IgA ACPA levels in RA patients versus healthy controls. Rather than prioritizing specificity, as is done for diagnostic tests, we aimed to define reliably detectable amounts of IgA ACPA, with both sensitivity and specificity not under 70% – 3 µg/ml for total IgA ACPA; 2.46 µg/ml for IgA1 and 0.6 µg/ml for IgA2 ACPA.

Results: Serum levels of both IgA ACPA subclasses were elevated in individuals at-risk, with no significant difference to patients with established IgG ACPA-positive RA. Interestingly, 41.4% of IgG ACPA-negative patients had detectable amounts of IgA ACPA. IgA1 ACPA, but not IgA2 ACPA levels were higher in individuals at-risk who developed RA in the next 14 months than in those who did not (4.54 vs. 2.05 µg/mL, p=0.03); and the percentage of those developing RA was higher in IgA1 ACPA-positive at-risk individuals (64.3% versus 35.3%). Interestingly, during the transition to RA, in the majority of IgA ACPA-positive individuals a decline in IgA1 ACPA levels at the time of RA diagnosis (-26%; p=0.085), as well as in the first months after the RA diagnosis (-38%; p=0.0002) was observed. This observation was confirmed in an independent cohort. IgA2 ACPA declined only after the diagnosis (33%; 10-64%; p=0.0237), and no significant change was observed for IgG ACPA.

Conclusion: Both IgA ACPA subclasses were elevated in individuals at-risk for RA. Positivity for IgA1 ACPA was associated with the progression to RA in the next 14 months. IgA1 ACPA levels declined in the months preceding the diagnosis of RA and in the months after the diagnosis, which might reflect pathophysiological events happening at the time of the disease outbreak.

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POS0518

EFFECT OF FILGOTINIB (FIL) ON BODY WEIGHT (BW) AND BODY MASS INDEX (BMI) AND EFFECT OF BASELINE BMI ON THE EFFICACY AND SAFETY OF FIL IN RHEUMATOID ARTHRITIS (RA)

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Background: FIL is a Janus kinase (JAK) 1 preferential inhibitor approved for the treatment (tx) of moderate to severe RA. Weight gain has been reported with other JAK inhibitors[1–3]; it is important to describe the effect of FIL on BW/BMI for physicians to correctly inform and appropriately treat patients.

Objectives: Our primary aim was to assess the effect of FIL on BW/BMI using data from the FINCH 1–3 studies. Secondary aims were to assess the efficacy and safety of FIL according to baseline BMI.

Methods: FINCH 1–3 (NCT02889796, NCT02873936, NCT02886728) were phase 3, randomised, double-blind, active/placebo (PBO)-controlled studies of FIL 100/200 mg (FIL100/FIL200) ± methotrexate (MTX) in patients with active RA who had an inadequate response to MTX (FINCH 1) or biologic DMARD (FINCH 2), or were MTX naïve (FINCH 3). We assessed changes from baseline (CFB) in BW and BMI by tx group and baseline BMI, and the efficacy and safety of FIL by baseline BMI (<25, 25–<30 or ≥30 kg/m^2). Efficacy measures included American College of Rheumatology (ACR)20/50/70 response, Disease Activity Score 28 with C-reactive protein (DAS28-CRP) and health assessment questionnaire disability index (HAQ-DI). Safety data were from 7 RA clinical trials (FINCH 1–4, DARWIN 1–3)[4].

Results: In FINCH 1–3, baseline disease characteristics such as HAQ-DI, DAS28-CRP and clinical disease activity index were similar across BMI subgroups for each tx group. There were no clinically relevant CFB in median BW or BMI in any tx group or differences between tx groups. Mean CFB in BMI (kg/m^2) were 0.4 with FIL200 and FIL100 and 0.3 with adalimumab (ADA) at Week 52 in FINCH 1; 0.2, 0.6 and –0.1 with FIL200, FIL100 and PBO, respectively, at Week 24 in FINCH 2; and 0.5, 0.6, 1.1 and 0.3 with FIL200+MTX, FIL100+MTX, FIL200 and MTX, respectively, at Week 52 in FINCH 3. CFB in BMI did not appear dependent on baseline BMI. FIL200±MTX was efficacious vs controls regardless of baseline BMI for most measures at each timepoint. In FINCH 1, in the <25, 25–<30 and ≥30 kg/m^2 BMI subgroups, DAS28-CRP <2.6 was achieved by 38%, 29% and 33% of the FIL200 group, 29%, 19% and 21% of the ADA group, and 7%, 10% and 11% of the PBO group at Week 12, respectively. Figure 1 shows ACR20 responders by baseline BMI in FINCH 1–3. Integrated safety data across baseline BMI subgroups are summarised in Table 1. VTE rate was numerically higher with FIL200 in the ≥30 than 25–<30 or <25 kg/m^2 BMI subgroups; serious infection rate was numerically higher with FIL100 in the <25 mg/m^2 subgroup vs other BMI subgroups.

Table 1. Exposure-adjusted incidence rate (95% CI) of AEs per 100 PYE by baseline BMI

	FIL dose (mg)	BMI (kg/m^2)		
		<25	25–<30	≥30
		PYE 3062.8	PYE 2640.1	PYE 2382.2
TEAEs	200	34.5 (32.0, 37.1)	35.7 (33.0, 38.6)	36.6 (33.7, 39.8)
	100	44.3 (40.4, 48.6)	43.0 (38.9, 47.5)	45.3 (41.1, 50.0)
Serious TEAEs	200	5.3 (4.4, 6.4)	5.8 (4.8, 7.1)	7.1 (5.8, 8.5)
	100	7.6 (6.0, 9.4)	6.5 (5.0, 8.4)	8.1 (6.4, 10.2)
Deaths	200	0.3 (0.2, 0.7)	0.5 (0.3, 1.0)	0.5 (0.2, 1.0)
	100	0.4 (0.1, 1.0)	0.3 (0.1, 1.0)	0.2 (0.1, 0.9)
Venous thrombotic and embolic events	200	0.1 (0.0, 0.4)	0.1 (0.0, 0.5)	0.5 (0.2, 1.0)
	100	0.1 (0.0, 0.7)	0.1 (0.0, 0.8)	0.2 (0.1, 0.9)
Major adverse cardiovascular events	200	0.3 (0.2, 0.7)	0.3 (0.1, 0.7)	0.5 (0.2, 1.0)
	100	0.6 (0.3, 1.3)	0.3 (0.1, 1.0)	0.6 (0.2, 1.4)
Serious infections	200	1.1 (0.7, 1.7)	1.7 (1.2, 2.5)	1.8 (1.2, 2.6)
	100	2.6 (1.8, 3.9)	1.2 (0.7, 2.2)	2.2 (1.4, 3.4)
Herpes zoster	200	1.6 (1.1, 2.2)	1.4 (1.0, 2.1)	1.8 (1.2, 2.6)
	100	1.0 (0.5, 1.8)	1.2 (0.7, 2.2)	1.0 (0.5, 2.0)
Malignancy excluding non-melanoma skin cancer	200	0.5 (0.3, 1.0)	0.7 (0.4, 1.3)	0.5 (0.3, 1.1)
	100	0.6 (0.3, 1.3)	0.4 (0.2, 1.2)	0.8 (0.4, 1.7)

BMI, body mass index; FIL, filgotinib; PYE, patient years of exposure; (TE)AE, (treatment-emergent) adverse event

Conclusion: FIL did not substantially affect CFB in BW or BMI. FIL200±MTX was generally more efficacious vs controls regardless of baseline BMI, and the rate of TEAEs was similar across baseline BMI subgroups.

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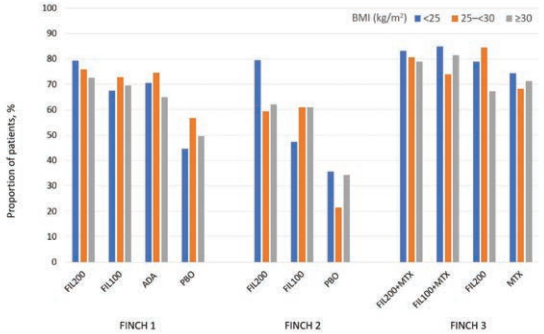
Figure 1. Proportion of patients to achieve ACR20 response at Week 12 (FINCH 1 and 2) or Week 24 (FINCH 3)



ACR, American College of Rheumatology; ADA, adalimumab; BMI, body mass index; FIL, filgotinib; MTX, methotrexate; PBO, placebo

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POS0519

RELATIONSHIP BETWEEN DISEASE ACTIVITY AND MAJOR ADVERSE EVENTS IN PATIENTS WITH RHEUMATOID ARTHRITIS ON TOFACITINIB OR TNF INHIBITORS: A POST HOC ANALYSIS OF ORAL SURVEILLANCE

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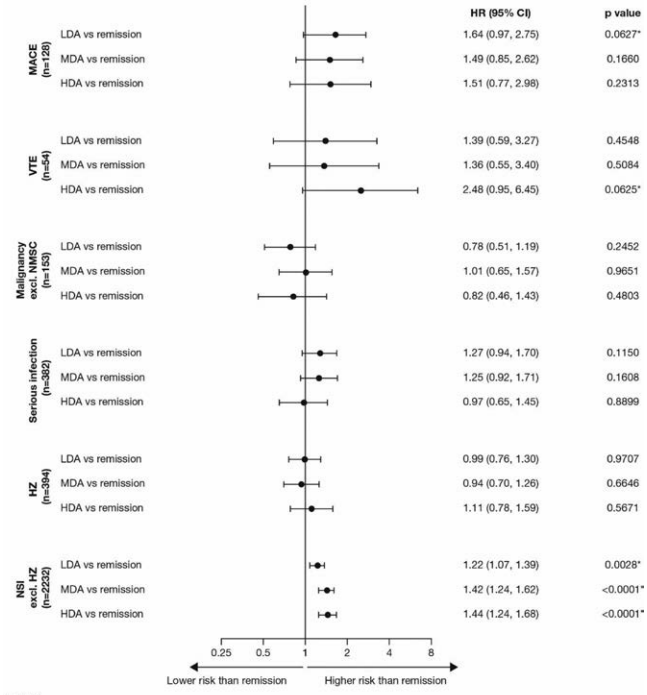
Background: Uncontrolled rheumatoid arthritis (RA) activity and acute disease flares are associated with higher risk of adverse outcomes such as cardiovascular (CV) disease, venous thromboembolism (VTE), malignancy and infection.[1-4]
Objectives: To evaluate associations of acute and cumulative Clinical Disease Activity Index (CDAI) measurements with major CV, malignancy, or infectious adverse events (AEs) of special interest in ORAL Surveillance.
Methods: ORAL Surveillance (NCT02092467) was a post-authorisation safety study of tofacitinib vs TNF inhibitors (TNFi) in patients (pts) aged ≥50 yrs with active RA despite methotrexate (MTX), and ≥1 additional CV risk factor. Pts were randomised 1:1:1 to tofacitinib 5 or 10 mg twice daily (BID) or subcutaneous TNFi. Two post hoc analyses were performed: (1) a time-varying multivariate Cox model examined risks of major AEs when pts were in CDAI-defined low (>2.8–≤10; LDA), moderate (>10–≤22; MDA) or high (>22; HDA) disease activity vs remission (≤2.8). The Cox model also included pt demographics, medical history, RA characteristics, prior treatments, baseline (BL) medications and treatment arm, pre-selected using backward selection; (2) area under the curve (AUC) per yr for CDAI prior to event or to study end (pts without event) was calculated and compared using an analysis of variance model with treatment arm, event status and interaction (supportive). Nominal p values <0.10 were considered evidence of associations.
Results: 4362 pts were included. Mean RA duration at BL was approximately 10 yrs. All pts were on MTX at BL, and 28% had previously been on one other synthetic disease-modifying antirheumatic drug (DMARD). Overall, 10% of pts had been on one biologic DMARD. Hazard ratios suggested that when pts had LDA, MDA or HDA vs remission, they were potentially at higher risk of developing major adverse CV events (MACE), VTE and non-serious infections (NSIs) excluding herpes zoster (HZ), but not malignancies, serious infections or HZ (Figure 1). Similarly, mean CDAI AUC trended higher for MACE, VTE and NSIs (Table 1).

Fig. HRs for major AEs of special interest during active RA vs remission as defined by CDAI



*p<0.10
HRs (95% CI) are shown on a logarithmic scale
CI, confidence interval; HR, hazard ratio; n, number of pts who experienced each AE; NMSC, non-melanoma skin cancer

Table 1. Cumulative CDAI (from BL to event) for pts with vs without events (AUC/yr)

Major AE	Pts with events		Pts without events		LS mean difference in pts with vs without events	p value
Treatment	n	LS mean AUC/yr	n	LS mean AUC/yr		
MACE						
Tofacitinib 5 mg BID	42	6275.4	1336	4607.3	1668.1	0.0018*
Tofacitinib 10 mg BID	50	5237.4	1306	4482.6	754.8	0.1253
TNFi	36	5234.5	1312	4851.5	383.0	0.5069
VTE						
Tofacitinib 5 mg BID	15	6546.7	1363	4614.4	1932.3	0.0293*
Tofacitinib 10 mg BID	31	6688.2	1323	4458.5	2229.7	0.0003*
TNFi	8	6423.6	1339	4839.4	1584.1	0.1907
Malignancy excl. NMSC						
Tofacitinib 5 mg BID	59	5249.3	1319	4618.9	630.4	0.1655
Tofacitinib 10 mg BID	55	4793.7	1301	4482.2	311.5	0.5077
TNFi	39	5561.4	1308	4826.3	735.1	0.1854
Serious infections						
Tofacitinib 5 mg BID	127	5710.2	1242	4577.5	1132.7	0.0004*
Tofacitinib 10 mg BID	150	5425.2	1197	4476.4	948.8	0.0013*
TNFi	105	6058.4	1240	4807.7	1250.7	0.0003*
HZ						
Tofacitinib 5 mg BID	175	5184.5	1199	4738.1	446.4	0.1101
Tofacitinib 10 mg BID	163	5549.1	1186	4481.3	1067.8	0.0002*
TNFi	56	5667.2	1291	4875.5	791.8	0.0930*
NSIs excl. HZ						
Tofacitinib 5 mg BID	760	6608.3	463	5122.5	1485.8	<0.0001*
Tofacitinib 10 mg BID	750	6587.8	426	5009.6	1578.2	<0.0001*
TNFi	722	6737.6	521	5217.5	1520.1	<0.0001*

*p<0.10. Data collected after pts who were randomised to tofacitinib 10 mg BID had their dose reduced to 5 mg BID were included in the tofacitinib 10 mg BID groupLS, least squares; n, number of pts in analysis of variance model