Efficacy and Safety of Upadacitinib Monotherapy in Methotrexate-naïve Patients with Moderately to Severely Active Rheumatoid Arthritis (SELECT-EARLY): A Randomized, Double-blind, Active-comparator, Multi-center, Multi-country Trial

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Study Design

- SELECT-EARLY: 48-week double-blind, randomised, active-comparator-controlled period followed by 4-year open-label LTE
  - Conducted at 236 sites in 43 countries in 947 patients
  - Eligible patients ≥18 years of age with active RA and symptoms ≥6 weeks
  - Patients were either methotrexate-naïve or had received methotrexate for ≤3 weekly doses and completed a 4-week washout
  - Key exclusion criteria: prior MTX intolerance or exposure to JAKi or bDMARD
- Patients randomised 1:1:1 to upadacitinib 15 or 30 mg QD monotherapy, or weekly methotrexate
- Rescue therapy* offered to patients who did not achieve ≥20% improvement from baseline in both TCJ and SJC at two consecutive visits beginning Week 12

*Non-steroidal anti-inflammatory drugs, low-potency analgesics, low-dose glucocorticoids, but not DMARDs.

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Endpoints

- Two separate primary endpoints assessed due to regulatory needs:
  - FDA: proportion of patients who achieved ACR50 at Week 12
  - EU/EMA: proportion of patients who achieved DAS28-CRP <2.6 at Week 24
- Key secondary endpoints at Weeks 12 and 24 included:
  - Change from baseline in DAS28-CRP, HAQ-DI, and SF-36 PCS
  - Proportion of patients achieving DAS28-CRP ≤3.2; ACR20/70
- Key secondary endpoints at Week 24:
  - Change from baseline in mTSS
  - Proportion of patients achieving DAS28-CRP <2.6, and those with no radiographic progression

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Baseline Characteristics

	MTX n=314	UPA 15mg QD m=317	UPA 30mg QD n=314
Time since RA diagnosis, years	2.6 (5.1)	2.9 (5.4)	2.8 (5.6)
Median time since RA diagnosis, years (min, max)	0.5 (0.0, 38.0)	0.5 (0.0, 36.5)	0.6 (0.0, 44.0)
Female	240 (76.4%)	241 (76.0%)	240 (76.4%)
Age, years	53.3 (12.9)	51.9 (12.6)	54.9 (12.6)
Previous csDMARD exposure	79 (25.2%)	80 (25.2%)	80 (25.5%)
MTX exposure	19 (6.1%)	30 (9.5%)	22 (7.0%)
MTX dose at Week 24, mg	19.2 (2.1)	-	-
Oral glucocorticoid use	163 (51.9%)	147 (46.4%)	137 (43.6%)
Oral glucocorticoid dose, mg*	6.4 (2.4)	6.4 (3.1)	6.9 (2.9)
Immunization history			
Bacillus Calmette-Guérin Vaccination*	118 (47.2%)	130 (52.2%)	93 (41.0%)
Hepatitis B immunization*	34 (11.9%)	40 (14.3%)	35 (13.3%)
Herpes zoster immunization*	4 (1.3%)	7 (2.3%)	8 (2.8%)

All demographics and most disease characteristics were well balanced across treatment arms at baseline

Values are mean (SD) or n (%), unless otherwise stated. *Based on prednisone equivalent dose. Only evaluated among patients with oral steroid use at baseline. Patients who had a missing baseline value or whose values were unknown for a variable were not counted in the denominator for that measure. †N=250, 249, and 227, respectively; ‡N=286, 280, and 264, respectively; § N = 299, 298, and 287, respectively; ||N=314, 317, and 311, respectively; **N=299, 301, and 304, respectively; ††N=299, 301, and 303, respectively; ‡‡N=309, 309, and 309, respectively; § § N=313, 316, and 313, respectively; ||||N=314, 316, and 310, respectively; ***N=313, 315, and 312, respectively.

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Baseline Characteristics

	MTX n=314	UPA 15mg QD m=317	UPA 30mg QD n=314
Disease characteristics			
Rheumatoid factor and ACPA positive	213 (67.8%)	230 (72.6%)	212 (67.7%)
Rheumatoid factor and/or ACPA positive	255 (81.2%)	279 (88.3%)	252 (80.5%)
Tender joint count of 68 joints	26.4 (16.2)	25.4 (14.4)	25.2 (15.0)
Swollen joint count of 66 joints	16.9 (10.6)	16.9 (10.4)	15.7 (9.7)
Patient's GA, 0-100 mm VAS*	65.8 (21.5)	66.6 (22.0)	64.9 (21.6)
Physician's GA, 0-100 mm VAS*	68.7 (16.5)	67.1 (17.0)	65.3 (16.6)
Pain, 0-100mm, VAS*	65.7 (21.5)	68.4 (20.6)	65.3 (21.5)
High-sensitivity C-reactive protein, mg/L	21.2 (22.1)	23.0 (27.4)	19.4 (22.6)
DAS28(CRP)*	5.9 (1.0)	5.9 (1.0)	5.8 (1.0)
Clinical disease activity index	40.5 (13.3)	40.4 (13.3)	39.3 (13.5)
Simplified disease activity index*	42.6 (14.0)	42.7 (13.9)	41.3 (14.4)
mTSS score*	13.3 (30.6)	18.1 (38.2)	17.2 (38.3)
mTSS Erosion score*	6.1 (15.5)	8.6 (19.3)	8.0 (18.9)
mTSS JSN score*	7.2 (16.2)	9.6 (20.1)	9.3 (20.3)
Morning Stiffness Duration, min*	128.5 (134.2)	168.9 (227.5)	136.4 (166.5)
Morning Stiffness Severity, 0-10 scale	6.3 (2.3)	6.6 (2.3)	6.4 (2.2)
HAQ-DI*	1.6 (0.7)	1.6 (0.7)	1.5 (0.7)
FACIT-F*	26.6 (11.7)	26.4 (11.9)	27.8 (11.1)
SF-36 PCS*	33.1 (7.5)	32.7 (7.7)	33.7 (7.2)

All demographics and most disease characteristics were well balanced across treatment arms at baseline

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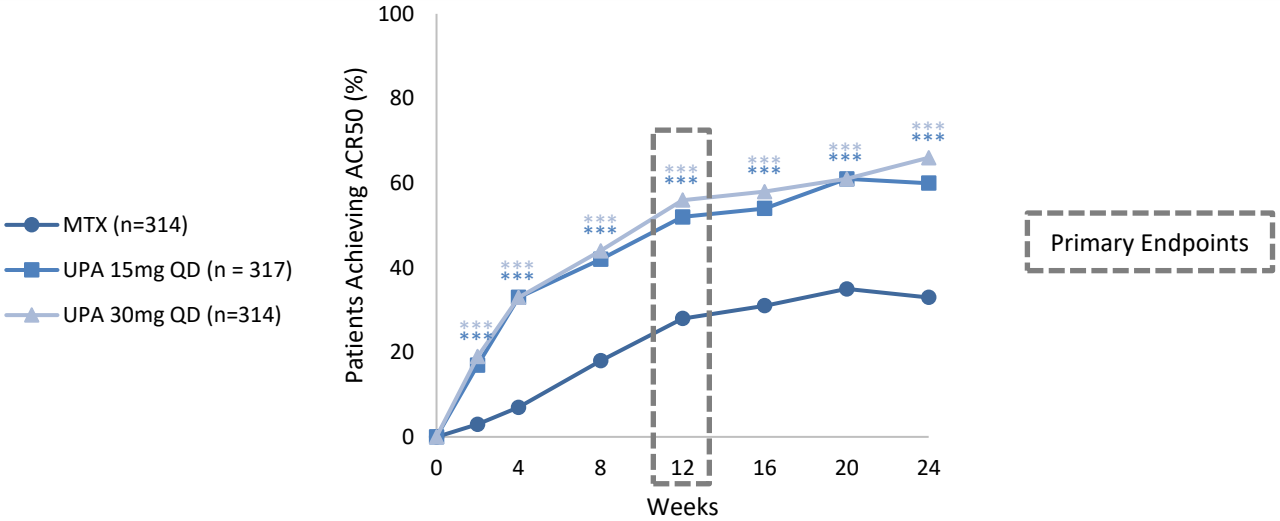
Primary Endpoint: ACR50 at Week 12



- Difference for upadacitinib 15 mg versus methotrexate: 24% (95% CI: 16–31; P<0.001); for upadacitinib 30 mg versus methotrexate: 28% (95% CI: 21–35; P<0.001)

At Week 12, ACR50 was achieved by significantly higher proportions of patients receiving either dose of upadacitinib monotherapy versus methotrexate

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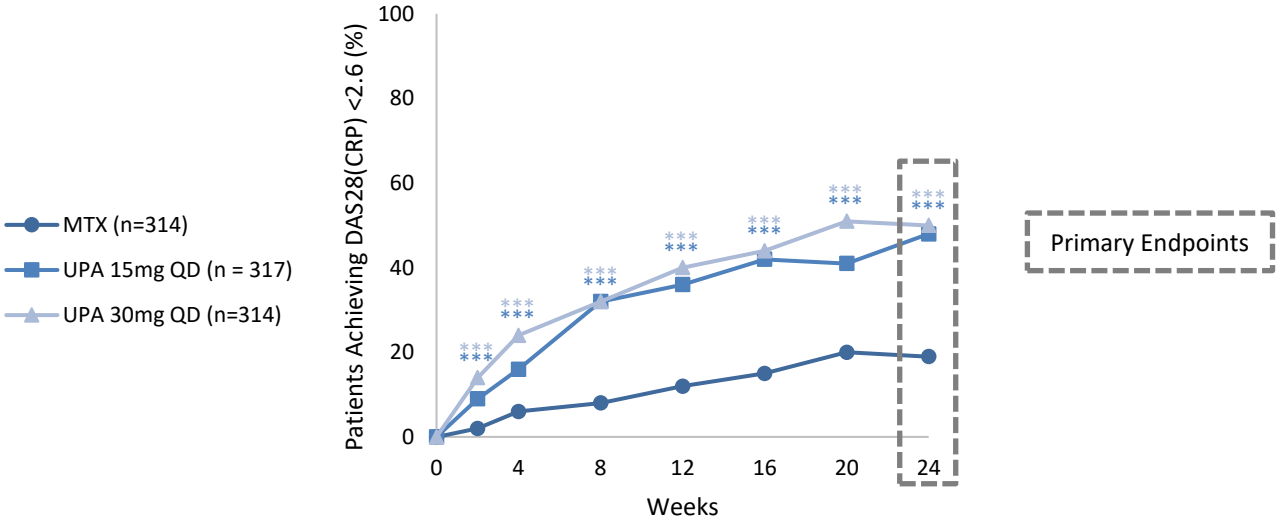
Primary Endpoint: DAS28-CRP at Week 24



- Difference for upadacitinib 15 mg versus methotrexate: 30% (95% CI: 23–37; P<0.001)
  for upadacitinib 30 mg versus methotrexate: 32% (95% CI: 25–39; P<0.001)

Differences between each upadacitinib group and methotrexate were significant at the first post-baseline visit and persisted through Week 24

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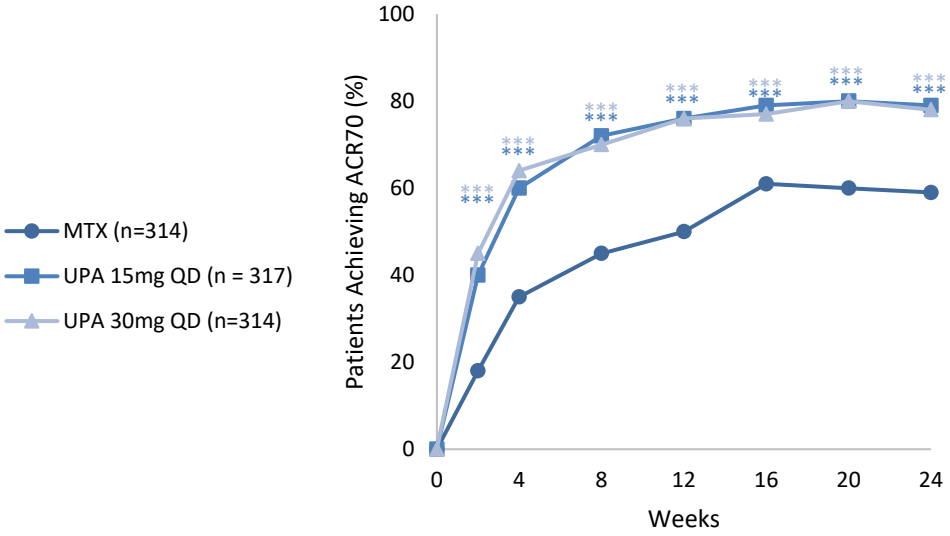
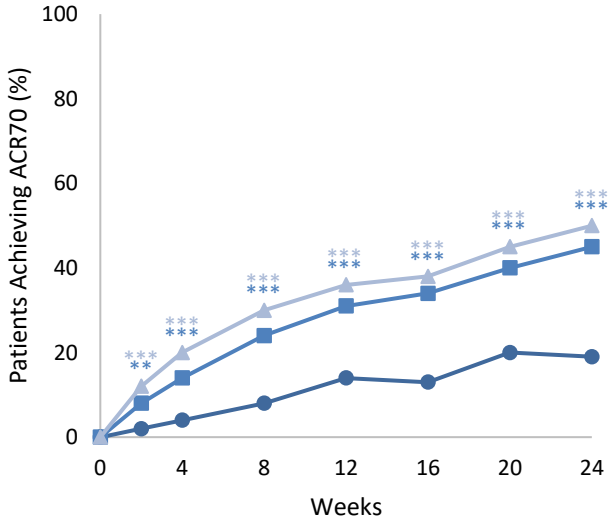
Proportions Achieving ACR20 and ACR70





ACR20 or 70 were achieved by significantly more patients receiving upadacitinib 15 or 30 mg than methotrexate

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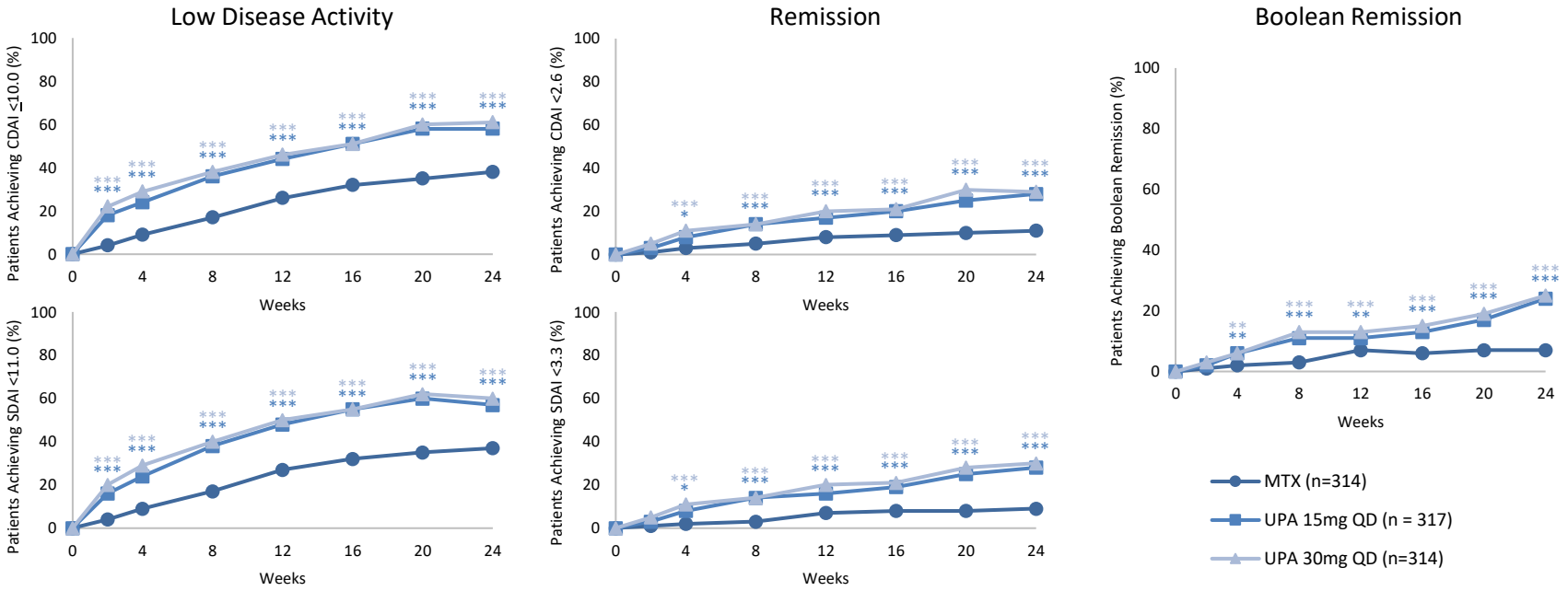
LDA and Remission over 24 Weeks



Significantly higher proportions of upadacitinib patients achieved LDA or CDAI/SDAI remission compared with methotrexate

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Treatment-Emergent AEs

		Upadacitinib		Difference (95% CI)	
	MTX (n=314)	**15mg QD** (n=317)	**30mg QD** (n=314)	**UPA 15mg** (QD – MTX)	**UPA 30mg** (QD – MTX)
Any AE	205 (64.3)	203 (64.0)	224 (71.3)	-1.2 (-8.7, 6.2)	6.1 (-1.2, 13.3)
Any SAE	13 (4.1)	15 (4.7)	20 (6.4)	0.6 (-2.6, 3.8)	2.2 (-1.3, 5.7)
Any AE leading to discontinuation of study drug	16 (5.1)	14 (4.4)	12 (3.8)	-0.7 (-4.0, 2.6)	-1.3 (-4.5, 2.0)
Deaths	1 (0.3)	2 (0.6)	3 (1.0)	0.3 (-0.8, 1.4)	0.6 (-0.6, 1.9)
Infection	103 (32.8)	104 (32/8)	115 (36.6)	0.0 (-7.3, 7.3)	3.8 (-3.6, 11.3)
Serious infection	4 (1.3)	5 (1.6)	8 (2.5)	0.3 (-1.5, 2.2)	1.3 (-0.9, 3.4)
Opportunistic infection	0	1 (0.3)	1 (0.3)	0.3 (-0.3, 0.9)	0.3 (-0.3, 0.9)
Herpes zoster	1 (0.3)	7 (2.2)	7 (2.2)	1.9 (0.2, 3.6)	1.9 (0.2, 3.7)
Hepatic disorder	17 (5.4)	19 (6.0)	14 (4.5)	0.6 (-0.3, 4.2)	-1.0 (-4.3, 2.4)
Anemia	6 (1.9)	9 (2.8)	13 (4.1)	0.9 (-1.4, 3.3)	2.2 (-0.4, 4.9)
Elevated CPK	3 (1.0)	9 (2.8)	35 (11.1)	1.9 (-0.2, 4.0)	10.2 (6.5, 13.8)
Gastrointestinal perforation	0	0	2 (0.6)	0	0.6 (-0.2, 1.5)
Malignancy (including/excluding NMSC)§	1 (0.3)	3 (0.9)	0	0.6 (-0.6, 1.9)	-0.3 (-0.9, 0.3)
MACE (adjudicated)	1 (0.3)	1 (0.3)	2 (0.6)	-0.0 (-0.9, 0.9)	0.3 (-0.8, 1.4)
VTE (adjudicated)	1 (0.3)	0	1 (0.3)	-0.3 (-0.9, 0.3)	0.0 (-0.9, 0.9)
PE	1 (0.3)	0	0	-	-
DVT	0	0	1 (0.3)	-	-

Through Week 24, SAE frequency was similar between methotrexate and upadacitinib, but slightly higher in the 30 mg arm, showing a similar trend to TEAEs

Values are n (%) unless otherwise stated. *Deaths (includes non-treatment emergent deaths): methotrexate: 1 due to acute MI, UPA 15 mg: 1 due to non-fatal MI and hypoxic ischemic encephalopathy, 1 death due to metastatic malignant melanoma, UPA 30 mg: 1 due to sudden CV death, 1 death due to pneumonia and sepsis, 1 death due to peritonitis. †Opportunistic infection: UPA 15 mg: 1 with cryptococcal pneumonia, UPA 30 mg: 1 with positive asymptomatic CMV test; ‡GI perforation (by GI Perforations SMQ): UPA 30 mg: 1 with large intestinal perforation, 1 with peritonitis; § Malignancies: methotrexate: 1 case of ovarian cancer, UPA 15 mg: 1 metastatic malignant melanoma, 1 squamous cell carcinoma of the lung, 1 uterine carcinoma in situ. No NMSC; ||MACE (adjudicated): methotrexate: 1 CV death, UPA 15 mg: 1 non-fatal myocardial infarction (MI), 1 CV death due to other CV causes; UPA 30 mg: 1 non-fatal MI and 1 CV death (sudden).

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Laboratory Variables

		MTX (n=312)	UPA 15 mg QD (n=315)	UPA 30 mg QD (n = 310)	UPA 15mg (QD – MTX)	UPA 30mg (QD – MTX)
Hemoglobin (g/L)	Mean (SD) change from baseline up to Week 24††	0.9 (10.0)	2.3 (10.6)	-0.7 (12.0)	1.5 (-0.4, 3.3)	-1.6 (-3.4, 0.3)
	Grade 3 (70–<80 or decreased 21–<30)	16 (5.1)	10 (3.2)	25 (8.0)‡‡	-	-
	Grade 4 (<70 or decreased ≥30)	5 (1.6)	1 (0.3)	10 (3.2)‡‡	-	-
Platelets (×109/L)	Mean (SD) change from baseline up to Week 24§§	-16.5 (66.2)	-26.9 (78.3)	-9.6 (73.6)	-10.4 (-22.6, 1.9)	6.9 (-5.5, 19.3)
	Grade 3 (20–<50)	0‡‡	0||||	0‡‡	-	-
	Grade 4 (<20)	0‡‡	0||||	1 (0.3)‡‡	-	-
Leukocytes (×109/L)	Mean (SD) change from baseline up to Week 24††	-1.0 (2.2)	-1.4 (2.5)	-1.4 (2.2)	-0.5 (-0.8, -0.1)	-0.4 (-0.80, 0.0)
	Grade 3 (1.0–<2.0)	0	0	2 (0.6)‡‡	-	-
	Grade 4 (<1.0)	0	0	2 (0.6)‡‡	-	-
Neutrophils (×109/L)	Mean (SD) change from baseline up to Week 24***	-0.8 (1.9)	-1.4 (2.4)	-1.4 (2.1)	-0.6 (-0.9, -0.2)	'-0.6 (-0.9, -0.2)
	Grade 3 (0.5–<1.0)	0	1 (0.3)	5 (1.6)	-	-
	Grade 4 (<0.5)	0	0	1 (0.3)	-	-
Lymphocytes (×109/L)	Mean (SD) change from baseline up to Week 24***	-0.1 (0.7)	0.1 (0.7)	0.1 (0.7)	0.2 (0.1, 0.3)	0.2 (0.1, 0.4)
	Grade 3 (0.5–<1.0)	43 (13.8)	29 (9.2)	38 (12.3)	-	-
	Grade 4 (<0.5)	2 (0.6)	0	2 (0.6)	-	-
ALT (U/L)	Grade 3 (3.0–<8 ×ULN)	11 (3.5)	4 (1.3)	5 (1.6)	-	-
	Grade 4 (>8 ×ULN)	3 (1.0)	2 (0.6)	0	-	-
AST (U/L)	Grade 3 (3.0–<8 ×ULN)	8 (2.6)	1 (0.3)	4 (1.3)	-	-
	Grade 4 (>8 ×ULN)	0	2 (0.6(	0	-	-

The proportion with elevated ALT was higher with methotrexate, and comparable between upadacitinib doses

Values are n (%) unless otherwise stated. **Patients with worsening in grade at any time during study including single isolated values, n (%). Grading based on OMERACT criteria. Actual patient numbers in each treatment arm may be slightly lower than that in the header; ††N=266, N=286, N=272, NA, NA, respectively; ‡‡N=311; § § N=264, N=284, N=270, NA, NA, respectively; ||||N=314; ***N=266, N=285, N=271, NA, NA, respectively.

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Conclusion

- Both doses of upadacitinib monotherapy were superior to methotrexate in all efficacy outcomes
  - Including multiple definitions of clinical remission and PROs
- Responses favouring upadacitinib were rapid, and persisted through 24 weeks
- The data are consistent with those reported previously in other Phase 3 upadacitinib trials
- AEs occurred at frequencies similar to or numerically less with upadacitinib 15 mg than methotrexate, with the exception of herpes zoster

Upadacitinib QD monotherapy demonstrated superior clinical, radiographic, and PROs versus methotrexate in methotrexate-naïve RA patients at increased risk for structural damage

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