

## 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<sup>2</sup>
- Absolute neutrophil count <1500/μL
- Absolute lymphocyte count <850/μL (<800/μL in SELECT-EARLY)<sup>8</sup>
- 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  $\geq 6$  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 ( $\geq 0.1$  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)
<b>Patients</b>	MTX-naïve	csDMARD-IR	MTX-IR	MTX-IR	bDMARD-IR
<b>Comparators</b>	MTX	PBO	PBO, ADA	PBO continued prior MTX	PBO
<b>Background treatment</b>	NA	csDMARDs	MTX	NA	csDMARDs
<b>Data</b>	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
<b>Cut-off date</b>	16 August 2018	22 March 2018	6 July 2018	25 May 2018	16 April 2018
<b>Treatment arm</b>					
<b>Description</b>					
<b>PBO pooled</b>					
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  $\geq 3.0$  E/100 PY of patients in any treatment group by decreasing frequency in upadacitinib 15 mg group

	PBO pooled	MTX pooled	ADA 40 mg EOW	UPA all phase 3 long-term	
	n=1042	n=530	n=579	Any UPA 15 mg QD n=2630	Any UPA 30 mg QD n=1204
	PY=256.8	PY=368.7	PY=467.8	PY=2655.1	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)
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	UPA 30 mg QD monotherapy
	n=635 PY=636.0	n=625 PY=647.4
<b>TEAEs, E/100 PY</b>		
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)
<b>AESIs, E/100 PY</b>		
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)
<b>Potentially clinically significant laboratory values, n/N Obs (%)</b>		
<b>Haemoglobin (g/L)</b>		
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)
<b>Platelets (×10<sup>9</sup>/L)</b>		
Grade 3 (20 to <50)	0/620	0/617
Grade 4 (<20)	0/620	1/617 (0.2)

Neutrophils ( $\times 10^9/L$ )		
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 ( $\times 10^9/L$ )		
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 ( $\times 10^9/L$ )		
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 $\times$ ULN)	16/621 (2.6)	19/618 (3.1)
Grade 4 (>8.0 $\times$ ULN)	3/621 (0.5)	2/618 (0.3)
AST (U/L)		
Grade 3 (3.0 to <8.0 $\times$ ULN)	6/621 (1.0)	11/618 (1.8)
Grade 4 (>8.0 $\times$ ULN)	3/621 (0.5)	2/618 (0.3)

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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)

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\*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						
Hazard ratio (95% CI)	Any UPA 15 mg QD			Any UPA 30 mg QD		
	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)	<b>3.243 (1.243, 8.466)</b>	1.762 (0.828, 3.747)	<b>1.927 (1.022, 3.636)</b>
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)	<b>2.997 (1.147, 7.832)</b>	<b>3.221 (1.271, 8.160)</b>	<b>4.427 (1.271, 15.418)</b>	<b>3.023 (1.171, 7.805)</b>	<b>4.989 (1.882, 13.225)</b>
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	<b>2.314 (1.137, 4.708)</b>	<b>2.701 (1.359, 5.370)</b>	<b>2.558 (1.230, 5.323)</b>	<b>2.697 (1.242, 5.857)</b>	<b>5.578 (2.891, 10.763)</b>	<b>3.073 (1.345, 7.021)</b>

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)
<b>Race</b>			
Non-white	388	5.6	1.795 (1.101, 2.926)
White	2242	3.1	Reference
<b>Geographic region</b>			
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
<b>Age, years</b>			
≥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

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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

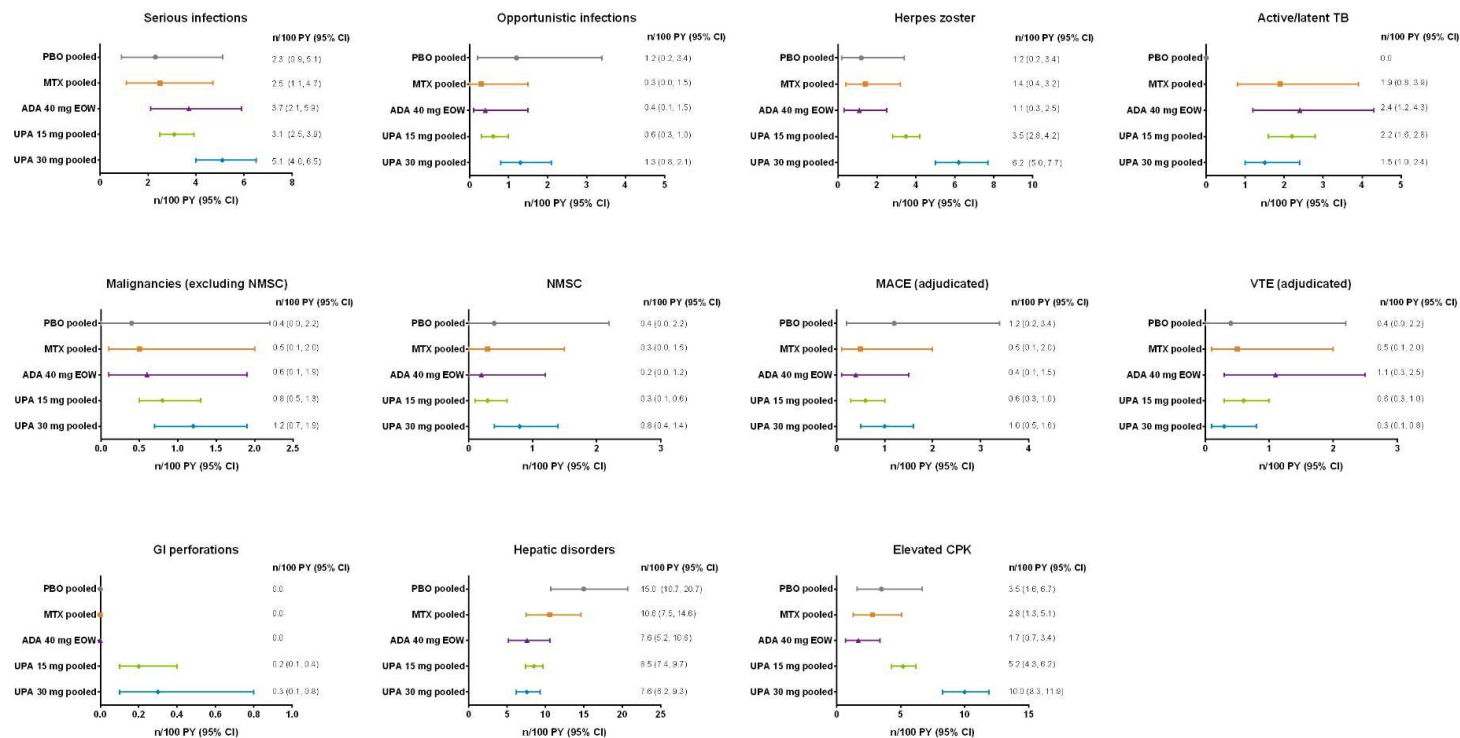
	UPA all phase 3 long-term				
	PBO pooled n=1042 PY=256.8	MTX pooled n=530 PY=368.7	ADA 40 mg EOW n=579 PY=467.8	UPA 15 mg QD n=2630 PY=2655.1	UPA 30 mg QD n=1204 PY=1365.0
E/100 PY (95% CI)	Short-term data up to 12/14 weeks	Long-term MTX monotherapy Mean exposure: 36 weeks (data censored at rescue)	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) <sup>†</sup>	0.0

\*Deaths are only treatment emergent.

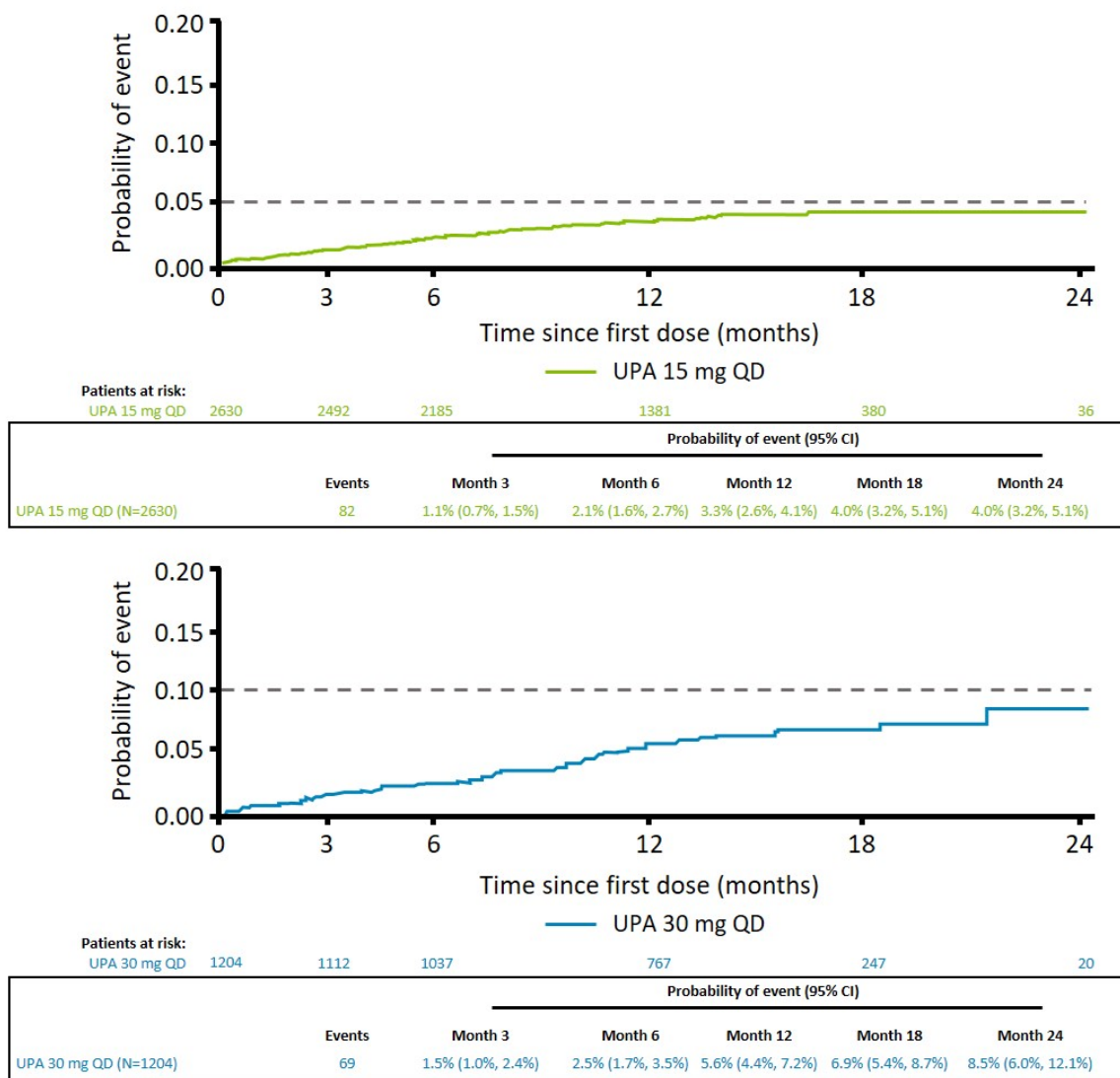
<sup>†</sup>Includes one fatal PE event: 55-year-old female developed PE after prolonged driving.

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

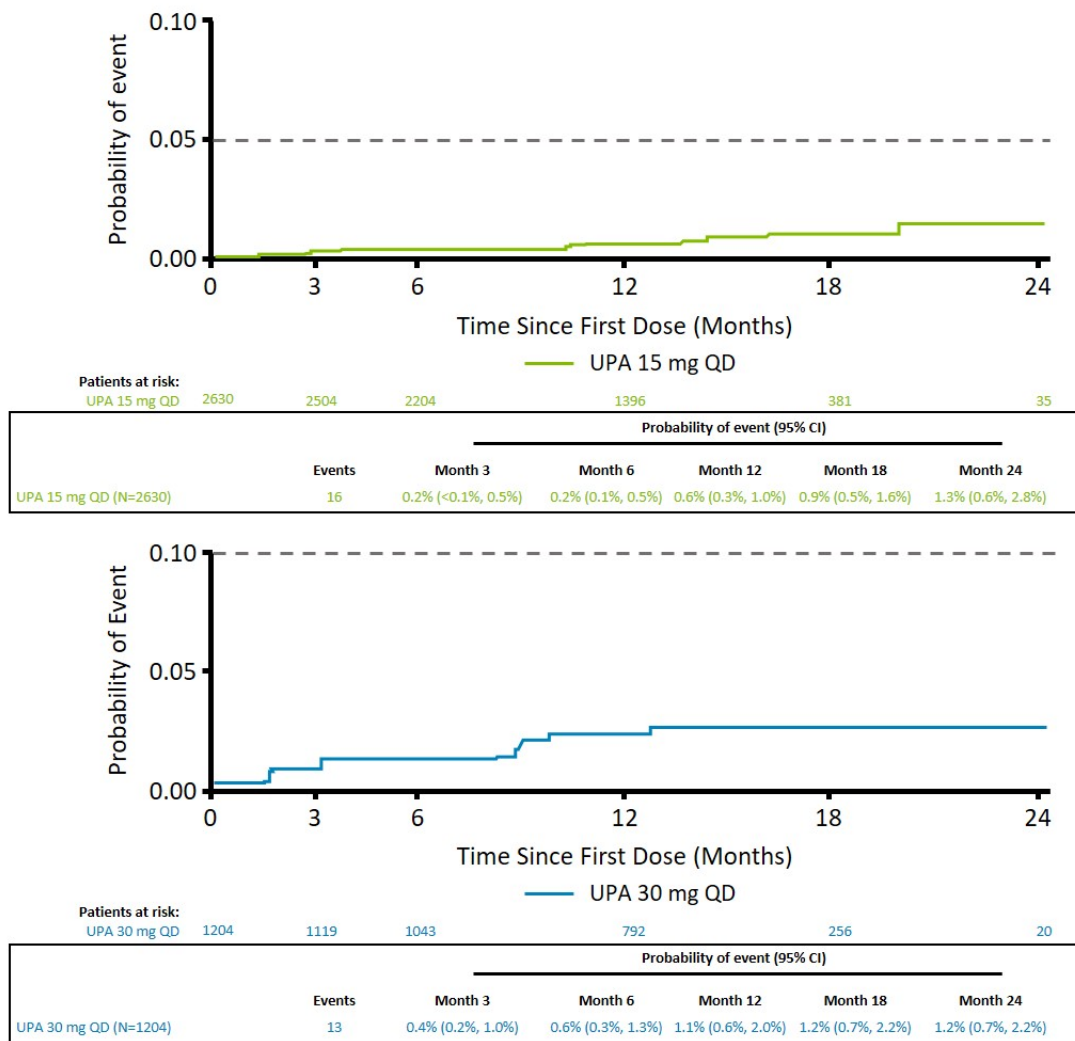
ADA, adalimumab; AEsI, adverse event of special interest; CI, confidence intervals; CPK, creatine phosphokinase; n/100 PY, incidence per 100 patient-years; EOW, every other week; GI, gastrointestinal; MACE, major adverse cardiovascular events; MTX, methotrexate; NMSC, non-melanoma skin cancer; PBO, placebo;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

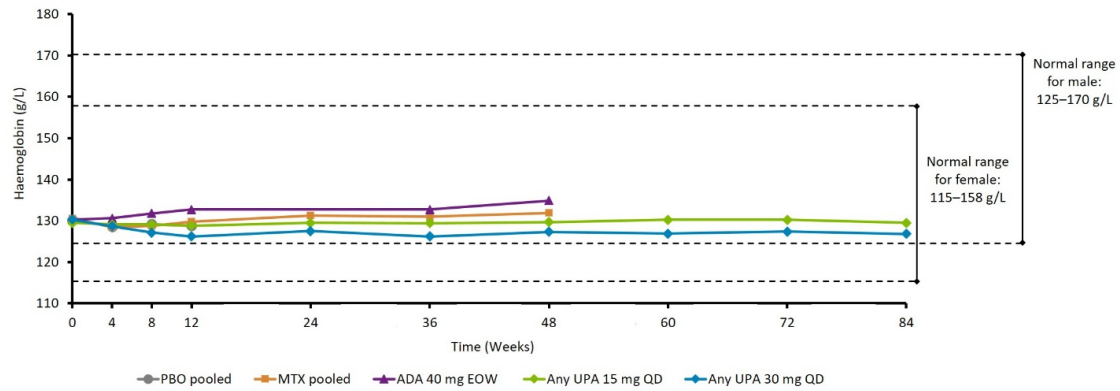
CI, confidence intervals; QD, once daily; UPA, upadacitinib.



**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.