (34.4)	48 (35.1)

Variables in bold significantly correlated with VAS sexual function score (P<0.05)

DAS28 (CRP), Disease Activity Score-28 using C-reactive protein; FACIT, Functional Assessment of Chronic Illness Therapy; HAQ-DI, Health Assessment Questionnaire Disability Index; MCS, mental component summary; PCS, physical component summary; RA, rheumatoid arthritis; SF-36, 36-Item Short Form Survey; S/TJC28, swollen/tender joint count based on 28 joints; VAS, visual analogue scale

Figure. Change from baseline in VAS sexual function over time for female and male subgroups in FINCH 1



Patients receiving placebo at Week 24 were re-randomised 1:1 to receive filgotinib 200 mg or 100 mg (data not shown)
* P≤0.05, ** P≤0.001 vs placebo
ADA, adalimumab; CI, confidence interval; FIL, filgotinib; LS, least-squares; MTX, methotrexate; PBO, placebo; VAS, visual analogue scale

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Session: Rheumatoid arthritis - comorbidity and clinical aspects *(POSTERS only)*

POS0411 (2021)

TARGETING JAK-STAT SIGNALLING ALTERS THE PHENOTYPIC CHARACTERISTICS OF PsA SYNOVIAL FIBROBLASTS IN RESPONSE TO THE JAK/STAT ACTIVATOR ONCOSTATIN M

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Background: Psoriatic arthritis (PsA) is a chronic inflammatory arthritis associated with psoriasis. The JAK/STAT pathway has been linked to the pathogenesis of PsA. Recently, JAK/STAT inhibitors (JAKi) have emerged as an encouraging class of drugs for the treatment of PsA. Only a few of these inhibitors have been approved for use in PsA patients with others currently in clinical trials.

Objectives: The aim of this study was to examine the effect of JAKi on primary PsA synovial fibroblasts (FLS) function.

Methods: Primary PsA FLS were isolated and cultured with JAKi (Peficitinib, Filgotinib, Baricitinib and Upadacitinib) in the presence of the pro-inflammatory JAK/STAT activator - Oncostatin M (OSM). The effect of JAKi on these cells was determined by Migration and Invasion Assays, ELISA and rtPCR. PsA FLS bioenergetics was assessed using an XF24 analyser, which simultaneously quantifies two energetic pathways- glycolysis (ECAR) and Oxidative phosphorylation (OCR).

Results: OSM-induced Migration and Invasion was supressed by all JAKi with Peficitinib, Filgotinib and Baracitinib showing the greatest effect. Analysis by ELISA and rtPCR showed reduction in MCP-1 and IL-6 expression in response to JAKi, in contrast, an increase in IL-8 was observed. These functional effects were accompanied by a change in the cellular bioenergetic profile of PsA FLS, where OSM significantly increased the ECAR:OCR ratio in favour of glycolysis where PsA FLS displayed a hypermetabolic phenotype. This effect was reversed in the presence of JAKi, which specifically targeted the glycolytic pathway with PsA FLS returning to a more quiescent phenotype.

Conclusion: This study demonstrates that JAK/STAT signalling mediates the complex interplay between inflammation and cellular metabolism in PsA pathogenesis, inhibition of which shows effective suppression of the pathogenic phenotype of PsA FLS that drives joint destruction.

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