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CLINICAL SCIENCE

Safety profile of upadacitinib in rheumatoid arthritis: integrated analysis from the SELECT phase III clinical programme

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Handling editor Josef S Smolen

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2020-218510).

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Some data in this paper have been presented previously at European League Against Rheumatism 2019 (Cohen SB, et al. *Ann Rheum Dis* 2019;78:357: Abstract THU0167) and ACR 2019.

Received 3 July 2020
Revised 1 October 2020
Accepted 3 October 2020
Published Online First 28 October 2020

To cite: Cohen SB, van Vollenhoven RF, Winthrop KL, *et al*. *Ann Rheum Dis* 2021;**80**:304–311.

ABSTRACT

Objectives This integrated analysis presents the safety profile of upadacitinib, a Janus kinase inhibitor, at 15 mg and 30 mg once daily in patients with moderately to severely active rheumatoid arthritis (RA).

Methods Treatment-emergent adverse events (TEAEs) and laboratory data from five randomised, placebo- or active-controlled phase III trials of upadacitinib for patients with RA were analysed and summarised. Exposure-adjusted event rates are shown for placebo (three trials; 12/14 weeks), methotrexate (two trials; mean exposure: 36 weeks), adalimumab (one trial; mean exposure: 42 weeks), upadacitinib 15 mg (five trials; mean exposure: 53 weeks) and upadacitinib 30 mg (four trials; mean exposure: 59 weeks).

Results 3834 patients received one or more doses of upadacitinib 15 mg (n=2630) or 30 mg (n=1204), for a total of 4020.1 patient-years of exposure. Upper respiratory tract infection, nasopharyngitis and urinary tract infection were the most commonly reported TEAEs with upadacitinib. Rates of serious infection were similar between upadacitinib 15 mg and adalimumab but higher compared with methotrexate. Rates of herpes zoster and creatine phosphokinase (CPK) elevations were higher in both upadacitinib groups versus methotrexate and adalimumab, and rates of gastrointestinal perforations were higher with upadacitinib 30 mg. Rates of deaths, malignancies, adjudicated major adverse cardiovascular events (MACEs) and venous thromboembolic events (VTEs) were similar across treatment groups.

Conclusion In the phase III clinical programme for RA, patients receiving upadacitinib had an increased risk of herpes zoster and CPK elevation versus adalimumab. Rates of malignancies, MACEs and VTEs were similar among patients receiving upadacitinib, methotrexate or adalimumab.

Trial registration numbers SELECT-EARLY: NCT02706873; SELECT-NEXT: NCT02675426; SELECT-COMPARE: NCT02629159; SELECT-MONOTHERAPY: NCT02706951; SELECT-BEYOND: NCT02706847.

Key messages

What is already known about this subject?

- Upadacitinib is a Janus kinase (JAK) inhibitor which has been studied across a spectrum of patients with moderately to severely active rheumatoid arthritis (RA); the efficacy of upadacitinib has been reported from the five randomised controlled trials (RCTs) which comprise the phase III SELECT clinical programme.
- JAK inhibitors have been associated with several safety risks, including herpes zoster, serious and opportunistic infections, thromboembolic events and changes in laboratory parameters.

What does this study add?

- This integrated safety analysis of upadacitinib, based on more than 3500 patients and 4000 patient-years of exposure, supports an acceptable safety profile for treatment of patients with RA and reports no new safety risks compared with other JAK inhibitors.
- Upadacitinib 15 mg once daily had a similar safety profile to that of adalimumab for rates of serious infections, malignancies, major adverse cardiovascular events and venous thromboembolic events but higher rates of herpes zoster and creatine phosphokinase elevations.

How might this impact on clinical practice or future developments?

- The results of this integrated safety analysis of five RCTs suggest that upadacitinib has a similar safety profile to other JAK inhibitors as demonstrated in their clinical development programmes.

INTRODUCTION

Oral targeted synthetic disease-modifying antirheumatic drugs, such as Janus kinase inhibitors (JAKis), have demonstrated at least similar efficacy to biologic disease-modifying antirheumatic drugs (bDMARDs) in randomised controlled trials (RCTs) as treatment for rheumatoid arthritis (RA). Shared decision-making between physicians and patients regarding treatment selection requires understanding benefits and risks, including the safety profiles of treatment options.

Upadacitinib is a JAKi engineered for increased selectivity for JAK1 over JAK2, JAK3 and tyrosine kinase 2.[1] Upadacitinib 15 mg once daily was recently approved in the USA and Europe for

patients with moderately to severely active RA who are intolerant of or have had an inadequate response to methotrexate (MTX).[2 3] Efficacy and safety of upadacitinib were studied in patients with moderately to severely active RA in five pivotal phase III RCTs: SELECT-NEXT,[4] SELECT-BEYOND,[5] SELECT-MONOTHERAPY,[6] SELECT-COMPARE[7] and SELECT-EARLY.[8] Here, we report an integrated analysis of the safety profile of upadacitinib 15 and 30 mg once daily from these trials.

METHODS

Studies

Data were pooled from the five SELECT trials (online supplemental table S1), which evaluated upadacitinib administered with or without background conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) in patients with moderately to severely active RA, including MTX-naive patients and those with an inadequate response or intolerance to one or more csDMARDs or bDMARDs.

Patients aged ≥18 years with active RA (≥6 swollen and ≥6 tender joints and high-sensitivity C-reactive protein ≥3 mg/L (≥5 mg/L in SELECT-EARLY[8] and SELECT-COMPARE[7] at screening) who met the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism classification criteria were enrolled.[9] Additional inclusion criteria in SELECT-EARLY and SELECT-COMPARE were erosive joint damage and/or autoantibody seropositivity.[7 8] Exclusion criteria are listed in the online supplemental material. Patients were tested for tuberculosis (TB) at screening; those with latent TB could enrol after initiating appropriate prophylactic treatment.

Patient and public involvement

Patients and the public were not involved in the design or analysis of this study.

Dosing

Depending on the study, patients received extended-release upadacitinib (15 or 30 mg once daily), placebo, MTX or subcutaneous adalimumab (40 mg every other week), as monotherapy or in combination with background csDMARDs. Patients were not permitted to switch between upadacitinib doses. MTX-naive patients randomised to MTX started oral medication at 10 mg/week (7.5 mg/week in China and Japan) and were titrated to a maximum of 20 mg/week (15 mg/week in Japan) through week 8, as tolerated.

Safety assessments

Data from patients who received one or more doses of study drug were integrated into five analysis sets (online supplemental table 1). The placebo-controlled analysis set included short-term data from patients who remained on stable doses of their current csDMARDs through week 12 (SELECT-NEXT[4] and SELECT-BEYOND)[5] or week 14 (SELECT-COMPARE).[7] The remaining four analysis sets included longer-term data up to 2.5 years. The MTX-controlled analysis set included pooled data from SELECT-EARLY[8 10] and SELECT-MONOTHERAPY,[6] censored at rescue. The adalimumab-controlled analysis set included patients randomised or rescued to adalimumab in SELECT-COMPARE.[7] Upadacitinib 15 mg data were pooled from all five studies; and upadacitinib 30 mg data were pooled from four studies (all except SELECT-COMPARE).

Adverse events (AEs) were assessed based on Outcome Measures in Rheumatology (OMERACT) criteria. Potentially clinically significant laboratory values (grades 2, 3 or 4) were determined by OMERACT criteria, except for creatine phosphokinase (CPK) and serum creatinine, which were based on the National Cancer Institute's Common Toxicity Criteria v4.03. Potentially clinically significant outliers were based on patient laboratory values meeting the criteria on one or more occasions.

Adverse events of special interest (AESIs) were selected due to their higher prevalence among RA populations, as a customary concern for immunomodulators, or because they were labelled/emerging risks with other JAKis. AEs were identified using the standardised Medical Dictionary for Regulatory Activities (MedDRA) query or company MedDRA query search criteria. A treatment-emergent adverse event (TEAE) was defined as an AE with onset on or after the first dose of study drug and no more than 30 days (70 days for adalimumab) after the last dose of study drug.

An independent external Data Monitoring Committee monitored unblinded clinical trial data. An independent Cardiovascular Adjudication Committee blindly adjudicated all deaths and potential cardiovascular (CV) events, including potential arterial and venous thromboembolic events (VTEs). Major adverse cardiovascular events (MACEs) included CV death, non-fatal myocardial infarction and non-fatal stroke. VTEs included deep vein thrombosis and pulmonary embolism (PE). Active/latent TB events and potential gastrointestinal (GI) perforations were assessed by the sponsor.

Statistical analyses

Baseline characteristics and exposure (last dose date minus first dose date plus 1, 7 and 14 days for upadacitinib, MTX and adalimumab) were summarised descriptively. TEAEs were summarised using the MedDRA version 19.1 system organ class and preferred term.

Exposure-adjusted event rates (EAERs) per 100 patient-years (PY) were summarised as events based on the treatment received at the time of each AE; multiple events occurring in the same patient were included in the numerator. 95% CIs were calculated using the Cochran-Mantel-Haenszel test (adjusted for each study). Exposure-adjusted incidence rates (EAIRs) per 100 PY were summarised as the number of patients with ≥1 event/100 PY (E/100 PY), with exposure calculated up to onset of the first event; 95% CIs were calculated using the exact method for the Poisson mean. Mean changes from baseline in laboratory parameters and vital signs were summarised.

HRs (95% CIs) for upadacitinib versus comparators were calculated using a Cox proportional hazards model including the prognostic factors of the treatment group and baseline covariates. Risk factors for herpes zoster (HZ) in upadacitinib-treated patients were identified using a univariate Cox regression model.

The standardised incidence ratio (SIR) for malignancy excluding non-melanoma skin cancer (NMSC) was calculated using age- and gender-specific malignancy data from the US National Cancer Institute Surveillance and Epidemiology and End Results database, 18 Registry Research Data 2000–2015; 95% CIs were calculated following a Poisson distribution. The standardised mortality ratio (SMR) used the WHO country-specific, age-specific and gender-specific death data for the general population; 95% CIs were calculated using Byar's approximation.

RESULTS

Patients and exposure

Across studies, 3834 patients received one or more doses of upadacitinib (15 mg once daily, n=2630; 30 mg once daily, n=1204)

Table 1 Demographics and baseline disease characteristics

Mean (SD) or n (%), unless specified	PBO pooled, n=1042	MTX pooled, n=530	ADA 40 mg EOW, n=579	UPA all phase III long term: Any UPA 15 mg once daily, n=2630	UPA all phase III long term: Any UPA 30 mg once daily, n=1204
	Short-term data up to 12/14 weeks	Long-term MTX monotherapy Mean exposure: 36 weeks (data censored at rescue)	Long-term ADA Mean exposure: 42 weeks (includes UPA→ADA post-switch)	Long-term UPA (monotherapy or in combination with MTX/other csDMARDs) Mean exposures: 53 weeks (UPA 15 mg) and 59 weeks (UPA 30 mg)	
Female	822 (78.9%)	419 (79.1%)	470 (81.2%)	2102 (79.9%)	948 (78.7%)
Age, years	54.8 (12.2)	54.1 (12.2)	54.1 (11.7)	54.1 (12.1)	55.3 (11.9)
Geographic region					
North America	321 (30.8%)	110 (20.8%)	122 (21.1%)	689 (26.2%)	429 (35.6%)
South/Central America	181 (17.4%)	121 (22.8%)	126 (21.8%)	529 (20.1%)	153 (12.7%)
Western Europe	92 (8.8%)	45 (8.5%)	29 (5.0%)	200 (7.6%)	129 (10.7%)
Eastern Europe	360 (34.5%)	164 (30.9%)	249 (43.0%)	934 (35.5%)	351 (29.2%)
Asia	37 (3.6%)	54 (10.2%)	18 (3.1%)	135 (5.1%)	85 (7.1%)
Other	51 (4.9%)	36 (6.8%)	35 (6.0%)	143 (5.4%)	57 (4.7%)
Time since RA diagnosis, years	9.0 (8.5)	3.9 (6.0)	8.2 (8.0)	7.7 (8.1)	7.0 (8.3)
Median (range)	6.4 (0.3 to 49.8)	1.2 (0.03 to 38.0)	5.5 (0.3 to 51.1)	4.8 (0.04 to 54.2)	3.7 (0.03 to 51.3)
DAS28-CRP	5.8 (0.9)	5.8 (1.0)	5.2 (1.3)	5.3 (1.3)	5.4 (1.2)
CRP, mg/L	16.5 (20.2)	18.5 (20.5)	14.2 (20.5)	17.0 (21.5)	15.9 (19.8)
Concomitant csDMARD at baseline					
MTX alone	914 (87.9%)	NA	576 (99.5%)	1769 (67.3%)	380 (31.6%)
MTX plus other csDMARD	68 (6.5%)	NA	0	103 (3.9%)	81 (6.7%)
csDMARD other than MTX	58 (5.6%)	NA	0	105 (4.0%)	100 (8.3%)
Prior bDMARD use	261 (25.0%)	0	57 (9.8%)	406 (15.4%)	281 (23.3%)
Concomitant steroids	573 (55.0%)	279 (52.6%)	349 (60.3%)*	1446 (55.0%)†	570 (47.3%)†
Seropositive (RF or ACPA)	880 (84.5%)	424 (80.0%)	497 (85.8%)	2237 (85.1%)	948 (78.7%)
Prior history of herpes zoster	58 (5.6%)	20 (3.8%)	22 (3.8%)	110 (4.2%)	87 (7.2%)
Prior history of herpes zoster vaccination	52 (5.1%)	17 (3.2%)	15 (2.6%)	80 (3.0%)	72 (6.0%)
Positive TB test at screening	124 (12.0%)	66 (12.5%)	77 (13.3%)	299 (11.4%)	119 (9.9%)
CV risk factors at baseline					
Medical history of hypertension	425 (40.8%)	203 (38.3%)	248 (42.8%)	1043 (39.7%)	481 (40.0%)
Diabetes mellitus	77 (7.4%)	36 (6.8%)	41 (7.1%)	212 (8.1%)	90 (7.5%)
History of tobacco/nicotine use (current+former)	371 (35.6%)	207 (39.1%)	199 (34.4%)	998 (37.9%)	509 (42.3%)
Elevated LDL-C (≥3.36 mmol/L)	275 (26.6%)	163 (30.9%)	200 (34.5%)	723 (27.5%)	318 (26.5%)
Lowered HDL-C (≤1.55 mmol/L)	594 (57.0%)	301 (56.8%)	283 (48.9%)	1504 (57.2%)	705 (58.6%)
Statin use at baseline	128 (12.3%)	60 (11.3%)	58 (10.0%)	300 (11.4%)	168 (14.0%)

All percentages calculated are on non-missing values.
*Baseline is redefined as start of ADA.
†Baseline is redefined as start of UPA.
ACPA, anti-citrullinated protein antibody; ADA, adalimumab; bDMARD, biologic disease-modifying antirheumatic drug; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CV, cardiovascular; DAS28-CRP, Disease Activity Score for 28 joints-CRP; EOW, every other week; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MTX, methotrexate; NA, not applicable; PBO, placebo; RA, rheumatoid arthritis; RF, rheumatoid factor; TB, tuberculosis; UPA, upadacitinib.

for a mean duration of approximately 1 year and 4020.1 PY of exposure. Sixty-six per cent (15 mg, 61%; 30 mg, 75%) and 4% (15 mg, 4%; 30 mg, 5%) of patients received ≥48 and ≥96 weeks of upadacitinib treatment, respectively, with a maximum exposure of 2.5 years. Most patients were female and had been diagnosed with RA for a median of 1.2–6.4 years (table 1).

Overview of AEs

The most common TEAEs (≥10 E/100 PY) with upadacitinib were upper respiratory tract infection, nasopharyngitis, urinary tract infection and, for upadacitinib 30 mg only, increased blood CPK (online supplemental table S2). The EAER of serious TEAEs (SAEs) with upadacitinib 15 mg was comparable with adalimumab but higher than MTX (table 2). SAE rates were higher with upadacitinib 30 versus 15 mg. Pneumonia was the most common SAE reported with both upadacitinib doses.

There were 22 treatment-emergent deaths reported with upadacitinib (n=11 each for upadacitinib 15 and 30 mg): 10 adjudicated CV deaths and 12 non-CV deaths (online supplemental material). Compared with the general population, the SMR for treatment-emergent deaths in the upadacitinib groups was 0.58 (95% CI: 0.37 to 0.85). There were two, one and four deaths among the placebo, MTX and adalimumab groups, respectively.

Rates of AEs, AESIs and laboratory abnormalities were generally similar between the upadacitinib monotherapy population (online supplemental table S3) and the overall upadacitinib population.

Table 2 TEAEs in patients with upadacitinib compared with placebo and active controls*

				UPA all phase III long term	
	PBO pooled, n=1042	MTX pooled, n=530	ADA 40 mg EOW, n=579	UPA 15 mg once daily, n=2630	UPA 30 mg once daily, n=1204
E/100 PY (95% CI), unless stated otherwise	Short-term data up to 12/14 weeks	Long-term MTX monotherapy Mean exposure: 36 weeks (data censored at rescue)	Long-term ADA Mean exposure: 42 weeks (includes UPA→ADA post-switch)	Long-term UPA (monotherapy or in combination with MTX/other csDMARDs) Mean exposures: 53 weeks (UPA 15 mg) and 59 weeks (UPA 30 mg)	
Total PY of exposure, years	256.8	368.7	467.8	2655.1	1365.0
Median exposure, days (range)	97.0 (1 to 128)	179.5 (7 to 865)	257.0 (14 to 894)	375.0 (2 to 898)	431.0 (1 to 857)
Any AE	447.4 (421.9 to 474.1)	321.7 (303.6 to 340.5)	294.8 (279.4 to 310.8)	295.7 (289.2 to 302.3)	368.7 (358.6 to 379.0)
Any SAE	9.3 (6.0 to 13.9)	11.9 (8.7 to 16.0)	15.6 (12.2 to 19.6)	15.0 (13.6 to 16.6)	21.3 (18.9 to 23.9)
Any AE leading to discontinuation	10.9 (7.2 to 15.8)	9.5 (6.6 to 13.2)	11.1 (8.3 to 14.6)	8.4 (7.4 to 9.6)	13.3 (11.5 to 15.4)
Deaths†	0.8 (0.1 to 2.8)	0.3 (0.0 to 1.5)	0.9 (0.2 to 2.2)	0.5 (0.3 to 0.8)	1.0 (0.5 to 1.7)

*Patients who switched from PBO, ADA or MTX to UPA were included in the UPA analysis set from the start of UPA treatment, while those who switched from UPA to ADA were included in the ADA dataset from the start of ADA. There was no switch between UPA doses in any study.
†Deaths included non-treatment-emergent deaths that occurred >30 days after the last dose of study drug (UPA 15 mg, 3; UPA 30 mg, 3; and ADA, 1). When non-treatment deaths are included, the exposures are 2925.0 PY for UPA 15 mg and 1410.3 PY for UPA 30 mg.
ADA, adalimumab; AE, adverse event; csDMARD, conventional synthetic disease-modifying antirheumatic drug; EOW, every other week; MTX, methotrexate; PBO, placebo; E/100 PY, event per 100 patient-years; SAE, serious adverse event; TEAE, treatment-emergent adverse event; UPA, upadacitinib.

AEs of special interest

EAERs (figure 1) and EAIRs (online supplemental figure S1) of AESIs are summarised by treatment.

Serious infection EAERs were similar between the upadacitinib 15 mg and adalimumab groups, both of which were higher versus MTX; the EAER was higher for upadacitinib 30 mg versus 15 mg (figure 1). Cox regression analyses showed that upadacitinib 30 mg, but not 15 mg, was associated with an increased risk of serious infections versus placebo and adalimumab (online supplemental table S4). The serious infection EAER in the upadacitinib 15 mg group did not increase over time, although some increases were observed in the upadacitinib 30 mg group between 6 and 12 months on treatment (online supplemental figure S2).

EAERs of opportunistic infections were similar across treatment groups, with the highest rate observed in the upadacitinib 30 mg group (figure 1). The majority of opportunistic infections observed with upadacitinib were mucosal candida infections. There were three events (0.1 E/100 PY) of serious opportunistic infections among patients receiving upadacitinib 15 mg

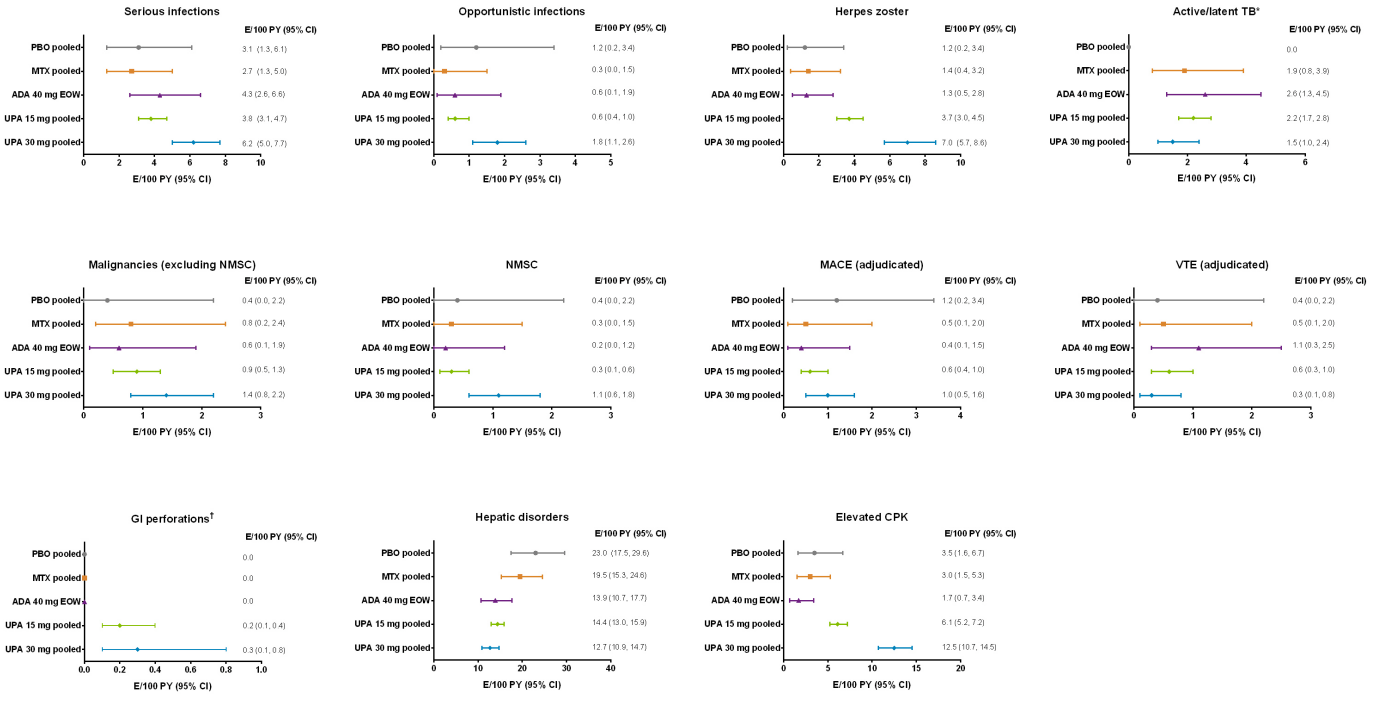

Figure 1 Event rates for AESIs. Additional details on AESIs are included in the online supplemental material. Incidence rates are shown in online supplemental figure S1.
*EAERs for active TB in E/100 PY: PBO, 0; MTX, 0; ADA, 0.2; UPA 15 mg, 0.1; UPA 30 mg, 0.1.
†Including all potential GI perforations; EAERs for confirmed GI perforations in E/100 PY: PBO, 0; MTX, 0; ADA, 0; UPA 15 mg, <0.1; UPA 30 mg, 0.3.
ADA, adalimumab; AESI, adverse event of special interest; CPK, creatine phosphokinase; E/100 PY, event per 100 patient-years; EAER, exposure-adjusted event rate; EOW, every other week; GI, gastrointestinal; MACE, major adverse cardiovascular event; MTX, methotrexate; NMSC, non-melanoma skin cancer; PBO, placebo; TB, tuberculosis; UPA, upadacitinib; VTE, venous thromboembolic event.

(bronchopulmonary aspergillosis, HZ disseminated and cryptococcal pneumonia) and none in the upadacitinib 30 mg group.

EAERs of HZ were greater with upadacitinib versus placebo, adalimumab and MTX (figure 1). Upadacitinib was associated with a higher risk of HZ than comparator groups (online supplemental table S4). Most HZ cases in the upadacitinib 15 and 30 mg groups were non-serious (96% and 93%) and involved a single dermatome (74% and 76%). There was one serious event of disseminated HZ, two non-serious ophthalmic HZ events and five non-serious postherpetic neuralgia events with upadacitinib 15 mg; and one non-serious event of disseminated HZ, one serious ophthalmic HZ event and six non-serious postherpetic neuralgia events with upadacitinib 30 mg. Both events of disseminated HZ had cutaneous involvement only. No deaths occurred as a result of HZ. Among patients treated with upadacitinib 15 mg, those who were Asian, aged ≥50 years or had a history of HZ had a higher risk of HZ (online supplemental table S5). At baseline, 2.6%–6.0% of patients across treatment groups reported a history of HZ vaccination. However, there was no evidence that prior HZ vaccination decreased HZ risk in upadacitinib-treated patients in this analysis.

EAERs of active/latent TB were similar between the upadacitinib, adalimumab and MTX groups; and no active/latent TB was reported in the placebo group (figure 1). Six patients had non-fatal active TB: three with upadacitinib 15 mg, two with 30 mg and one with adalimumab (online supplemental material). The overall rate of active TB was 0.1 E/100 PY (five events; exposure: 4020.1 PY) with upadacitinib.

The EAERs of NMSC and malignancies excluding NMSC were generally comparable across treatment groups, with the highest rates observed with upadacitinib 30 mg (figure 1). The age- and gender-adjusted SIR (95% CI) for non-NMSC malignancies with upadacitinib 15 mg, 1.05 (0.66 to 1.60), was within the expected range for the general US population. The observed types of non-NMSC malignancies reflected those expected in patients with RA (online supplemental material).

Nine potential GI perforations were identified with upadacitinib, occurring between 73 and 341 days after treatment initiation, and no events with placebo, MTX or adalimumab. Two of the five events (<0.1 E/100 PY) in the upadacitinib 15 mg group and all four events (0.3 E/100 PY) in the 30 mg group were assessed as GI perforations by the sponsor (online supplemental material).

EAERs of adjudicated MACE were comparable across treatment groups and did not increase over time with upadacitinib treatment (figure 1; online supplemental table S6; online supplemental figure S3). Dose-dependent increases in total cholesterol and low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were observed with upadacitinib treatment. LDL-C/HDL-C ratios remained constant throughout, with no apparent association of LDL-C levels with occurrence of MACE.

EAERs of adjudicated VTE were comparable across treatment groups (figure 1; online supplemental table S6). There was one fatal PE in the upadacitinib 15 mg group in a woman aged 55 years who developed PE after prolonged driving. There was no evidence of a dose relationship in VTE rate with upadacitinib nor a pattern of time-to-VTE-onset (23–1127 days of upadacitinib treatment). VTE in upadacitinib groups did not appear to be associated with increased platelet count (online supplemental material). There were two events of arterial thrombosis in the upadacitinib 30 mg group and none in the 15 mg group (online supplemental material).

Laboratory abnormalities

Slight decreases in haemoglobin were observed with upadacitinib 30 mg but not 15 mg (mean change from baseline at week 12 of −3.9 and −0.5 g/L, respectively, vs −1.5 g/L with placebo; online supplemental figure S4). The proportion of patients with grade 3/4 decreases in haemoglobin were generally similar between MTX and upadacitinib 15 mg and were highest with upadacitinib 30 mg (table 3).

The proportions of patients with grade 3 decreases in neutrophils were similar across treatment groups, with a greater proportion with upadacitinib 30 mg. Grade 4 decreases in neutrophils were rare. Mean lymphocyte counts increased over the first 36 weeks of treatment, followed by slight decreases afterwards. The proportions of patients with grade 3 decreases in lymphocytes were comparable between MTX and both upadacitinib groups and were higher than those for placebo and adalimumab. Grade 4 decreases were most frequent in the upadacitinib 30 mg group. There was no clear association between infectious events, including HZ, and decreased neutrophil or lymphocyte counts.

The proportions of patients experiencing grade 3 elevations in transaminases were similar between MTX and both upadacitinib groups and were greater than those in the placebo and adalimumab groups. Grade 4 increases occurred in few patients across treatment groups. Most transaminase elevations did not result in treatment discontinuation and resolved or were resolving regardless of whether upadacitinib was discontinued. There were no cases of probable drug-induced liver injury attributable to upadacitinib.

CPK elevations, including grade 3/4 increases, were more frequent with upadacitinib versus placebo, MTX or adalimumab (figure 1; table 3; online supplemental table S4). The greatest rise in CPK levels occurred for both upadacitinib doses at week 4 (50.1 and 74.3 U/L with 15 and 30 mg), after which CPK levels rose less markedly before plateauing around weeks 36 to 48. CPK elevations were typically asymptomatic; few led to discontinuation (two with upadacitinib 15 mg; three with 30 mg). One patient who received upadacitinib 30 mg had a serious event of rhabdomyolysis, with an alternative aetiology of influenza, which resulted in treatment interruption.

DISCUSSION

Based on an integrated analysis of the SELECT clinical trial programme, the overall safety profile of upadacitinib appeared comparable with other JAKis,[11–13] with no new or unexpected safety risks identified.

Treatment with upadacitinib was associated with an increased risk of HZ and CPK elevations versus placebo, MTX and adalimumab according to Cox regression analyses. Rates of deaths and malignancies with upadacitinib appeared consistent with expected rates from the general population. The serious infection rate observed with upadacitinib 15 mg was similar to that reported for other marketed RA therapies.[14–16] The rates of serious infections, HZ, CPK elevations and neutropaenia were higher for the unapproved upadacitinib 30 mg dose compared with the approved upadacitinib 15 mg dose.

Consistent with previously reported data for other JAKis,[11 12 17 18] HZ rates were higher with upadacitinib versus placebo, MTX and adalimumab, and higher HZ rates among upadacitinib were observed in older patients and those in Asia. The majority of HZ cases reported with upadacitinib were non-serious and involved a single dermatome. Few patients enrolled in the SELECT programme received HZ vaccination (limited to Zostavax) prior to randomisation. Information about the impact

Table 3 Proportion of patients with potentially clinically significant haematological and clinical chemistry values

				UPA all phase III long term	
	PBO pooled, n=1042	MTX pooled, n=530	ADA 40 mg EOW, n=579	Any UPA 15 mg once daily, n=2630	Any UPA 30 mg once daily, n=1204
n/N Obs (%)	Short-term data up to 12/14 weeks	Long-term MTX monotherapy Mean exposure: 36 weeks (data censored at rescue)	Long-term ADA Mean exposure: 42 weeks (includes UPA→ADA post-switch)	Long-term UPA (monotherapy or in combination with MTX/other csDMARDs) Mean exposures: 53 weeks (UPA 15 mg) and 59 weeks (UPA 30 mg)	
Haemoglobin (g/L)					
Grade 3 (70 to <80 or decreased 21 to <30)	23/1036 (2.2)	28/526 (5.3)	18/576 (3.1)	150/2622 (5.7)	133/1193 (11.1)
Grade 4 (<70 or decreased ≥30)	8/1036 (0.8)	12/526 (2.3)	6/576 (1.0)	39/2622 (1.5)	49/1193 (4.1)
Platelets ($\times 10^9$/L)					
Grade 3 (20 to <50)	0/1032	0/525	0/576	1/2619 (<0.1)	1/1192 (<0.1)
Grade 4 (<20)	0/1032	0/525	0/576	1/2619 (<0.1)	1/1192 (<0.1)
Neutrophils ($\times 10^9$/L)					
Grade 3 (0.5 to <1.0)	1/1036 (<0.1)	2/526 (0.4)	2/576 (0.3)	22/2622 (0.8)	28/1192 (2.3)
Grade 4 (<0.5)	0/1036	0/526	1/576 (0.2)	7/2622 (0.3)	2/1192 (0.2)
Lymphocytes ($\times 10^9$/L)					
Grade 3 (0.5 to <1.0)	119/1036 (11.5)	79/526 (15.0)	44/576 (7.6)	451/2622 (17.2)	250/1192 (21.0)
Grade 4 (<0.5)	7/1036 (0.7)	5/526 (1.0)	2/576 (0.3)	30/2622 (1.1)	29/1192 (2.4)
Leucocytes ($\times 10^9$/L)					
Grade 3 (1.0 to <2.0)	0/1036	0/526	1/576 (0.2)	9/2622 (0.3)	7/1193 (0.6)
Grade 4 (<1.0)	0/1036	0/526	0/576	0/2622	2/1193 (0.2)
ALT (U/L)					
Grade 3 (3.0 to <8.0× ULN)	13/1037 (1.3)	23/527 (4.4)	9/577 (1.6)	76/2620 (2.9)	37/1195 (3.1)
Grade 4 (>8.0× ULN)	2/1037 (0.2)	5/527 (0.9)	3/577 (0.5)	11/2620 (0.4)	6/1195 (0.5)
AST (U/L)					
Grade 3 (3.0 to <8.0× ULN)	6/1036 (0.6)	13/527 (2.5)	6/577 (1.0)	46/2620 (1.8)	17/1195 (1.4)
Grade 4 (>8.0× ULN)	1/1036 (<0.1)	1/527 (0.2)	4/577 (0.7)	7/2620 (0.3)	5/1195 (0.4)
CPK (U/L)					
Grade 3 (>5.0 to 10.0× ULN)	3/1037 (0.3)	2/527 (0.4)	1/577 (0.2)	38/2620 (1.5)	22/1196 (1.8)
Grade 4 (>10.0× ULN)	0/1037	0/527	1/577 (0.2)	10/2620 (0.4)	11/1196 (0.9)

N Obs indicates the number of patients with baseline and post-baseline values for the respective parameters.
ADA, adalimumab; ALT, alanine transaminase; AST, aspartate transaminase; CPK, creatine phosphokinase; csDMARD, conventional synthetic disease-modifying antirheumatic drug; EOW, every other week; MTX, methotrexate; PBO, placebo; ULN, upper limit of normal; UPA, upadacitinib.

of newer inactivated HZ vaccines (although not yet available worldwide) on the risk of HZ among patients receiving upadacitinib and other JAKis is necessary to inform clinical practice.

VTE is an emerging AESI among patients receiving JAKis,[2 3 19–22] but longer-term data are needed to characterise the risk of VTE with JAKi therapy. Patients with RA are at increased risk of VTE (incidence rates 0.3–0.8/100 PY)[23 24] compared with the general population, with a 2.4-fold increased rate.[25] In this analysis, the rates of adjudicated VTE were similar across both doses of upadacitinib, placebo, adalimumab and MTX, with no evidence of a dose relationship with upadacitinib treatment. In view of the increased risk of VTE and underlying VTE risk factors among patients with RA, patients should be promptly evaluated for signs and symptoms of possible thrombosis and appropriately treated during JAKi therapy.

Patients with RA receiving anti-interleukin 6 (IL-6) receptor therapy are at increased risk of GI perforation, with one study reporting a lower GI perforation rate of 0.27 E/100 PY with the IL-6 receptor inhibitor tocilizumab.[26 27] Although JAKis also inhibit IL-6 signalling,[28 29] GI perforations with upadacitinib 15 mg (0.08 E/100 PY) were observed at similar rates to tumour necrosis factor inhibitors (0.05 E/100 PY) and other JAKis (0.04–0.10 E/100 PY).[13 27 29] Upadacitinib 30 mg had higher rates of GI perforations (0.29 E/100 PY), although this was based on a limited number of events.

Decreases in haemoglobin and neutrophils, and increases in transaminase and CPK, observed with upadacitinib, were consistent with laboratory changes observed with other JAKis.[12 13] In vitro data suggest that JAKi-associated increase in CPK may represent restoration of myoblast differentiation.[30] Most laboratory abnormalities were resolved, and most patients experiencing them were able to remain on the study drug. Although engineered for increased JAK1 selectivity,[1] the effects of upadacitinib on parameters such as haemoglobin suggest that upadacitinib (particularly the unapproved 30 mg dose) may have some effects on JAK2. However, maximal efficacy of upadacitinib was achieved at the 15 mg dose with comparable safety to the approved doses of other JAKis, with no additional efficacy benefit observed with the 30 mg dose.[2 3 31] In contrast, the use of less selective JAKis at higher doses is associated with improved efficacy but is limited due to increased safety risks.[21 32–35]

The limited placebo exposure time prevented the placebo-controlled analysis of longer-term safety. However, longer-term controlled data versus MTX monotherapy (SELECT-EARLY) and adalimumab (SELECT-COMPARE) offer the opportunity to compare the safety profile of upadacitinib to other RA therapies.

As patients were not allowed to change upadacitinib doses, this allowed an unadulterated comparison of the safety profile of the upadacitinib 15 and 30 mg doses. While upadacitinib monotherapy was well tolerated with comparable safety to the overall upadacitinib population, further analyses are required to identify any differences in long-term safety between upadacitinib administered as monotherapy and in combination with csDMARDs. Despite a robust trial programme, the data remain limited by exposures to date, with ongoing monitoring still underway. As these data are from RCTs with specific eligibility criteria and clear follow-up protocols, this may limit the generalisability of these results to clinical practice. Monitoring by a specialist is recommended for oral treatments such as upadacitinib, as with all antirheumatic therapies.

Based on integrated data from five phase III RCTs, with 3834 patients and 4020.1 PY of exposure, no new safety risks emerged with upadacitinib compared with other approved JAKis. These results support an acceptable safety profile of upadacitinib 15 mg once daily for the treatment of moderately to severely active RA. Follow-up of patients receiving upadacitinib will continue in long-term extensions of clinical trials and postmarketing studies.

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Acknowledgements AbbVie funded this study and participated in the study design, research, analysis, data collection, interpretation of data, reviewing and approval of the publication. All authors had access to relevant data and participated in the drafting, review and approval of this publication. No honoraria or payments were made for authorship. AbbVie thank Tim Shaw, Senior Scientific Director/RA Lead, Global Medical Affairs, AbbVie, and Ruta Sawant, PhD, Manager, Health Economics & Outcomes Research, AbbVie, for their valuable input. Medical writing support was provided by Siddharth Mukherjee, PhD, CMPP of AbbVie and Hilary Wong, PhD, of 2 the Nth (Cheshire, UK) and was funded by AbbVie.

Contributors SBC, LB, GRB and CAFZ were involved in the acquisition of data. All authors were involved in the analysis and interpretation of the data, drafting the article and revising it for critically important intellectual content, and reviewing and approving the final version of the manuscript.

Funding AbbVie funded the study and had a role in the study design, data collection, data analysis, data interpretation and writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Competing interests SBC received grants and consultation fees from Amgen, AbbVie, Boehringer Ingelheim, Gilead, Pfizer, Roche and Sandoz. RFvV received grants from AbbVie, Arthrogen, BMS, GSK, Lilly, Pfizer and UCB and personal fees from AbbVie, AstraZeneca, Biotest, BMS, Celgene, GSK, Janssen, Lilly, Medac, Merck, Novartis, Pfizer, Roche and UCB. KLW received consulting fees and research grants from AbbVie, BMS, Lilly, Pfizer, Roche and UCB. CAFZ received research grants from Amgen, GSK, Lilly, Merck, Novartis, Pfizer, Sanofi-Aventis, Servier and Roche, participated on advisory boards and speaker's bureau for Merck, Pfizer, and Sanofi-Aventis and served as a consultant for Pfizer. YT received speaking fees and/or honoraria from AbbVie, Asahi-Kasei, Astellas, BMS, Chugai, Daiichi-Sankyo, Eisai, Gilead, GSK, Janssen, Lilly, Mitsubishi-Tanabe, Novartis, Pfizer, Sanofi and YL Biologics and received research grants from Asahi-Kasei, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi-Tanabe, Takeda and UCB. LB received speaking fees, consulting fees and research grants from AbbVie, Amgen, BMS, Celgene, Gilead, Janssen, Lilly, Merck, Novartis, Pfizer, Roche, Sanofi and UCB. YZ, NK, BH and JVE are full-time employees of AbbVie and may hold AbbVie stock or stock options. GRB received speaking or consulting fees from AbbVie, Gilead, Janssen, Lilly, MSD, Pfizer, Roche and UCB.

Patient consent for publication Not required.

Ethics approval Studies were conducted in compliance with the Declaration of Helsinki, International Conference on Harmonisation of Technical Regulations for Pharmaceuticals for Human Use guidelines, and applicable local country regulations. All study-related documents were approved by independent ethics committees and institutional review boards. All patients provided written, informed consent.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymised, individual and trial-level data (analysis datasets), as well as other information (eg, protocols and Clinical Study Reports), provided the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research and will be provided following review and approval of a research proposal and statistical analysis plan and execution of a Data Sharing Agreement. Data requests can be submitted at any time, and the data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit https://www.abbvie.com/ourscience/clinicaltrials/clinicaltrialsdataandinformationsharing/dataandinformationsharingwithqualifiedresearchers.html.

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Correction: *Safety profile of upadacitinib in rheumatoid arthritis: integrated analysis from the SELECT phase III clinical programme*

Cohen SB, van Vollenhoven RF, Winthrop KL, *et al*. Safety profile of upadacitinib in rheumatoid arthritis: integrated analysis from the SELECT phase III clinical programme. *Ann of Rheum Dis* 2021;80:304–1. doi:10.1136/annrheumdis-2020-218510.

The link for reference 2 should be: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211675s001lbl.pdf

The correct author name for reference 21 should be European Medicines Agency.

The correct citation details for reference 25 should be Arthritis Care Res 2013; 65:1600-7.

Ann Rheum Dis 2021;**80**:e83. doi:10.1136/annrheumdis-2020-218510corr1

SUPPLEMENTARY MATERIAL

Exclusion criteria

- Cerebrovascular accident or myocardial infarction within the past 6 months
- Malignancy, except for successfully treated non-melanoma skin cancer (NMSC) or localised carcinoma *in situ* of the cervix
- Gastrointestinal (GI) perforation or diverticulitis
- Active infection requiring treatment with parenteral anti-infectives within 30 days, or oral anti-infectives within 14 days, prior to the first dose of study drug
- Serum aspartate transaminase or alanine transaminase >2× the upper limit of normal
- Estimated glomerular filtration rate <40 mL/min/1.73 m^2
- Absolute neutrophil count <1500/µL
- Absolute lymphocyte count <850/µL (<800/µL in SELECT-EARLY)[8]
- Haemoglobin <100 g/L

Deaths

The causes of the 10 treatment-emergent cardiovascular (CV) deaths with upadacitinib were cardiac failure, cardiac arrest, myocardial infarction, haemorrhagic stroke, pulmonary embolism (PE) or sudden cardiac deaths. The causes of the 12 treatment-emergent non-CV deaths with upadacitinib included infections (pneumonia, sepsis, meningitis, peritonitis), cancer, other non-CV causes or undetermined/unknown causes. There were six non-treatment-emergent deaths due to cancer, CV

events, or undetermined/unknown causes that occurred >30 days after the last dose of study drug (n=3 each for upadacitinib 15 and 30 mg).

Additional details on adverse events of special interest (AESIs)

Tuberculosis (TB)

9.9–11.4% of patients in the upadacitinib groups had positive TB tests at baseline. For patients with a negative TB test result at screening, an annual TB retest was performed. Among the five patients (<0.1 events per 100 patient-years [E/100 PY]) on upadacitinib with active TB, three had latent TB at screening. Of these, one completed the recommended ≥6 months of isoniazid therapy, one was treated with isoniazid for 3 months but did not complete the full 6-month treatment for unknown reasons, and one was treated with isoniazid but did not refill their isoniazid prescription after running out on day 10. Two of the five patients manifested signs and symptoms of extrapulmonary TB: female genital tract and peritoneum (one patient receiving upadacitinib 15 mg) and mediastinal lymph nodes (one patient receiving upadacitinib 30 mg). One patient with active TB lived in a high-TB burden country (South Africa), and another was residing with household members with a history of TB. The patient on adalimumab with active TB (pulmonary TB) had a negative TB test at screening. The study drug was discontinued for all patients with active TB.

Malignancies

There were no notable patterns of the types of malignancies observed. The most common malignancies (≥0.1 E/100 PY) were basal cell carcinoma (0.2 E/100 PY), squamous cell carcinoma of the skin (0.1 E/100 PY), and invasive ductal breast carcinoma (0.1 E/100 PY) in the upadacitinib 15 mg group and squamous cell carcinoma of the skin (0.6 E/100 PY), basal cell carcinoma (0.4 E/100 PY), adenocarcinoma of the colon (0.1 E/100 PY), malignant melanoma (0.1 E/100 PY), and prostate cancer (0.1 E/100 PY) in the upadacitinib 30 mg group. The EAER of lymphoma was <0.1/100 PY in both upadacitinib groups. Per

study protocol, study drug was discontinued in all patients who developed malignancies (except NMSC and carcinoma *in situ* of the cervix) during the study.

GI perforations

Two events with upadacitinib 15 mg (one perforated appendix associated with acute appendicitis on day 289; one anal fistula requiring surgical repair on day 168) and four events with upadacitinib 30 mg (three events of intestinal perforation on days 77, 133 and 341; one event of peritonitis on day 73) were determined to be true GI perforations based on sponsor medical review.

Venous thromboembolic events (VTE)

Three patients who experienced VTE while receiving upadacitinib 15 mg had a history of VTE. Four patients with PE were on concomitant hormonal therapy or contraception: two with upadacitinib 15 mg and one each with upadacitinib 30 mg and placebo. Slight decreases in mean platelet count from baseline were observed after 4 weeks of upadacitinib therapy, and values returned to baseline by week 60. There were no adjudicated VTE that occurred in patients with a platelet value of $>600 \times 10^9$/L at the time of the event.

Arterial thrombosis

Two patients experienced arterial thrombosis events in this analysis, neither was assessed as related to the study drug. Both of these events were non-cardiac and non-neurologic and therefore not considered to be CV events per protocol. One patient with a history of vascular stents (femoral and bypass graft) developed an obliterating arteriopathy in the common iliac artery of the lower limb after receiving upadacitinib 30 mg for 92 days. Upadacitinib treatment was temporarily interrupted while the patient was treated for the arteriopathy, which resolved. The other patient, who had a history of peripheral vascular disease developed a left popliteal artery aneurysm and peripheral artery thrombosis after receiving upadacitinib 30 mg for 281 days. The patient underwent resection of the popliteal artery aneurysm with implantation of a vascular graft and the peripheral artery thrombosis was reported

following surgery later that day. The patient then underwent surgical repair for the thrombosis and recovered.

Limitations of statistical comparisons between upadacitinib and comparators

Any statistical comparisons between upadacitinib and comparator arms should be interpreted with caution for the following reasons:

- Many of the AESIs evaluated were rare events and the limited sample size or exposure may bias the result
- Upadacitinib data may be overrepresented due to differences in sample size and exposure time between upadacitinib and comparator arms
- Upadacitinib is currently only approved in patients with rheumatoid arthritis and an inadequate response to conventional synthetic disease-modifying antirheumatic drugs (csDMARD), therefore data suggesting an increased risk with upadacitinib versus placebo (with background csDMARDs) or methotrexate should be treated with caution

Supplementary Table S1 Characteristics of the treatment arms

	SELECT-EARLY (NCT02706873)	SELECT-NEXT (NCT02675426)	SELECT-COMPARE (NCT02629159)	SELECT-MONOTHERAPY (NCT02706951)	SELECT-BEYOND (NCT02706847)
Patients	MTX-naïve	csDMARD-IR	MTX-IR	MTX-IR	bDMARD-IR
Comparators	MTX	PBO	PBO, ADA	PBO continued prior MTX	PBO
Background treatment	NA	csDMARDs	MTX	NA	csDMARDs
Data	Week 48 and beyond through cut-off date	Week 60 and beyond through cut-off date	Week 48 and beyond through cut-off date	Week 48 and beyond through cut-off date	Week 60 and through cut-off date
Cut-off date	16 August 2018	22 March 2018	6 July 2018	25 May 2018	16 April 2018
Treatment arm					
Description					
PBO pooled					
All phase 3 patients exposed to PBO control (short-term)		✓	✓		✓

MTX pooled					
All phase 3 patients exposed to MTX monotherapy; data censored at rescue	✓			✓	
ADA 40 mg EOW					
All phase 3 patients exposed to ADA; includes UPA → ADA post-switch			✓		
UPA 15 mg QD pooled					
All phase 3 patients exposed to UPA 15 mg +/− csDMARDs	✓	✓	✓	✓	✓
UPA 30 mg QD pooled					
All phase 3 patients exposed to UPA 30 mg +/− csDMARDs	✓	✓		✓	✓

ADA, adalimumab; bDMARD, biologic disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; EOW, every other week; IR, inadequate response; MTX, methotrexate; NA, not applicable; PBO, placebo; QD, once daily; UPA, upadacitinib.

Supplementary Table S2 TEAEs occurring in ≥3.0 E/100 PY of patients in any treatment group by decreasing frequency in upadacitinib 15 mg group

	PBO pooled n=1042 PY=256.8	MTX pooled n=530 PY=368.7	ADA 40 mg EOW n=579 PY=467.8	UPA all phase 3 long-term	
				Any UPA 15 mg QD n=2630 PY=2655.1	Any UPA 30 mg QD n=1204 PY=1365.0
MedDRA 19.1 Preferred Term, Events (E/100 PY)	Short-term data up to 12/14 weeks	Long-term MTX monotherapy Mean exposure: 36 weeks (data censored at rescue)	Long-term ADA Mean exposure: 42 weeks (includes UPA→ADA post-switch)	Long-term UPA (monotherapy or in combination with MTX/other csDMARDs) Mean exposures: 53 weeks (UPA 15 mg) and 59 weeks (UPA 30 mg)	
Upper respiratory tract infection	40 (15.6)	42 (11.4)	33 (7.1)	357 (13.4)	205 (15.0)
Nasopharyngitis	35 (13.6)	44 (11.9)	32 (6.8)	283 (10.7)	154 (11.3)
Urinary tract infection	36 (14.0)	39 (10.6)	45 (9.6)	268 (10.1)	187 (13.7)
Bronchitis	21 (8.2)	26 (7.1)	30 (6.4)	183 (6.9)	97 (7.1)
ALT increased	28 (10.9)	30 (8.1)	29 (6.2)	165 (6.2)	78 (5.7)
Blood CPK increased	9 (3.5)	--	--	163 (6.1)	170 (12.5)
Hypertension	22 (8.6)	22 (6.0)	23 (4.9)	146 (5.5)	70 (5.1)
Worsening rheumatoid arthritis	39 (15.2)	38 (10.3)	36 (7.7)	131 (4.9)	86 (6.3)

AST increased	21 (8.2)	23 (6.2)	20 (4.3)	126 (4.7)	55 (4.0)
Nausea	24 (9.3)	49 (13.3)	--	109 (4.1)	52 (3.8)
Cough	10 (3.9)	--	16 (3.4)	103 (3.9)	56 (4.1)
Diarrhoea	28 (10.9)	13 (3.5)	24 (5.1)	95 (3.6)	48 (3.5)
Headache	40 (15.6)	--	21 (4.5)	91 (3.4)	65 (4.8)
Sinusitis	--	18 (4.9)	16 (3.4)	91 (3.4)	--
Herpes zoster	--	--	--	89 (3.4)	86 (6.3)
Gastroenteritis	--	--	--	84 (3.2)	46 (3.4)
Anaemia	17 (6.6)	--	--	83 (3.1)	45 (3.3)
Influenza-like illness	--	12 (3.3)	--	--	44 (3.2)
Influenza	--	--	--	--	46 (3.4)
Pneumonia	--	--	--	--	44 (3.2)
Neutropenia	--	--	15 (3.2)	--	74 (5.4)
Weight increased	--	--	--	--	42 (3.1)
Rash	--	13 (3.5)	--	--	55 (4.0)

Leucopenia	--	17 (4.6)	--	--	53 (3.9)
Oral herpes	--	--	--	--	42 (3.1)
Back pain	14 (5.5)	--	--	--	--
Lymphopenia	13 (5.1)	16 (4.3)	--	--	--
Arthralgia	12 (4.7)	--	19 (4.1)	--	--
Fatigue	12 (4.7)	--	--	--	--
Gastritis	11 (4.3)	--	--	--	--
Upper abdominal pain	10 (3.9)	--	--	--	--
Dizziness	9 (3.5)	--	--	--	--
Contusion	8 (3.1)	--	--	--	--
Haematuria	8 (3.1)	--	--	--	--
Insomnia	8 (3.1)	--	--	--	--
Muscle spasms	8 (3.1)	--	--	--	--
Pharyngitis	8 (3.1)	15 (4.1)	--	--	--
Vomiting	8 (3.1)	--	--	--	--

Dyspepsia	--	16 (4.3)	--	--	--
Injection-site reaction	--	--	28 (6.0)	--	--
Injection-site rash	--	--	18 (3.8)	--	--

--, indicates TEAEs occurring <3.0 E/100 PY in that particular treatment group.

ADA, adalimumab; ALT, alanine transaminase; AST, aspartate transaminase; CPK, creatine phosphokinase; csDMARD, conventional synthetic disease-modifying antirheumatic drug; E/100 PY, event per 100 patient-years; EOW, every other week; MedDRA, Medical Dictionary for Regulatory Activities; MTX, methotrexate; PBO, placebo; PY, patient year; QD, once daily; TEAE, treatment-emergent adverse event; UPA, upadacitinib.

Supplementary Table S3 TEAEs and laboratory abnormalities in patients receiving upadacitinib monotherapy*

	UPA monotherapy all phase 3 long-term	
	UPA 15 mg QD monotherapy **n=635** **PY=636.0**	**UPA 30 mg QD monotherapy** **n=625** **PY=647.4**
TEAEs, E/100 PY		
Any AE	1914 (300.9)	2195 (339.0)
Any SAE	103 (16.2)	105 (16.2)
Any AE leading to discontinuation	66 (10.4)	66 (10.2)
Deaths	4 (0.6)	7 (1.1)
AESIs, E/100 PY		
Serious infections	28 (4.4)	28 (4.3)
Opportunistic infections	4 (0.6)	12 (1.9)
Herpes zoster	31 (4.9)	41 (6.3)

Active/latent TB	16 (2.5)	16 (2.5)
Malignancies (excluding NMSC)	9 (1.4)	6 (0.9)
NMSC	1 (0.2)	1 (0.2)
Hepatic disorders	82 (12.9)	92 (14.2)
GI perforations	1 (0.2)	3 (0.5)
MACE (adjudicated)	6 (0.9)	9 (1.4)
VTE (adjudicated)	4 (0.6)	1 (0.2)
Elevated CPK	55 (8.6)	121 (18.7)
Potentially clinically significant laboratory values, n/N Obs (%)		
Haemoglobin (g/L)		
Grade 3 (70 to <80 or decreased 21 to <30)	37/621 (6.0)	64/618 (10.4)
Grade 4 (<70 or decreased ≥30)	6/621 (1.0)	19/618 (3.1)
Platelets ($\times 10^9$/L)		
Grade 3 (20 to <50)	0/620	0/617
Grade 4 (<20)	0/620	1/617 (0.2)

Neutrophils (×10^9/L)		
Grade 3 (0.5 to <1.0)	3/621 (0.5)	11/617 (1.8)
Grade 4 (<0.5)	0/621	2/617 (0.3)
Lymphocytes (×10^9/L)		
Grade 3 (0.5 to <1.0)	74/621 (11.9)	105/617 (17.0)
Grade 4 (<0.5)	2/621 (0.3)	8/617 (1.3)
Leukocytes (×10^9/L)		
Grade 3 (1.0 to <2.0)	1/621 (0.2)	4/618 (0.6)
Grade 4 (<1.0)	0/621	2/618 (0.3)
ALT (U/L)		
Grade 3 (3.0 to <8.0× ULN)	16/621 (2.6)	19/618 (3.1)
Grade 4 (>8.0× ULN)	3/621 (0.5)	2/618 (0.3)
AST (U/L)		
Grade 3 (3.0 to <8.0× ULN)	6/621 (1.0)	11/618 (1.8)
Grade 4 (>8.0× ULN)	3/621 (0.5)	2/618 (0.3)

CPK (U/L)		
Grade 3 (>5.0 to 10.0× ULN)	10/621 (1.6)	13/619 (2.1)
Grade 4 (>10.0× ULN)	3/621 (0.5)	10/619 (1.6)

*Pooled monotherapy data from SELECT-EARLY and SELECT-MONOTHERAPY.

N Obs indicates the number of patients with baseline and postbaseline values for the respective parameters.

AE, adverse event; AESI, AE of special interest; ALT, alanine transaminase; AST, aspartate transaminase; CPK, creatine phosphokinase; E/100 PY, event per 100 patient-years; GI, gastrointestinal; MACE, major adverse cardiovascular events; NMSC, non-melanoma skin cancer; QD, once daily; SAE, serious adverse event; TB, tuberculosis; TEAE, treatment-emergent AE; ULN, upper limit of normal; UPA, upadacitinib; VTE, venous thromboembolic events.

Supplementary Table S4 Hazard ratios of AESIs with upadacitinib versus comparators based on a Cox proportional hazards model

	UPA all phase 3 long-term					
	Any UPA 15 mg QD			Any UPA 30 mg QD		
Hazard ratio (95% CI)	**Versus PBO pooled**	**Versus MTX pooled**	**Versus ADA 40 mg EOW**	**Versus PBO pooled**	**Versus MTX pooled**	**Versus ADA 40 mg EOW**
Serious infections	1.555 (0.634, 3.811)	1.567 (0.730, 3.360)	0.820 (0.471, 1.427)	**3.243 (1.243, 8.466)**	1.762 (0.828, 3.747)	**1.927 (1.022, 3.636)**
Opportunistic infections	0.841 (0.210, 3.364)	2.005 (0.222, 18.117)	1.536 (0.337, 7.000)	2.561 (0.637, 10.300)	5.198 (0.644, 41.964)	2.144 (0.397, 11.590)
Herpes zoster	2.621 (0.771, 8.910)	**2.997 (1.147, 7.832)**	**3.221 (1.271, 8.160)**	**4.427 (1.271, 15.418)**	**3.023 (1.171, 7.805)**	**4.989 (1.882, 13.225)**
Malignancies (excluding NMSC)	1.860 (0.219, 15.793)	2.463 (0.524, 11.572)	0.686 (0.182, 2.593)	4.379 (0.449, 42.716)	1.540 (0.305, 7.779)	2.504 (0.602, 10.412)
NMSC	0.513 (0.032, 8.315)	0.282 (0.017, 4.825)	1.123 (0.131, 9.590)	1.418 (0.120, 16.808)	1.312 (0.132, 13.054)	2.037 (0.201, 20.659)
MACE (adjudicated)	0.582 (0.135, 2.515)	2.093 (0.392, 11.178)	1.327 (0.288, 6.112)	1.235 (0.233, 6.552)	2.734 (0.577, 12.954)	1.696 (0.282, 10.189)
VTE (adjudicated)	1.974 (0.225, 17.331)	1.078 (0.190, 6.128)	0.510 (0.164, 1.582)	4.284 (0.152, 120.442)	0.162 (0.010, 2.649)	0.397 (0.042, 3.772)
Hepatic disorders	1.003 (0.685, 1.469)	0.685 (0.441, 1.064)	1.320 (0.909, 1.917)	0.653 (0.378, 1.129)	0.916 (0.602, 1.392)	1.013 (0.606, 1.694)
Elevated CPK	**2.314 (1.137, 4.708)**	**2.701 (1.359, 5.370)**	**2.558 (1.230, 5.323)**	**2.697 (1.242, 5.857)**	**5.578 (2.891, 10.763)**	**3.073 (1.345, 7.021)**

Adjusted for race, age, weight, body mass index, estimated glomerular filtration rate at screening, region, concomitant csDMARDs use at baseline, concomitant corticosteroid use at baseline, and for herpes zoster only, prior history of herpes zoster and prior history of herpes zoster vaccination. Data not available for GI perforations as there were no cases in the comparator groups. Bold values indicate statistically significant risk.

ADA, adalimumab; AESI, adverse event of special interest; CI, confidence intervals; CPK, creatine phosphokinase; csDMARD, conventional synthetic disease-modifying antirheumatic drug; EOW, every other week; MACE, major adverse cardiovascular events; MTX, methotrexate; NMSC, non-melanoma skin cancer; PBO, placebo; QD, once daily; TB, tuberculosis; UPA, upadacitinib; VTE, venous thromboembolic events.

Supplementary Table S5 Risk factors for herpes zoster in patients receiving upadacitinib 15 mg based on a univariate Cox regression model

	UPA 15 mg QD (N=2630)		
	N	**n/100 PY**	**Hazard ratio (95% CI)**
Race			
Non-white	388	5.6	1.795 (1.101, 2.926)
White	2242	3.1	Reference
Geographic region			
North America	689	3.6	0.333 (0.177, 0.628)
South/Central America	529	3.4	0.313 (0.152, 0.642)
Europe	1134	2.6	0.231 (0.124, 0.430)
Other	143	3.0	0.271 (0.090, 0.818)
Asia	135	11.1	Reference
Age, years			
≥65	518	4.4	2.142 (1.137, 4.033)

50 to <65	1270	4.0	1.958 (1.131, 3.390)
<50	842	2.0	Reference
History of herpes zoster			
Yes	110	45.8	24.194 (15.941, 36.719)
No	2520	1.9	Reference

Only significant risk factors (p>0.05) are presented.

CI, confidence intervals; HR, hazard ratio; n/100 PY, incidence per 100 patient-years; QD, once daily; UPA, upadacitinib.

Supplementary Table S6 Adjudicated MACE and VTE

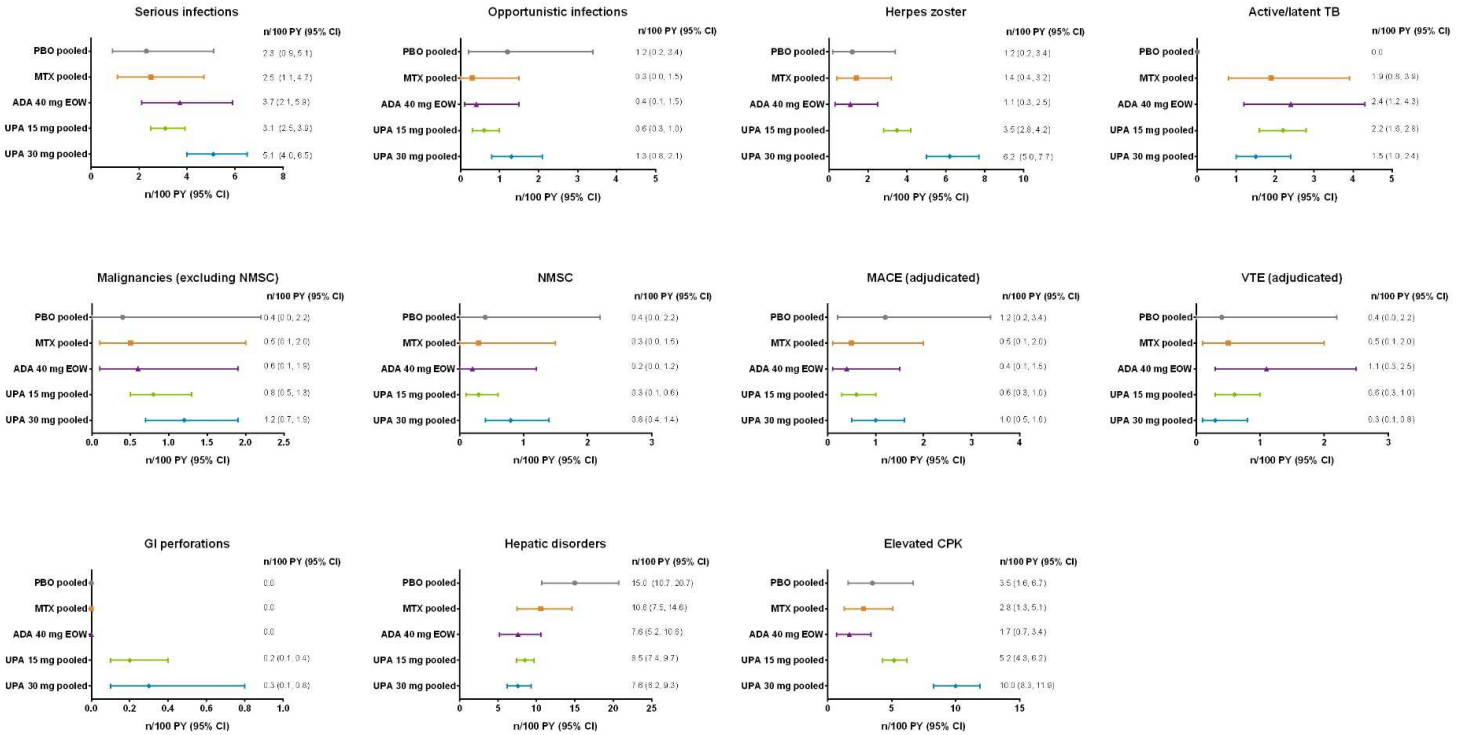
				UPA all phase 3 long-term	
	PBO pooled	**MTX pooled**	**ADA 40 mg EOW**	**UPA 15 mg QD**	**UPA 30 mg QD**
	n=1042	**n=530**	**n=579**	**n=2630**	**n=1204**
	PY=256.8	**PY=368.7**	**PY=467.8**	**PY=2655.1**	**PY=1365.0**
E/100 PY (95% CI)	**Short-term data up to 12/14 weeks**	**Long-term MTX monotherapy Mean exposure: 36 weeks (data censored at rescue)**	**Long-term ADA Mean exposure: 42 weeks (includes UPA→ADA post-switch)**	**Long-term UPA (monotherapy or in combination with MTX/other csDMARDs) Mean exposures: 53 weeks (UPA 15 mg) and 59 weeks (UPA 30 mg)**	
Any MACE (adjudicated)	1.2 (0.2, 3.4)	0.5 (0.1, 2.0)	0.4 (0.1, 1.5)	0.6 (0.4, 1.0)	1.0 (0.5, 1.6)
CV death*	0.4 (0, 2.2)	0.3 (0.0, 1.5)	0.2 (0.0, 1.2)	0.3 (0.1, 0.5)	0.4 (0.1, 0.9)
Non-fatal MI	0.8 (0.1, 2.8)	0.0	0.0	0.2 (0.1, 0.5)	0.4 (0.1, 0.9)
Non-fatal stroke	0.0	0.3 (0.0, 1.5)	0.2 (0.0, 1.2)	0.2 (0.0, 0.4)	0.2 (0.0, 0.6)
Any VTE (adjudicated)	0.4 (0.0, 2.2)	0.5 (0.1, 2.0)	1.1 (0.3, 2.5)	0.6 (0.3, 1.0)	0.3 (0.1, 0.8)
Non-fatal DVT alone	0.0	0.3 (0.0, 1.5)	0.2 (0.0, 1.2)	0.3 (0.1, 0.6)	0.2 (0.0, 0.6)
Non-fatal PE alone	0.4 (0.0, 2.2)	0.5 (0.1, 2.0)	0.9 (0.2, 2.2)	0.4 (0.2, 0.7)	0.1 (0.0, 0.5)

Non-fatal DVT and PE	0.0	0.3 (0.0, 1.5)	0.0	0.2 (0.0, 0.4)	<0.1 (0.0, 0.4)
Fatal DVT/PE	0.0	0.0	0.0	<0.1 (0.0, 0.2)†	0.0

*Deaths are only treatment emergent.

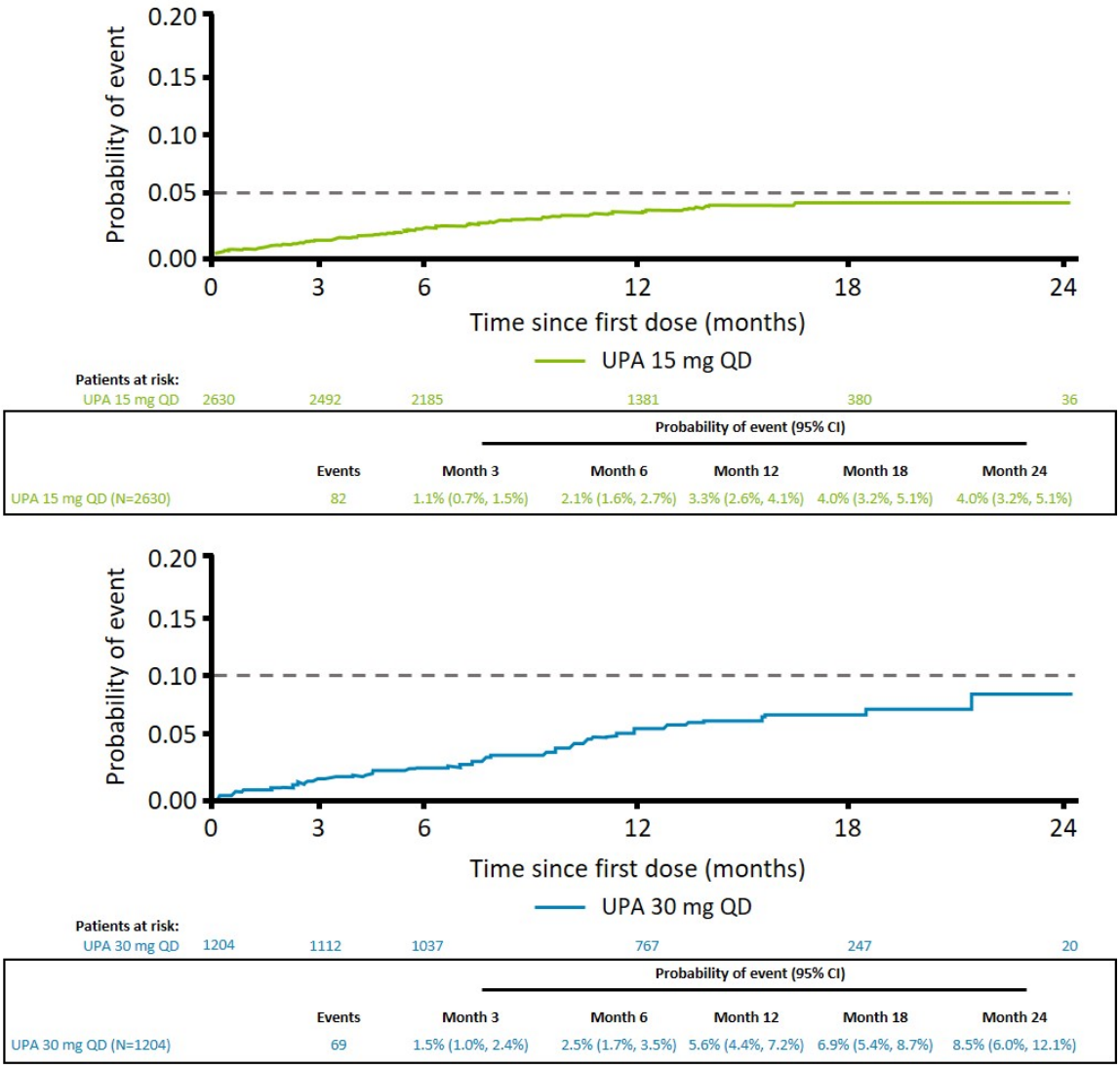
†Includes one fatal PE event: 55-year-old female developed PE after prolonged driving.

ADA, adalimumab; CI, confidence intervals; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CV, cardiovascular; DVT, deep vein thrombosis; E/100 PY, event per 100 patient-years; EOW, every other week; MACE, major adverse cardiovascular events; MI, myocardial infarction; MTX, methotrexate; PBO, placebo; PE, pulmonary embolism; QD, once daily; UPA, upadacitinib; VTE, venous thromboembolic events.



Supplementary Figure S1 Incidence rates for AESIs

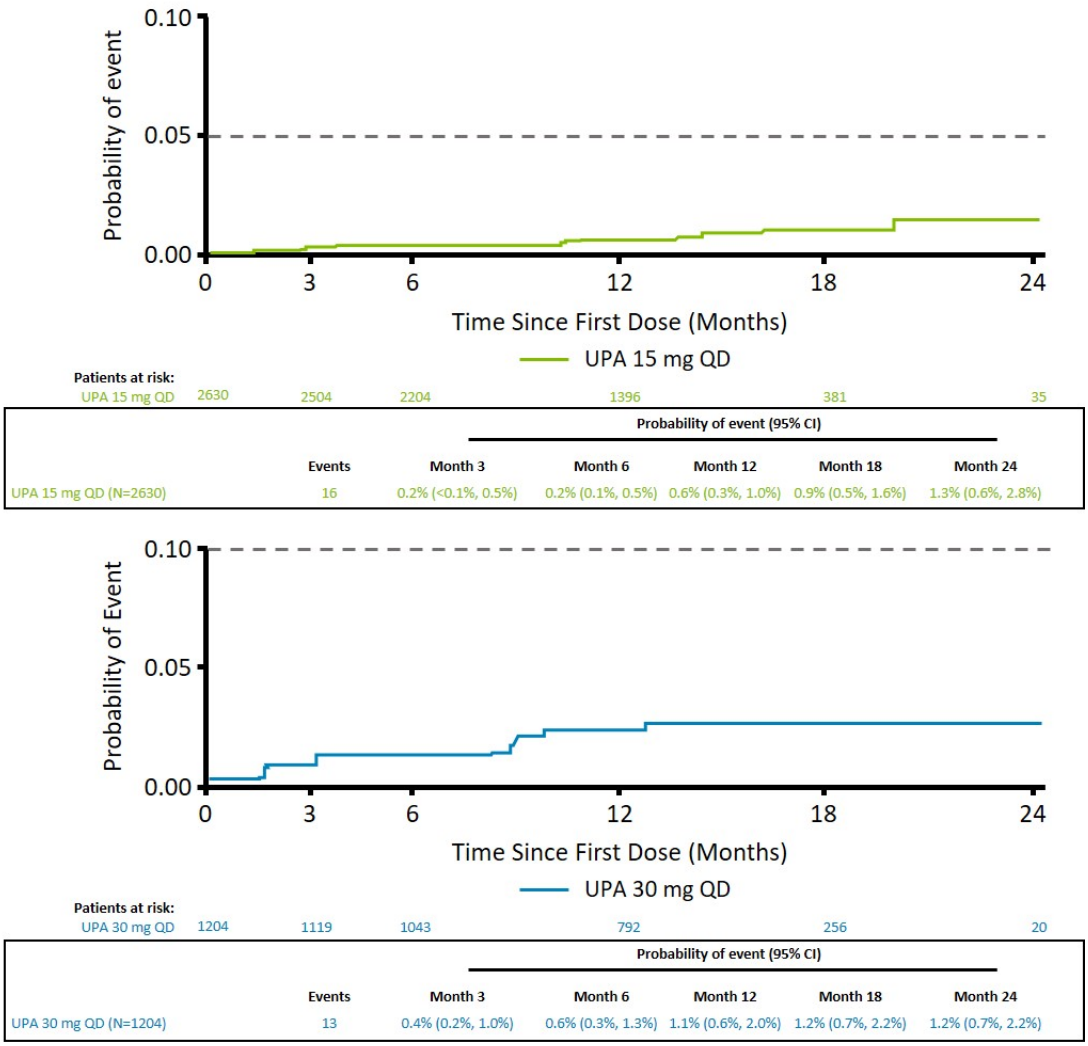
ADA, adalimumab; AESI, adverse event of special interest; CI, confidence intervals; CPK, creatine phosphokinase; n/100 PY, incidence per 100 patient-years; EOW, every other week; GI, gastrointestinal; MACE, major adverse cardiovascular events; MTX, methotrexate; NMSC, non-melanoma skin cancer; PBO, placebo; TB, tuberculosis; UPA, upadacitinib; VTE, venous thromboembolic events.



Supplementary Figure S2 Probability of treatment-emergent serious infections with upadacitinib 15 and 30 mg over 24 months of exposure.

The 'patients at risk' decrease over time, so the increasing probability should be interpreted with caution.

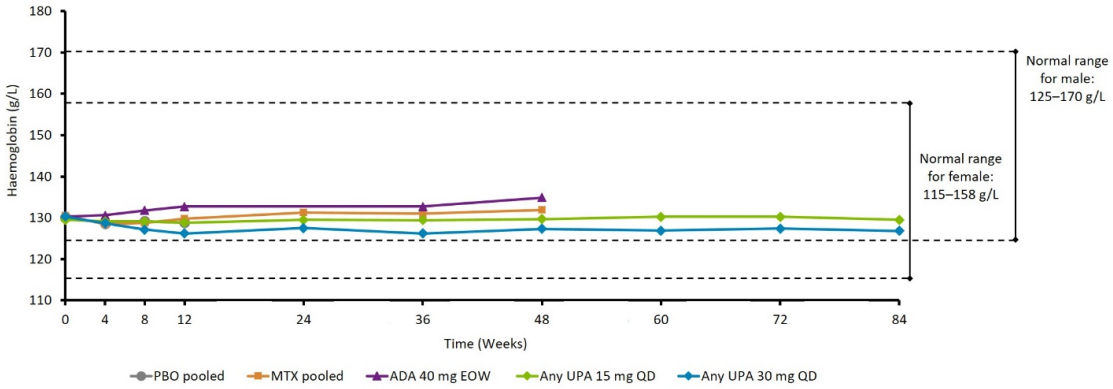
CI, confidence intervals; QD, once daily; UPA, upadacitinib.



Supplementary Figure S3 Probability of treatment-emergent MACE with upadacitinib 15 and 30 mg over 24 months of exposure.

The 'patients at risk' decrease over time, so the increasing probability should be interpreted with caution.

CI, confidence intervals; MACE, major adverse cardiovascular events; QD, once daily; UPA, upadacitinib.



Supplementary Figure S4 Mean haemoglobin levels over time.

ADA, adalimumab; EOW, every other week; MTX, methotrexate; PBO, placebo; QD, once daily; UPA, upadacitinib.

SUPPLEMENTARY MATERIAL

Exclusion criteria

- Cerebrovascular accident or myocardial infarction within the past 6 months
- Malignancy, except for successfully treated non-melanoma skin cancer (NMSC) or localised carcinoma *in situ* of the cervix
- Gastrointestinal (GI) perforation or diverticulitis
- Active infection requiring treatment with parenteral anti-infectives within 30 days, or oral anti-infectives within 14 days, prior to the first dose of study drug
- Serum aspartate transaminase or alanine transaminase >2× the upper limit of normal
- Estimated glomerular filtration rate <40 mL/min/1.73 m^2
- Absolute neutrophil count <1500/µL
- Absolute lymphocyte count <850/µL (<800/µL in SELECT-EARLY)[8]
- Haemoglobin <100 g/L

Deaths

The causes of the 10 treatment-emergent cardiovascular (CV) deaths with upadacitinib were cardiac failure, cardiac arrest, myocardial infarction, haemorrhagic stroke, pulmonary embolism (PE) or sudden cardiac deaths. The causes of the 12 treatment-emergent non-CV deaths with upadacitinib included infections (pneumonia, sepsis, meningitis, peritonitis), cancer, other non-CV causes or undetermined/unknown causes. There were six non-treatment-emergent deaths due to cancer, CV

events, or undetermined/unknown causes that occurred >30 days after the last dose of study drug (n=3 each for upadacitinib 15 and 30 mg).

Additional details on adverse events of special interest (AESIs)

Tuberculosis (TB)

9.9–11.4% of patients in the upadacitinib groups had positive TB tests at baseline. For patients with a negative TB test result at screening, an annual TB retest was performed. Among the five patients (<0.1 events per 100 patient-years [E/100 PY]) on upadacitinib with active TB, three had latent TB at screening. Of these, one completed the recommended ≥6 months of isoniazid therapy, one was treated with isoniazid for 3 months but did not complete the full 6-month treatment for unknown reasons, and one was treated with isoniazid but did not refill their isoniazid prescription after running out on day 10. Two of the five patients manifested signs and symptoms of extrapulmonary TB: female genital tract and peritoneum (one patient receiving upadacitinib 15 mg) and mediastinal lymph nodes (one patient receiving upadacitinib 30 mg). One patient with active TB lived in a high-TB burden country (South Africa), and another was residing with household members with a history of TB. The patient on adalimumab with active TB (pulmonary TB) had a negative TB test at screening. The study drug was discontinued for all patients with active TB.

Malignancies

There were no notable patterns of the types of malignancies observed. The most common malignancies (≥0.1 E/100 PY) were basal cell carcinoma (0.2 E/100 PY), squamous cell carcinoma of the skin (0.1 E/100 PY), and invasive ductal breast carcinoma (0.1 E/100 PY) in the upadacitinib 15 mg group and squamous cell carcinoma of the skin (0.6 E/100 PY), basal cell carcinoma (0.4 E/100 PY), adenocarcinoma of the colon (0.1 E/100 PY), malignant melanoma (0.1 E/100 PY), and prostate cancer (0.1 E/100 PY) in the upadacitinib 30 mg group. The EAER of lymphoma was <0.1/100 PY in both upadacitinib groups. Per

study protocol, study drug was discontinued in all patients who developed malignancies (except NMSC and carcinoma *in situ* of the cervix) during the study.

GI perforations

Two events with upadacitinib 15 mg (one perforated appendix associated with acute appendicitis on day 289; one anal fistula requiring surgical repair on day 168) and four events with upadacitinib 30 mg (three events of intestinal perforation on days 77, 133 and 341; one event of peritonitis on day 73) were determined to be true GI perforations based on sponsor medical review.

Venous thromboembolic events (VTE)

Three patients who experienced VTE while receiving upadacitinib 15 mg had a history of VTE. Four patients with PE were on concomitant hormonal therapy or contraception: two with upadacitinib 15 mg and one each with upadacitinib 30 mg and placebo. Slight decreases in mean platelet count from baseline were observed after 4 weeks of upadacitinib therapy, and values returned to baseline by week 60. There were no adjudicated VTE that occurred in patients with a platelet value of $>600 \times 10^9$/L at the time of the event.

Arterial thrombosis

Two patients experienced arterial thrombosis events in this analysis, neither was assessed as related to the study drug. Both of these events were non-cardiac and non-neurologic and therefore not considered to be CV events per protocol. One patient with a history of vascular stents (femoral and bypass graft) developed an obliterating arteriopathy in the common iliac artery of the lower limb after receiving upadacitinib 30 mg for 92 days. Upadacitinib treatment was temporarily interrupted while the patient was treated for the arteriopathy, which resolved. The other patient, who had a history of peripheral vascular disease developed a left popliteal artery aneurysm and peripheral artery thrombosis after receiving upadacitinib 30 mg for 281 days. The patient underwent resection of the popliteal artery aneurysm with implantation of a vascular graft and the peripheral artery thrombosis was reported

following surgery later that day. The patient then underwent surgical repair for the thrombosis and recovered.

Limitations of statistical comparisons between upadacitinib and comparators

Any statistical comparisons between upadacitinib and comparator arms should be interpreted with caution for the following reasons:

- Many of the AESIs evaluated were rare events and the limited sample size or exposure may bias the result
- Upadacitinib data may be overrepresented due to differences in sample size and exposure time between upadacitinib and comparator arms
- Upadacitinib is currently only approved in patients with rheumatoid arthritis and an inadequate response to conventional synthetic disease-modifying antirheumatic drugs (csDMARD), therefore data suggesting an increased risk with upadacitinib versus placebo (with background csDMARDs) or methotrexate should be treated with caution

Supplementary Table S1 Characteristics of the treatment arms

	SELECT-EARLY (NCT02706873)	SELECT-NEXT (NCT02675426)	SELECT-COMPARE (NCT02629159)	SELECT-MONOTHERAPY (NCT02706951)	SELECT-BEYOND (NCT02706847)
Patients	MTX-naïve	csDMARD-IR	MTX-IR	MTX-IR	bDMARD-IR
Comparators	MTX	PBO	PBO, ADA	PBO continued prior MTX	PBO
Background treatment	NA	csDMARDs	MTX	NA	csDMARDs
Data	Week 48 and beyond through cut-off date	Week 60 and beyond through cut-off date	Week 48 and beyond through cut-off date	Week 48 and beyond through cut-off date	Week 60 and through cut-off date
Cut-off date	16 August 2018	22 March 2018	6 July 2018	25 May 2018	16 April 2018
Treatment arm					
Description					
PBO pooled					
All phase 3 patients exposed to PBO control (short-term)		✓	✓		✓

MTX pooled					
All phase 3 patients exposed to MTX monotherapy; data censored at rescue	✓			✓	
ADA 40 mg EOW					
All phase 3 patients exposed to ADA; includes UPA → ADA post-switch			✓		
UPA 15 mg QD pooled					
All phase 3 patients exposed to UPA 15 mg +/− csDMARDs	✓	✓	✓	✓	✓
UPA 30 mg QD pooled					
All phase 3 patients exposed to UPA 30 mg +/− csDMARDs	✓	✓		✓	✓

ADA, adalimumab; bDMARD, biologic disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; EOW, every other week; IR, inadequate response; MTX, methotrexate; NA, not applicable; PBO, placebo; QD, once daily; UPA, upadacitinib.

Supplementary Table S2 TEAEs occurring in ≥3.0 E/100 PY of patients in any treatment group by decreasing frequency in upadacitinib 15 mg group

	PBO pooled n=1042 PY=256.8	MTX pooled n=530 PY=368.7	ADA 40 mg EOW n=579 PY=467.8	UPA all phase 3 long-term	
				Any UPA 15 mg QD n=2630 PY=2655.1	Any UPA 30 mg QD n=1204 PY=1365.0
MedDRA 19.1 Preferred Term, Events (E/100 PY)	Short-term data up to 12/14 weeks	Long-term MTX monotherapy Mean exposure: 36 weeks (data censored at rescue)	Long-term ADA Mean exposure: 42 weeks (includes UPA→ADA post-switch)	Long-term UPA (monotherapy or in combination with MTX/other csDMARDs) Mean exposures: 53 weeks (UPA 15 mg) and 59 weeks (UPA 30 mg)	
Upper respiratory tract infection	40 (15.6)	42 (11.4)	33 (7.1)	357 (13.4)	205 (15.0)
Nasopharyngitis	35 (13.6)	44 (11.9)	32 (6.8)	283 (10.7)	154 (11.3)
Urinary tract infection	36 (14.0)	39 (10.6)	45 (9.6)	268 (10.1)	187 (13.7)
Bronchitis	21 (8.2)	26 (7.1)	30 (6.4)	183 (6.9)	97 (7.1)
ALT increased	28 (10.9)	30 (8.1)	29 (6.2)	165 (6.2)	78 (5.7)
Blood CPK increased	9 (3.5)	--	--	163 (6.1)	170 (12.5)
Hypertension	22 (8.6)	22 (6.0)	23 (4.9)	146 (5.5)	70 (5.1)
Worsening rheumatoid arthritis	39 (15.2)	38 (10.3)	36 (7.7)	131 (4.9)	86 (6.3)

AST increased	21 (8.2)	23 (6.2)	20 (4.3)	126 (4.7)	55 (4.0)
Nausea	24 (9.3)	49 (13.3)	--	109 (4.1)	52 (3.8)
Cough	10 (3.9)	--	16 (3.4)	103 (3.9)	56 (4.1)
Diarrhoea	28 (10.9)	13 (3.5)	24 (5.1)	95 (3.6)	48 (3.5)
Headache	40 (15.6)	--	21 (4.5)	91 (3.4)	65 (4.8)
Sinusitis	--	18 (4.9)	16 (3.4)	91 (3.4)	--
Herpes zoster	--	--	--	89 (3.4)	86 (6.3)
Gastroenteritis	--	--	--	84 (3.2)	46 (3.4)
Anaemia	17 (6.6)	--	--	83 (3.1)	45 (3.3)
Influenza-like illness	--	12 (3.3)	--	--	44 (3.2)
Influenza	--	--	--	--	46 (3.4)
Pneumonia	--	--	--	--	44 (3.2)
Neutropenia	--	--	15 (3.2)	--	74 (5.4)
Weight increased	--	--	--	--	42 (3.1)
Rash	--	13 (3.5)	--	--	55 (4.0)

Leucopenia	--	17 (4.6)	--	--	53 (3.9)
Oral herpes	--	--	--	--	42 (3.1)
Back pain	14 (5.5)	--	--	--	--
Lymphopenia	13 (5.1)	16 (4.3)	--	--	--
Arthralgia	12 (4.7)	--	19 (4.1)	--	--
Fatigue	12 (4.7)	--	--	--	--
Gastritis	11 (4.3)	--	--	--	--
Upper abdominal pain	10 (3.9)	--	--	--	--
Dizziness	9 (3.5)	--	--	--	--
Contusion	8 (3.1)	--	--	--	--
Haematuria	8 (3.1)	--	--	--	--
Insomnia	8 (3.1)	--	--	--	--
Muscle spasms	8 (3.1)	--	--	--	--
Pharyngitis	8 (3.1)	15 (4.1)	--	--	--
Vomiting	8 (3.1)	--	--	--	--

Dyspepsia	--	16 (4.3)	--	--	--
Injection-site reaction	--	--	28 (6.0)	--	--
Injection-site rash	--	--	18 (3.8)	--	--

--, indicates TEAEs occurring <3.0 E/100 PY in that particular treatment group.

ADA, adalimumab; ALT, alanine transaminase; AST, aspartate transaminase; CPK, creatine phosphokinase; csDMARD, conventional synthetic disease-modifying antirheumatic drug; E/100 PY, event per 100 patient-years; EOW, every other week; MedDRA, Medical Dictionary for Regulatory Activities; MTX, methotrexate; PBO, placebo; PY, patient year; QD, once daily; TEAE, treatment-emergent adverse event; UPA, upadacitinib.

Supplementary Table S3 TEAEs and laboratory abnormalities in patients receiving upadacitinib monotherapy*

	UPA monotherapy all phase 3 long-term	
	UPA 15 mg QD monotherapy **n=635** **PY=636.0**	**UPA 30 mg QD monotherapy** **n=625** **PY=647.4**
TEAEs, E/100 PY		
Any AE	1914 (300.9)	2195 (339.0)
Any SAE	103 (16.2)	105 (16.2)
Any AE leading to discontinuation	66 (10.4)	66 (10.2)
Deaths	4 (0.6)	7 (1.1)
AESIs, E/100 PY		
Serious infections	28 (4.4)	28 (4.3)
Opportunistic infections	4 (0.6)	12 (1.9)
Herpes zoster	31 (4.9)	41 (6.3)

Active/latent TB	16 (2.5)	16 (2.5)
Malignancies (excluding NMSC)	9 (1.4)	6 (0.9)
NMSC	1 (0.2)	1 (0.2)
Hepatic disorders	82 (12.9)	92 (14.2)
GI perforations	1 (0.2)	3 (0.5)
MACE (adjudicated)	6 (0.9)	9 (1.4)
VTE (adjudicated)	4 (0.6)	1 (0.2)
Elevated CPK	55 (8.6)	121 (18.7)
Potentially clinically significant laboratory values, n/N Obs (%)		
Haemoglobin (g/L)		
Grade 3 (70 to <80 or decreased 21 to <30)	37/621 (6.0)	64/618 (10.4)
Grade 4 (<70 or decreased ≥30)	6/621 (1.0)	19/618 (3.1)
Platelets ($\times 10^9$/L)		
Grade 3 (20 to <50)	0/620	0/617
Grade 4 (<20)	0/620	1/617 (0.2)

Neutrophils (×10^9/L)		
Grade 3 (0.5 to <1.0)	3/621 (0.5)	11/617 (1.8)
Grade 4 (<0.5)	0/621	2/617 (0.3)
Lymphocytes (×10^9/L)		
Grade 3 (0.5 to <1.0)	74/621 (11.9)	105/617 (17.0)
Grade 4 (<0.5)	2/621 (0.3)	8/617 (1.3)
Leukocytes (×10^9/L)		
Grade 3 (1.0 to <2.0)	1/621 (0.2)	4/618 (0.6)
Grade 4 (<1.0)	0/621	2/618 (0.3)
ALT (U/L)		
Grade 3 (3.0 to <8.0× ULN)	16/621 (2.6)	19/618 (3.1)
Grade 4 (>8.0× ULN)	3/621 (0.5)	2/618 (0.3)
AST (U/L)		
Grade 3 (3.0 to <8.0× ULN)	6/621 (1.0)	11/618 (1.8)
Grade 4 (>8.0× ULN)	3/621 (0.5)	2/618 (0.3)

CPK (U/L)		
Grade 3 (>5.0 to 10.0× ULN)	10/621 (1.6)	13/619 (2.1)
Grade 4 (>10.0× ULN)	3/621 (0.5)	10/619 (1.6)

*Pooled monotherapy data from SELECT-EARLY and SELECT-MONOTHERAPY.

N Obs indicates the number of patients with baseline and postbaseline values for the respective parameters.

AE, adverse event; AESI, AE of special interest; ALT, alanine transaminase; AST, aspartate transaminase; CPK, creatine phosphokinase; E/100 PY, event per 100 patient-years; GI, gastrointestinal; MACE, major adverse cardiovascular events; NMSC, non-melanoma skin cancer; QD, once daily; SAE, serious adverse event; TB, tuberculosis; TEAE, treatment-emergent AE; ULN, upper limit of normal; UPA, upadacitinib; VTE, venous thromboembolic events.

Supplementary Table S4 Hazard ratios of AESIs with upadacitinib versus comparators based on a Cox proportional hazards model

	UPA all phase 3 long-term					
	Any UPA 15 mg QD			Any UPA 30 mg QD		
Hazard ratio (95% CI)	**Versus PBO pooled**	**Versus MTX pooled**	**Versus ADA 40 mg EOW**	**Versus PBO pooled**	**Versus MTX pooled**	**Versus ADA 40 mg EOW**
Serious infections	1.555 (0.634, 3.811)	1.567 (0.730, 3.360)	0.820 (0.471, 1.427)	**3.243 (1.243, 8.466)**	1.762 (0.828, 3.747)	**1.927 (1.022, 3.636)**
Opportunistic infections	0.841 (0.210, 3.364)	2.005 (0.222, 18.117)	1.536 (0.337, 7.000)	2.561 (0.637, 10.300)	5.198 (0.644, 41.964)	2.144 (0.397, 11.590)
Herpes zoster	2.621 (0.771, 8.910)	**2.997 (1.147, 7.832)**	**3.221 (1.271, 8.160)**	**4.427 (1.271, 15.418)**	**3.023 (1.171, 7.805)**	**4.989 (1.882, 13.225)**
Malignancies (excluding NMSC)	1.860 (0.219, 15.793)	2.463 (0.524, 11.572)	0.686 (0.182, 2.593)	4.379 (0.449, 42.716)	1.540 (0.305, 7.779)	2.504 (0.602, 10.412)
NMSC	0.513 (0.032, 8.315)	0.282 (0.017, 4.825)	1.123 (0.131, 9.590)	1.418 (0.120, 16.808)	1.312 (0.132, 13.054)	2.037 (0.201, 20.659)
MACE (adjudicated)	0.582 (0.135, 2.515)	2.093 (0.392, 11.178)	1.327 (0.288, 6.112)	1.235 (0.233, 6.552)	2.734 (0.577, 12.954)	1.696 (0.282, 10.189)
VTE (adjudicated)	1.974 (0.225, 17.331)	1.078 (0.190, 6.128)	0.510 (0.164, 1.582)	4.284 (0.152, 120.442)	0.162 (0.010, 2.649)	0.397 (0.042, 3.772)
Hepatic disorders	1.003 (0.685, 1.469)	0.685 (0.441, 1.064)	1.320 (0.909, 1.917)	0.653 (0.378, 1.129)	0.916 (0.602, 1.392)	1.013 (0.606, 1.694)
Elevated CPK	**2.314 (1.137, 4.708)**	**2.701 (1.359, 5.370)**	**2.558 (1.230, 5.323)**	**2.697 (1.242, 5.857)**	**5.578 (2.891, 10.763)**	**3.073 (1.345, 7.021)**

Adjusted for race, age, weight, body mass index, estimated glomerular filtration rate at screening, region, concomitant csDMARDs use at baseline, concomitant corticosteroid use at baseline, and for herpes zoster only, prior history of herpes zoster and prior history of herpes zoster vaccination. Data not available for GI perforations as there were no cases in the comparator groups. Bold values indicate statistically significant risk.

ADA, adalimumab; AESI, adverse event of special interest; CI, confidence intervals; CPK, creatine phosphokinase; csDMARD, conventional synthetic disease-modifying antirheumatic drug; EOW, every other week; MACE, major adverse cardiovascular events; MTX, methotrexate; NMSC, non-melanoma skin cancer; PBO, placebo; QD, once daily; TB, tuberculosis; UPA, upadacitinib; VTE, venous thromboembolic events.

Supplementary Table S5 Risk factors for herpes zoster in patients receiving upadacitinib 15 mg based on a univariate Cox regression model

	UPA 15 mg QD (N=2630)		
	N	**n/100 PY**	**Hazard ratio (95% CI)**
Race			
Non-white	388	5.6	1.795 (1.101, 2.926)
White	2242	3.1	Reference
Geographic region			
North America	689	3.6	0.333 (0.177, 0.628)
South/Central America	529	3.4	0.313 (0.152, 0.642)
Europe	1134	2.6	0.231 (0.124, 0.430)
Other	143	3.0	0.271 (0.090, 0.818)
Asia	135	11.1	Reference
Age, years			
≥65	518	4.4	2.142 (1.137, 4.033)

50 to <65	1270	4.0	1.958 (1.131, 3.390)
<50	842	2.0	Reference
History of herpes zoster			
Yes	110	45.8	24.194 (15.941, 36.719)
No	2520	1.9	Reference

Only significant risk factors (p>0.05) are presented.

CI, confidence intervals; HR, hazard ratio; n/100 PY, incidence per 100 patient-years; QD, once daily; UPA, upadacitinib.

Supplementary Table S6 Adjudicated MACE and VTE

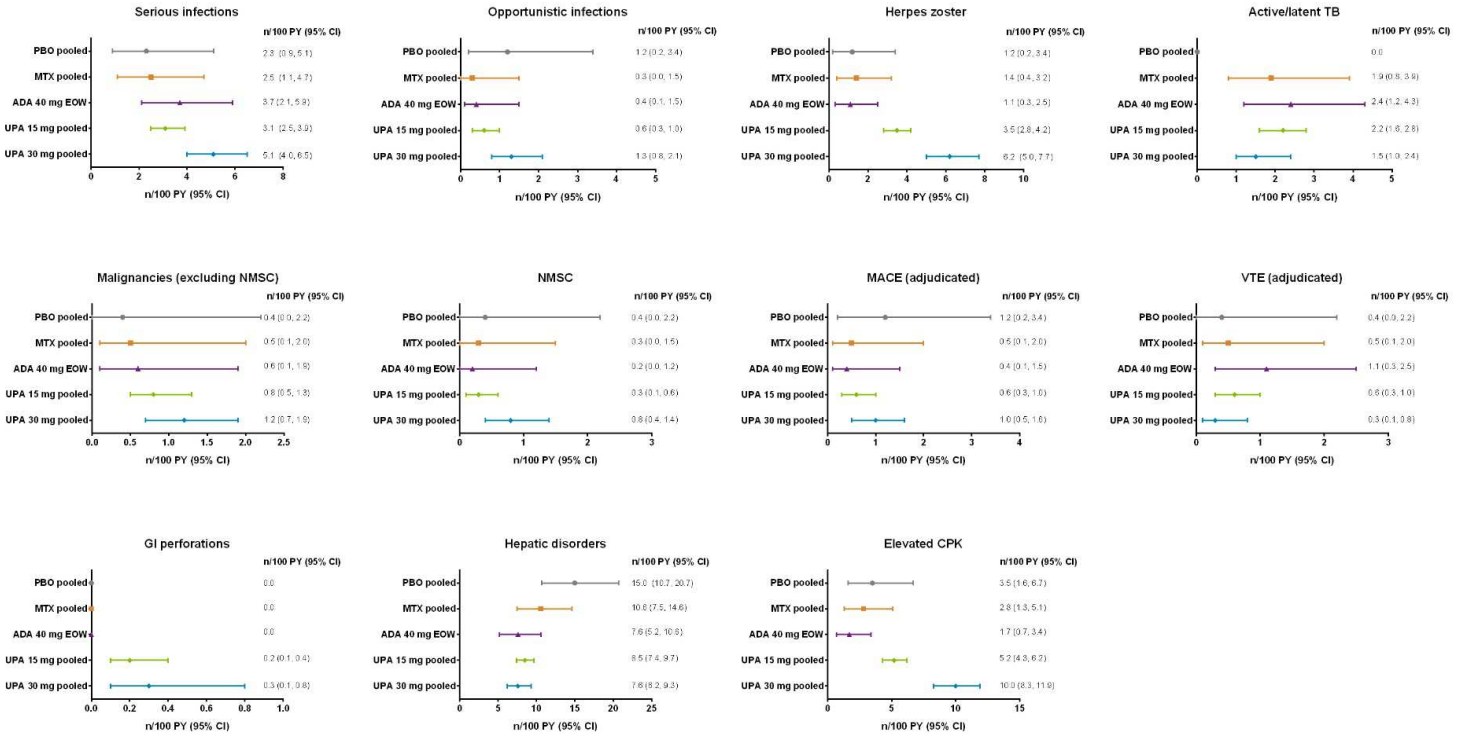
				UPA all phase 3 long-term	
	PBO pooled	**MTX pooled**	**ADA 40 mg EOW**	**UPA 15 mg QD**	**UPA 30 mg QD**
	n=1042	**n=530**	**n=579**	**n=2630**	**n=1204**
	PY=256.8	**PY=368.7**	**PY=467.8**	**PY=2655.1**	**PY=1365.0**
E/100 PY (95% CI)	**Short-term data up to 12/14 weeks**	**Long-term MTX monotherapy Mean exposure: 36 weeks (data censored at rescue)**	**Long-term ADA Mean exposure: 42 weeks (includes UPA→ADA post-switch)**	**Long-term UPA (monotherapy or in combination with MTX/other csDMARDs) Mean exposures: 53 weeks (UPA 15 mg) and 59 weeks (UPA 30 mg)**	
Any MACE (adjudicated)	1.2 (0.2, 3.4)	0.5 (0.1, 2.0)	0.4 (0.1, 1.5)	0.6 (0.4, 1.0)	1.0 (0.5, 1.6)
CV death*	0.4 (0, 2.2)	0.3 (0.0, 1.5)	0.2 (0.0, 1.2)	0.3 (0.1, 0.5)	0.4 (0.1, 0.9)
Non-fatal MI	0.8 (0.1, 2.8)	0.0	0.0	0.2 (0.1, 0.5)	0.4 (0.1, 0.9)
Non-fatal stroke	0.0	0.3 (0.0, 1.5)	0.2 (0.0, 1.2)	0.2 (0.0, 0.4)	0.2 (0.0, 0.6)
Any VTE (adjudicated)	0.4 (0.0, 2.2)	0.5 (0.1, 2.0)	1.1 (0.3, 2.5)	0.6 (0.3, 1.0)	0.3 (0.1, 0.8)
Non-fatal DVT alone	0.0	0.3 (0.0, 1.5)	0.2 (0.0, 1.2)	0.3 (0.1, 0.6)	0.2 (0.0, 0.6)
Non-fatal PE alone	0.4 (0.0, 2.2)	0.5 (0.1, 2.0)	0.9 (0.2, 2.2)	0.4 (0.2, 0.7)	0.1 (0.0, 0.5)

Non-fatal DVT and PE	0.0	0.3 (0.0, 1.5)	0.0	0.2 (0.0, 0.4)	<0.1 (0.0, 0.4)
Fatal DVT/PE	0.0	0.0	0.0	<0.1 (0.0, 0.2)†	0.0

*Deaths are only treatment emergent.

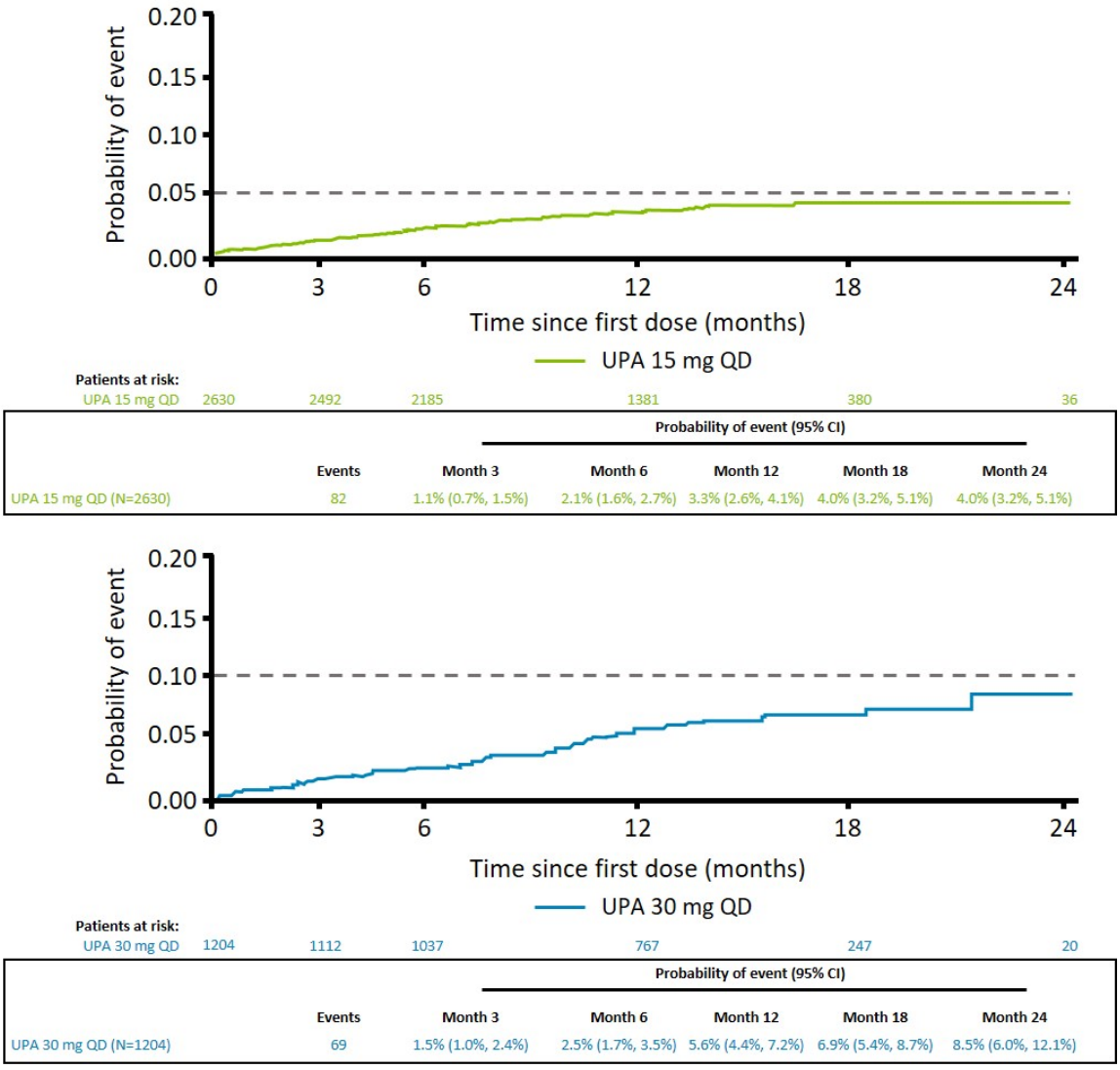
†Includes one fatal PE event: 55-year-old female developed PE after prolonged driving.

ADA, adalimumab; CI, confidence intervals; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CV, cardiovascular; DVT, deep vein thrombosis; E/100 PY, event per 100 patient-years; EOW, every other week; MACE, major adverse cardiovascular events; MI, myocardial infarction; MTX, methotrexate; PBO, placebo; PE, pulmonary embolism; QD, once daily; UPA, upadacitinib; VTE, venous thromboembolic events.



Supplementary Figure S1 Incidence rates for AESIs

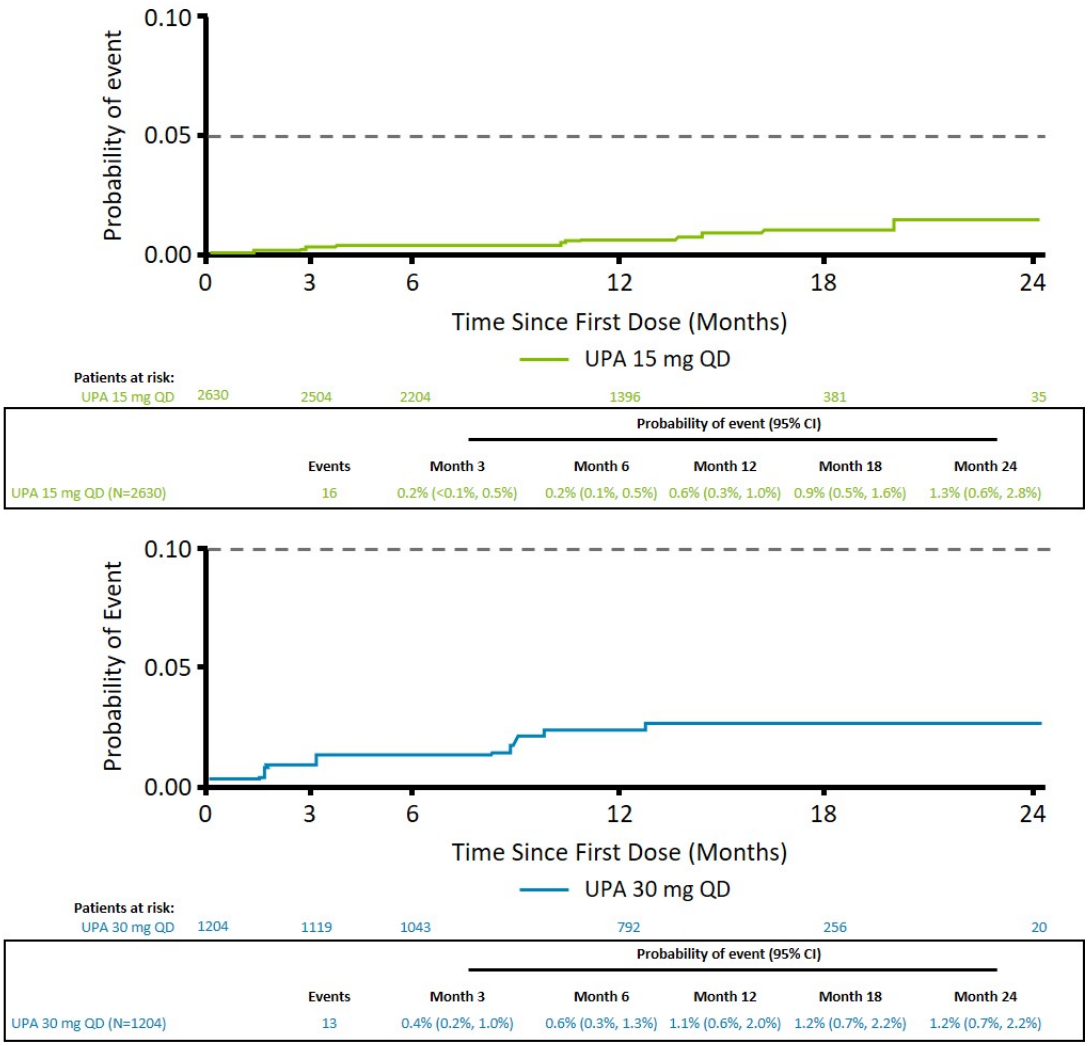
ADA, adalimumab; AESI, adverse event of special interest; CI, confidence intervals; CPK, creatine phosphokinase; n/100 PY, incidence per 100 patient-years; EOW, every other week; GI, gastrointestinal; MACE, major adverse cardiovascular events; MTX, methotrexate; NMSC, non-melanoma skin cancer; PBO, placebo; TB, tuberculosis; UPA, upadacitinib; VTE, venous thromboembolic events.



Supplementary Figure S2 Probability of treatment-emergent serious infections with upadacitinib 15 and 30 mg over 24 months of exposure.

The 'patients at risk' decrease over time, so the increasing probability should be interpreted with caution.

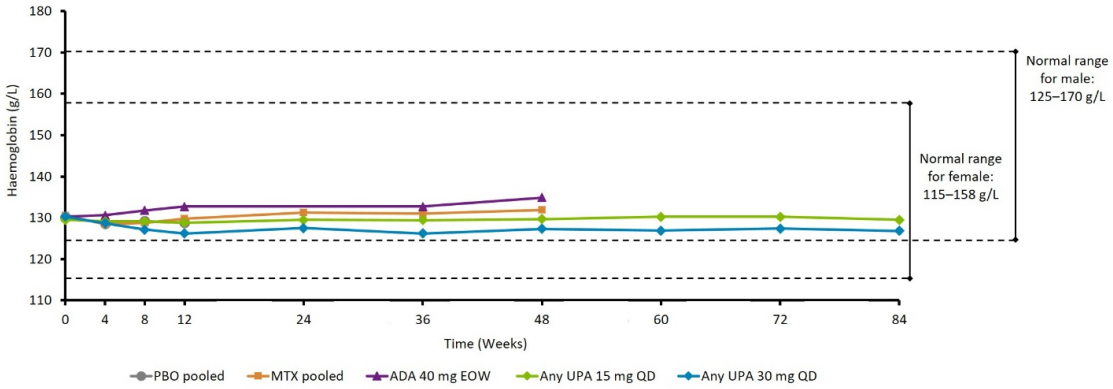
CI, confidence intervals; QD, once daily; UPA, upadacitinib.



Supplementary Figure S3 Probability of treatment-emergent MACE with upadacitinib 15 and 30 mg over 24 months of exposure.

The 'patients at risk' decrease over time, so the increasing probability should be interpreted with caution.

CI, confidence intervals; MACE, major adverse cardiovascular events; QD, once daily; UPA, upadacitinib.



Supplementary Figure S4 Mean haemoglobin levels over time.

ADA, adalimumab; EOW, every other week; MTX, methotrexate; PBO, placebo; QD, once daily; UPA, upadacitinib.