

SUPPLEMENTAL MATERIALS

EXTENDED METHODS

Exclusion Criteria

Cardiovascular exclusion criteria in the SELECT trials were as follows:

- Moderate to severe congestive heart failure (New York Heart Association class III or IV)
- Recent (within past 6 months) cerebrovascular accident, myocardial infarction, or coronary stenting
- Uncontrolled hypertension as defined by a confirmed systolic blood pressure >160 mmHg or diastolic blood pressure >100 mm Hg
- Clinically relevant or significant electrocardiogram (ECG) abnormalities, including ECG with QT interval corrected for heart rate (QTc) using Fridericia's correction formula (QTcF) >500 msec
- Any other condition which, in the opinion of the investigator, would put the patient at risk by participating in the protocol

EXTENDED RESULTS

Adjudicated MACE

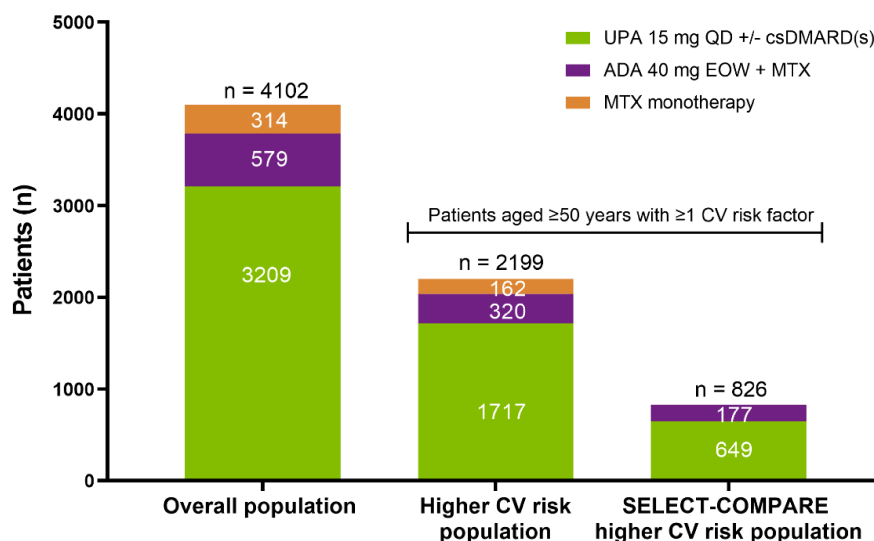
In the overall higher-risk population, 10 non-fatal strokes, 9 non-fatal myocardial infarctions, 1 fatal stroke, and 10 other fatal MACE events (one patient experienced both a fatal and non-fatal MACE) were reported on upadacitinib 15 mg. In the adalimumab group, 3 non-fatal strokes and 1 fatal MACE were reported.

Adjudicated VTE

In the overall higher-risk population, 31 VTE events were reported on upadacitinib: 12 non-fatal PEs, 10 non-fatal DVTs, 7 non-fatal cases of concurrent PE and DVT, and 2 fatal PEs. Of the 5 VTE events reported on adalimumab, all were non-fatal (4 non-fatal PEs and 1 non-fatal DVT).

Supplemental Figure 1. Patient populations and patient treatment exposures

A



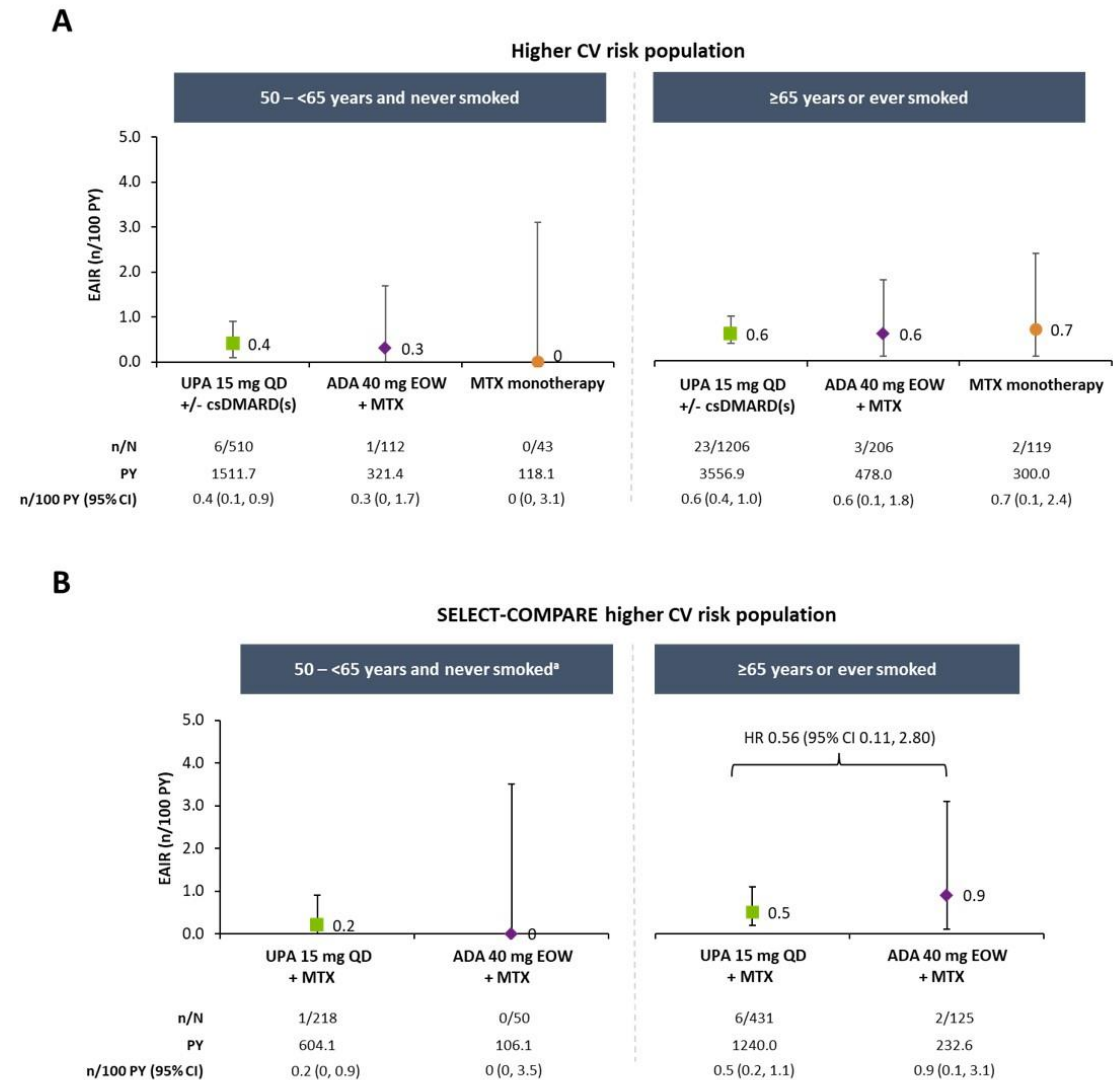
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	UPA 15 mg QD +/- csDMARD(s)	ADA 40 mg EOW + MTX	MTX monotherapy ^a
Treatment exposure, PY			
Overall population	10134.6	1459.0	835.3
Higher CV risk population	5107.2	800.7	418.6
SELECT-COMPARE higher CV risk population	1851.6	339.2	NA
Duration of exposure, median years (Q1–Q3) [maximum]			
Overall population	3.7 (1.4–4.7) [6.1]	2.2 (0.5–4.6) [6.1]	2.6 (0.5–4.6) [5.2]
Higher CV risk population	3.2 (1.0–4.7) [6.0]	2.1 (0.4–4.6) [6.0]	2.3 (0.5–4.6) [5.2]
SELECT-COMPARE higher CV risk population	4.0 (0.5–4.7) [6.0]	0.5 (0.3–4.6) [6.0]	NA

ADA, adalimumab; csDMARD, conventional synthetic DMARD; CV, cardiovascular; EOW, every other week; PY, patient-years; QD, once daily; UPA, upadacitinib.

^aIncludes MTX exposure as monotherapy from patients starting on MTX monotherapy and censored at the time of rescue to UPA plus MTX.

Supplemental Figure 2. Exposure-adjusted incidence of adjudicated MACE in higher CV risk populations by age and smoking status



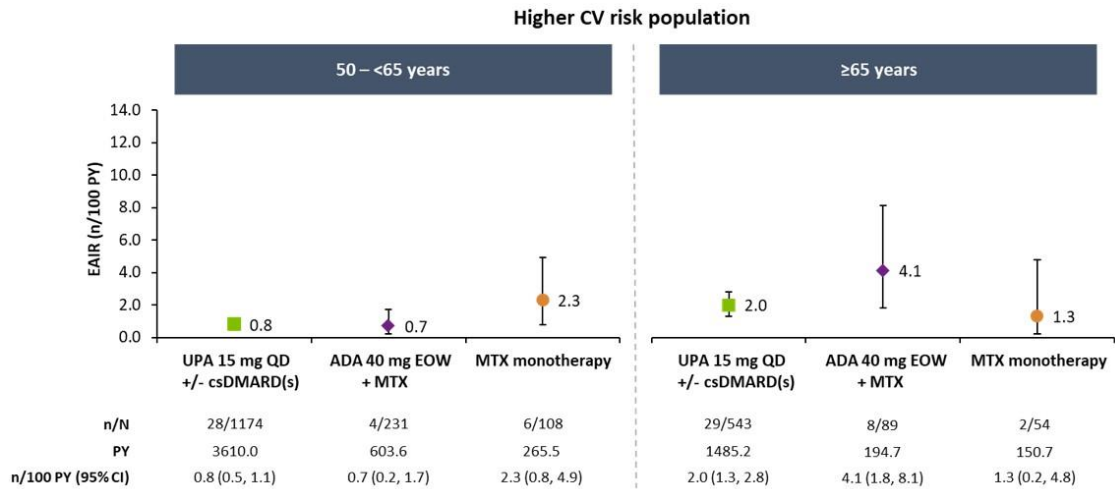
ADA, adalimumab; csDMARD, conventional synthetic DMARD; EAIR, exposure-adjusted incidence rate; EOW, every other week; HR, hazard ratio; MACE, major adverse cardiovascular event; MTX, methotrexate; PY, patient-years; QD, once daily; UPA, upadacitinib.

*No events occurred in adalimumab-treated patients aged 50–<65 years and never smoked.

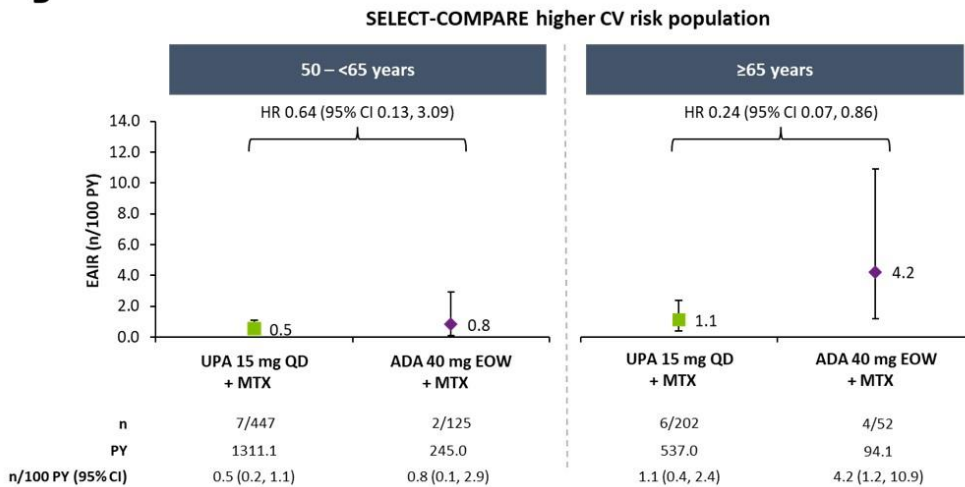
MACE defined as cardiovascular death (includes acute myocardial infarction, sudden cardiac death, heart failure, cardiovascular procedure-related death, death due to cardiovascular hemorrhage, fatal stroke, pulmonary embolism, and other cardiovascular causes), non-fatal myocardial infarction, and non-fatal stroke.

Supplemental Figure 3. Exposure-adjusted incidence of malignancies (excluding NMSC) in higher CV risk populations by age

A



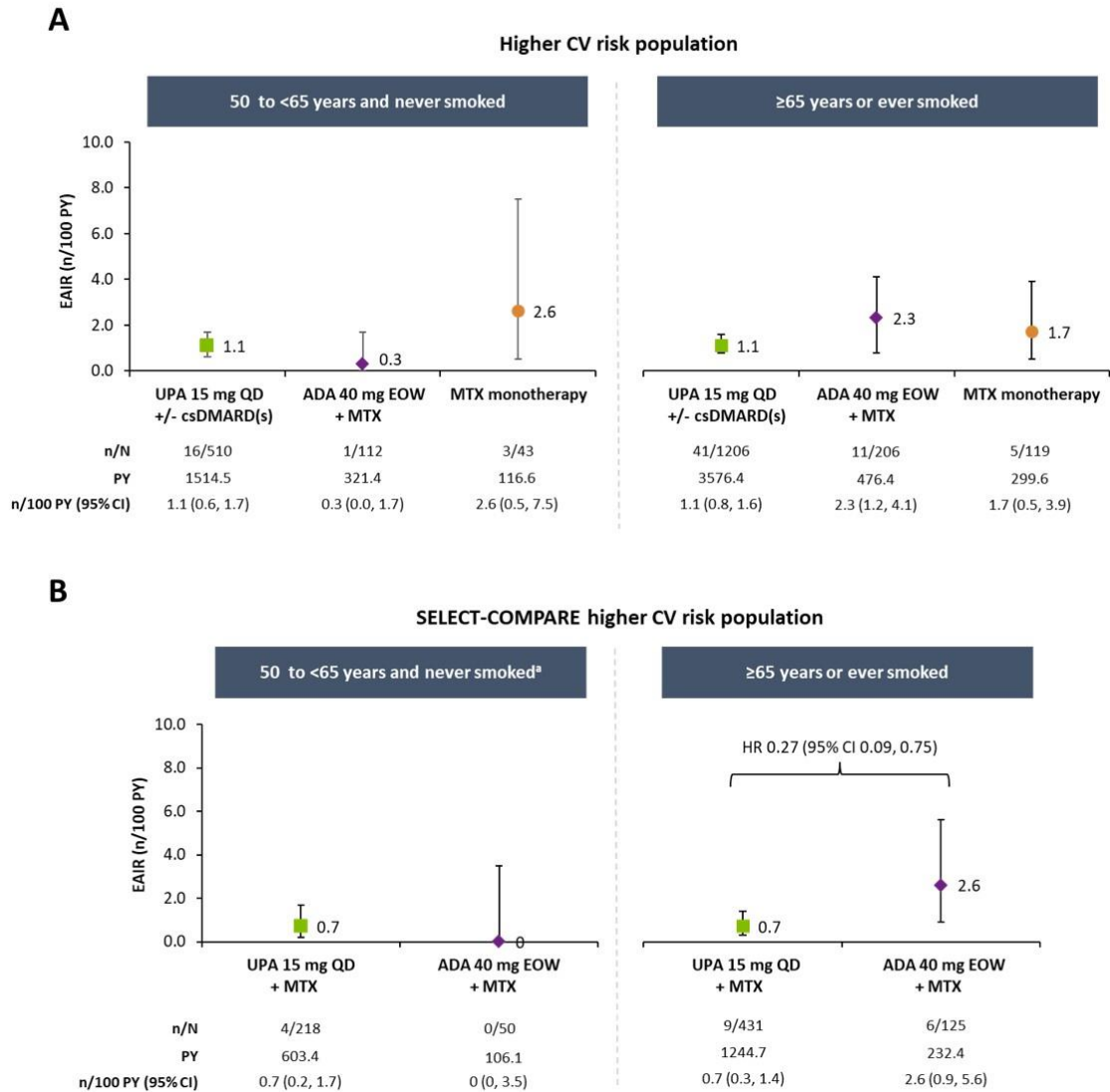
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ADA, adalimumab; csDMARD, conventional synthetic DMARD; EAIR, exposure-adjusted incidence rate; EOW, every other week; HR, hazard ratio; MTX, methotrexate; NMSC, non-melanoma skin cancer; PY, patient-years; QD, once daily; UPA, upadacitinib.

Data are presented as treatment-emergent malignancy rates, with a data cutoff of no more than 30 days after the last dose of study drug for upadacitinib or MTX and up to 70 days for adalimumab if patients discontinued prematurely from the study.

Supplemental Figure 4. Exposure-adjusted incidence of malignancies (excluding NMSC) in higher CV risk populations by age and smoking status

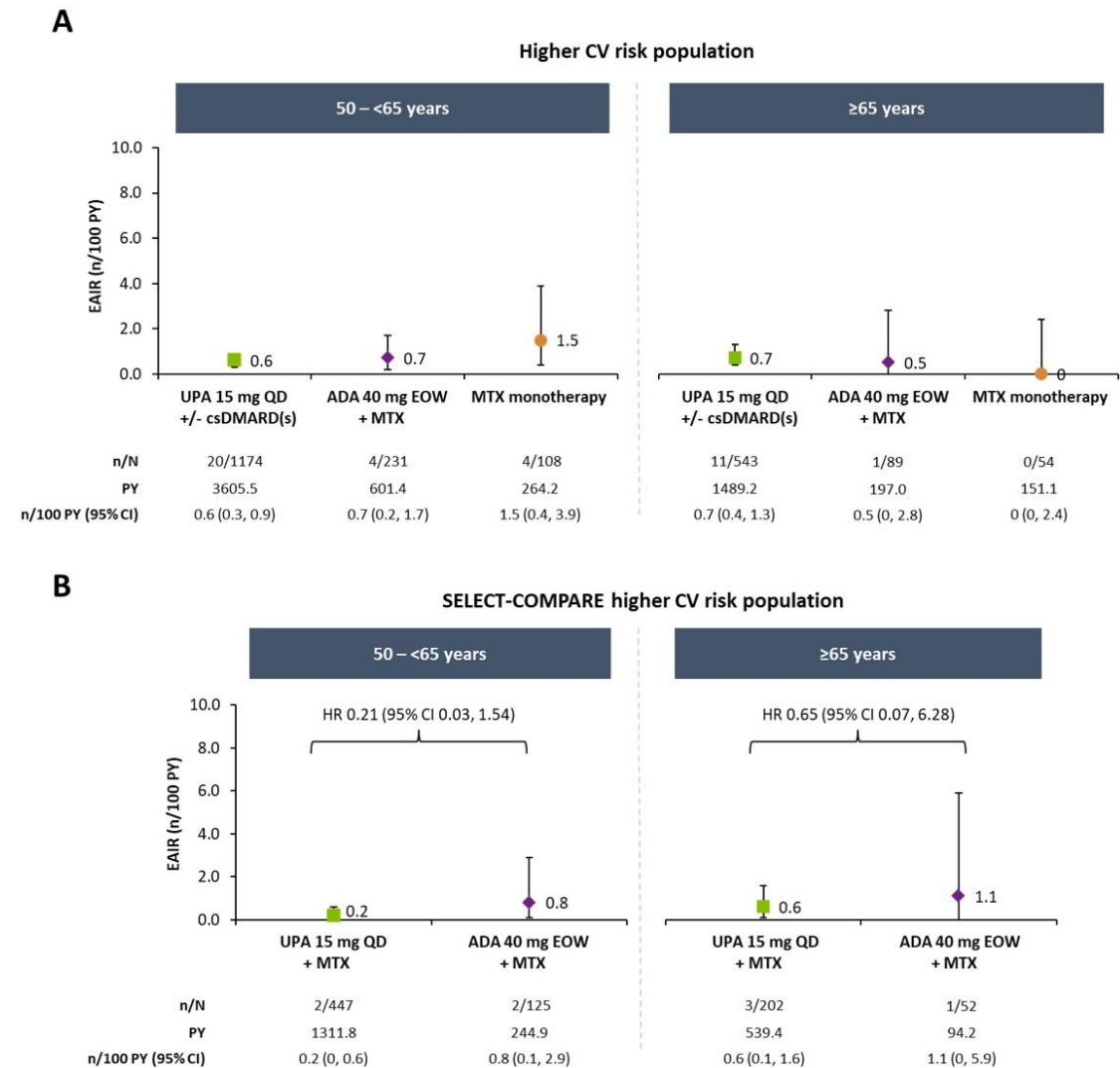


ADA, adalimumab; csDMARD, conventional synthetic DMARD; EAIR, exposure-adjusted incidence rate; EOW, every other week; HR, hazard ratio; MTX, methotrexate; NMSC, non-melanoma skin cancer; PY, patient-years; QD, once daily; UPA, upadacitinib.

^aNo events occurred in adalimumab-treated patients aged 50–<65 years and never smoked.

Data are presented as treatment-emergent malignancy rates, with a data cutoff of no more than 30 days after the last dose of study drug for upadacitinib or MTX and up to 70 days for adalimumab if patients discontinued prematurely from the study.

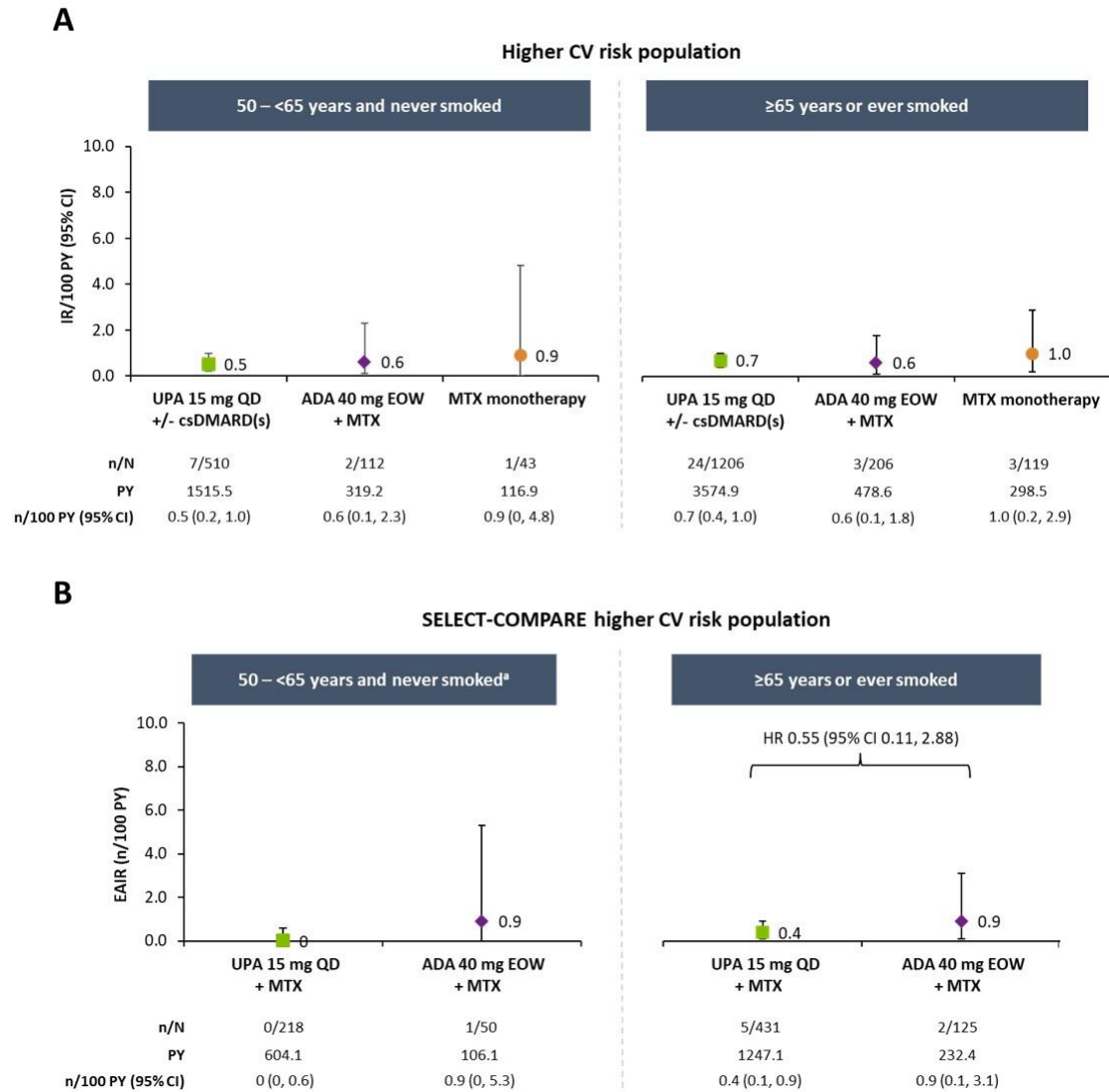
Supplemental Figure 5. Exposure-adjusted incidence of VTE in higher CV risk populations by age



ADA, adalimumab; csDMARD, conventional synthetic DMARD; EAIR, exposure-adjusted incidence rate; EOW, every other week; HR, hazard ratio; MTX, methotrexate; PY, patient-years; QD, once daily; UPA, upadacitinib; VTE, venous thromboembolism.

VTE events include deep vein thrombosis and pulmonary embolism.

Supplemental Figure 6. Exposure-adjusted incidence of adjudicated VTE in higher CV risk populations by age and smoking status



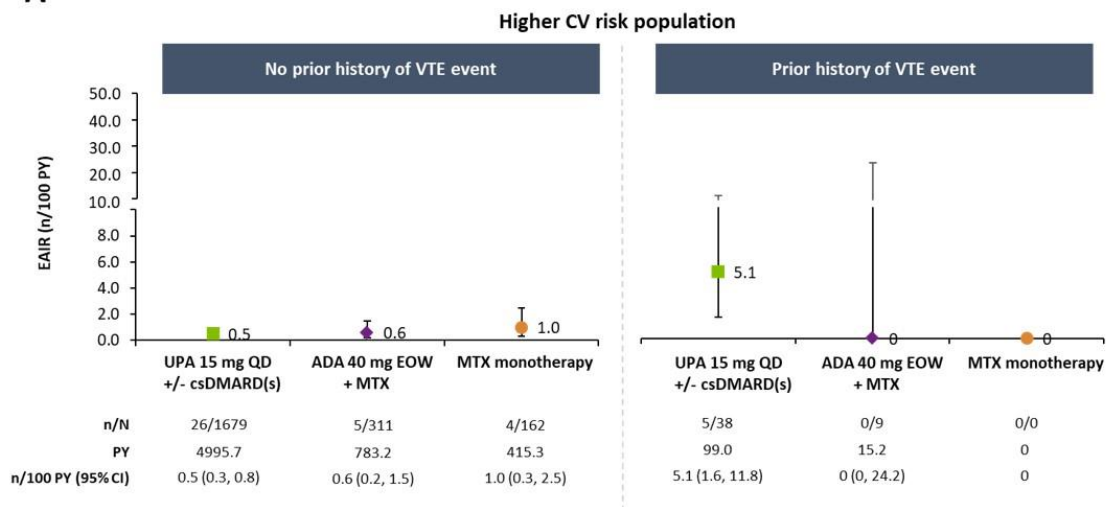
ADA, adalimumab; csDMARD, conventional synthetic, DMARD; EAIR, exposure-adjusted incidence rate; EOW, every other week; HR, hazard ratio; MTX, methotrexate; PY, patient-years; QD, once daily; UPA, upadacitinib; VTE, venous thromboembolism.

*No events occurred in upadacitinib-treated patients aged 50–65 years and never smoked.

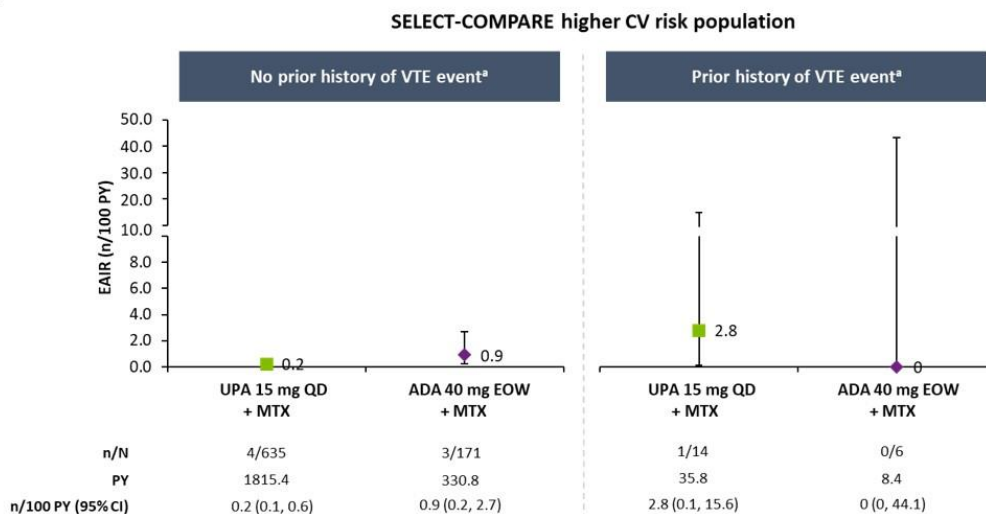
VTE events include deep vein thrombosis and pulmonary embolism.

Supplemental Figure 7. Exposure-adjusted incidence of adjudicated VTE by prior medical history of VTE

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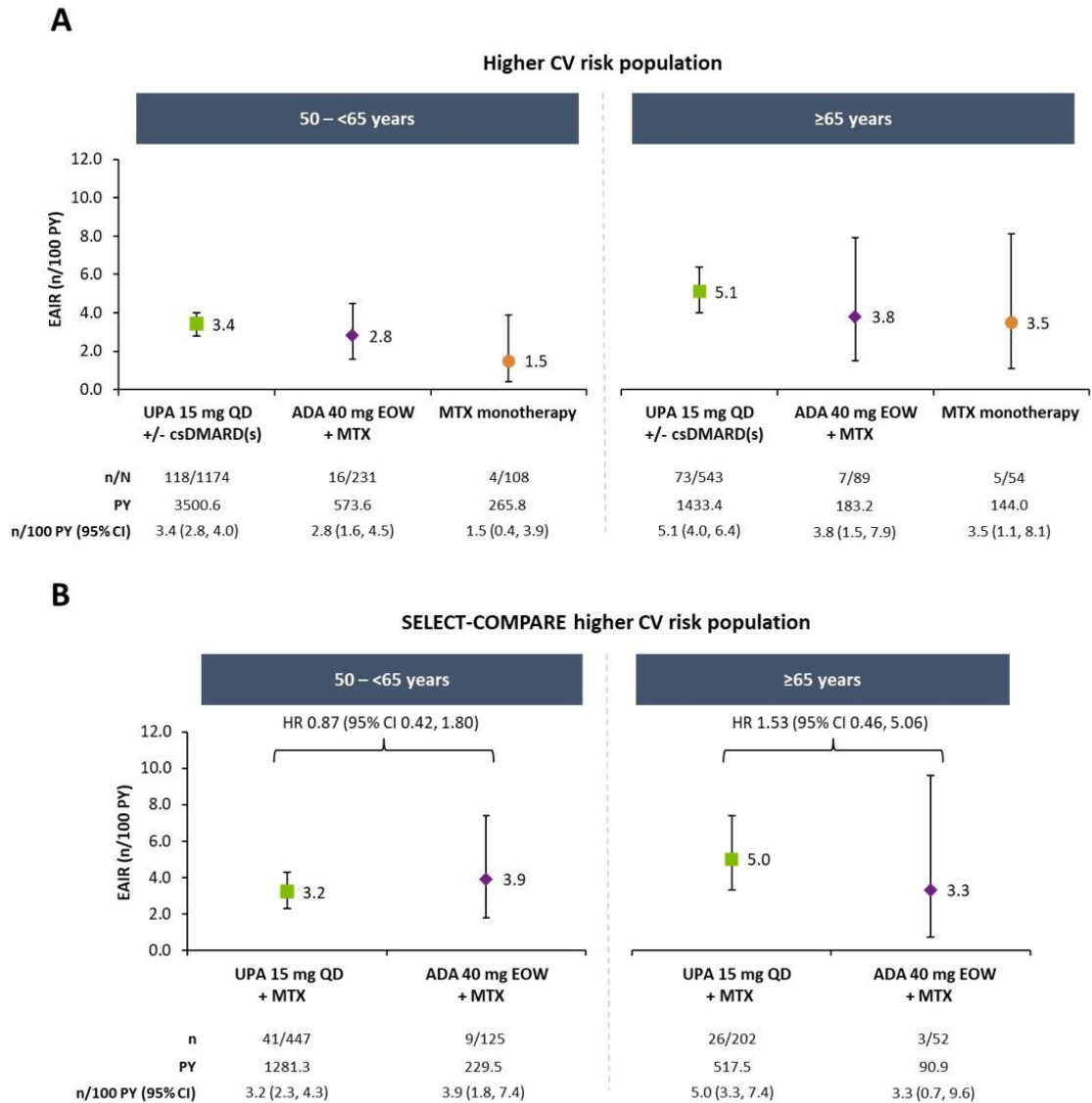


ADA, adalimumab; csDMARD, conventional synthetic, DMARD; EAIR, exposure-adjusted incidence rate; EOW, every other week; HR, hazard ratio; MTX, methotrexate; PY, patient-years; QD, once daily; UPA, upadacitinib; VTE, venous thromboembolism.

^aDue to the small number of events in these subgroups, hazard ratios for upadacitinib vs adalimumab were not calculated.

VTE events include deep vein thrombosis and pulmonary embolism.

Supplemental Figure 8. Exposure-adjusted incidence of serious infections in higher CV risk populations by age



ADA, adalimumab; csDMARD, conventional synthetic, DMARD; EAIR, exposure-adjusted incidence rate; EOW, every other week; HR, hazard ratio; MTX, methotrexate; PY, patient-years; QD, once daily; UPA, upadacitinib.

Supplemental Table 1. Overview of upadacitinib SELECT phase 3 trials and treatment groups

	Patient population	Background	Length of double-blind period	Switch pattern	Primary reference	Treatment ^a	Patients contributing to overall population, n (%) ^b	Patients contributing to higher-risk population, n (%) ^b
SELECT-EARLY	MTX-naïve	-	48 weeks	N/A	van Vollenhoven, et al. <i>Arthritis Rheumatol</i> 2020;72:1607-1620	UPA 15 mg QD	335 (10.4)	148 (8.6)
						MTX	314 (100%)	162 (100%)
SELECT-MONOTHERAPY	MTX-IR	-	14 weeks	Pts originally randomized to MTX switched to UPA 15 mg or UPA 30 mg at week 14	Smolen, et al. <i>Lancet</i> 2019; 393: 2303-11	UPA 15 mg QD	318 (9.9)	183 (10.7)
SELECT-NEXT	csDMARD-IR	csDMARD	12 weeks	Pts originally randomized to PBO switched to UPA 15 mg or UPA 30 mg at week 12	Burmester, et al. <i>Lancet</i> 2018; 391: 2503-12	UPA 15 mg QD	324 (10.1)	184 (10.7)
SELECT-BEYOND	bDMARD-IR	csDMARD	24 weeks	Pts originally randomized to PBO switched (blinded) to UPA 15 mg or UPA 30 mg at week 12	Genovese, et al. <i>Lancet</i> 2018; 391: 2513-24	UPA 15 mg QD	236 (7.4)	147 (8.6)

SELECT-COMPARE	MTX-IR	MTX	48 weeks	Pts originally randomized to UPA were switched to ADA, PBO to UPA 15 mg and ADA to UPA 15 mg at weeks 14, 18, 22, or 26 based on response. Any remaining PBO pts were switched to UPA 15 mg at week 26 regardless of response	Fleischmann, et al. <i>Arthritis Rheumatol</i> 2019; 71: 1788-1800	UPA 15 mg QD	1417 (44.2%)	737 (42.9%)
						ADA 40 mg EOW	579 (100%)	320 (100%)
SELECT-CHOICE	bDMARD-IR	csDMARD	24 weeks	Pts originally randomized to ABA were switched to UPA 15 mg at week 24	Rubbert-Roth, et al. <i>N Engl J Med</i> 2020; 15: 1511-21	UPA 15 mg QD	579 (18.0)	318 (18.5)

ABA, abatacept; ADA, adalimumab; bDMARD, biologic DMARD; csDMARD, conventional synthetic, DMARD; EOW, every other week; IR, incomplete responder; MTX, methotrexate; pts, patients; QD, once daily; UPA, upadacitinib.

^aPatients enrolled in SELECT-COMPARE who switched from upadacitinib 15 mg to adalimumab or vice versa were included in integrated analyses of the overall SELECT population, with assignment based on drug exposure at the time of event.

^bPopulation sizes in the denominator are based on the total number of patients who contributed to each treatment group. For the overall population, n = 3209 on UPA 15 mg, n = 579 on ADA, and n = 314 on MTX monotherapy. For the overall higher CV risk population, n = 1717 on UPA 15 mg, n = 320 on ADA, and n = 162 on MTX monotherapy.

Supplemental Table 2. Exposure-adjusted incidence of malignancies (excluding NMSC) and cancer subtypes in the overall higher CV risk population

Event	UPA 15 mg QD +/- csDMARD(s) (n = 1717)		ADA 40 mg EOW + MTX (n = 320)		MTX monotherapy (n = 162)	
	n (%)	n/100 PY (95% CI) [PY]	n (%)	n/100 PY (95% CI) [PY]	n (%)	n/100 PY (95% CI) [PY]
Malignancies (excluding NMSC)	57 (3.3)	1.1 (0.8, 1.4) [51095.2]	12 (3.8)	1.5 (0.8, 2.6) [798.3]	8 (4.9)	1.9 (0.8, 3.8) [416.2]
Lung cancer	13 (0.8)	0.3 (0.1, 0.4) [5106.6]	2 (0.6)	0.2 (0, 0.9) [800.7]	1 (0.6)	0.2 (0, 1.3) [418.3]
Breast cancer	8 (0.5)	0.2 (0.1, 0.3) [5106.7]	1 (0.3)	0.1 (0, 0.7) [800.6]	0	0 (0, 0.9) [418.6]
Lymphoma	3 (0.2)	< 0.1 (0, 0.2) [5104.9]	3 (0.9)	0.4 (0.1, 1.1) [800.8]	0	0 (0, 0.9) [418.6]
Prostate cancer	1 (0.1)	< 0.1 (0, 0.1) [5107.1]	0	0 (0, 0.5) [800.7]	0	0 (0, 0.9) [418.6]
Colorectal cancer	5 (0.3)	< 0.1 (0, 0.2) [5106.6]	3 (0.9)	0.4 (0.1, 1.1) [800.4]	1 (0.6)	0.2 (0, 1.3) [418.3]
Pancreatic cancer	2 (0.1)	< 0.1 (0, 0.1) [5107.0]	0	0 (0, 0.5) [800.7]	0	0 (0, 0.9) [418.6]
Melanoma	4 (0.2)	< 0.1 (0, 0.2) [5107.0]	1 (0.3)	0.1 (0, 0.7) [800.6]	0	0 (0, 0.9) [418.6]

ADA, adalimumab; csDMARD, conventional synthetic, DMARD; EOW, every other week; MTX, methotrexate; NMSC, non-melanoma skin cancer; PY, patient-years; QD, once daily; UPA, upadacitinib.

Safety data are presented as treatment-emergent rates, with a data cutoff of no more than 30 days after the last dose of study drug for upadacitinib or MTX and up to 70 days for adalimumab if patients discontinued prematurely from the study.

Supplemental Table 3. Exposure-adjusted incidence of serious infections in the overall higher CV risk population

Event	UPA 15 mg QD +/- csDMARD(s) (n = 1717)		ADA 40 mg EOW + MTX (n = 320)		MTX monotherapy (n = 162)	
	n (%)	n/100 PY (95% CI) [PY]	n (%)	n/100 PY (95% CI) [PY]	n (%)	n/100 PY (95% CI) [PY]
Any serious infection	191 (11.1)	3.9 (3.3, 4.5) [4934.0]	23 (7.2)	3.0 (1.9, 4.6) [756.8]	9 (5.6)	2.2 (1.0, 4.2) [409.8]
Pneumonia	41 (2.4)	0.8 (0.6, 1.1) [5069.4]	5 (1.6)	0.6 (0.2, 1.5) [792.2]	2 (1.2)	0.5 (0.1, 1.7) [415.5]
COVID-19 pneumonia	39 (2.3)	0.8 (0.5, 1.0) [5084.1]	1 (0.3)	0.1 (0, 0.7) [800.1]	1 (0.6)	0.2 (0, 1.3) [417.8]
COVID-19	23 (1.3)	0.5 (0.3, 0.7) [5094.7]	1 (0.3)	0.1 (0, 0.7) [799.5]	0	0 (0, 0.9) [418.6]
Sepsis	13 (0.8)	0.3 (0.1, 0.4) [5099.8]	3 (0.9)	0.4 (0.1, 1.1) [797.2]	0	0 (0, 0.9) [418.6]
Cellulitis	10 (0.6)	0.2 (0.1, 0.4) [5094.3]	3 (0.9)	0.4 (0.1, 1.1) [790.0]	2 (1.2)	0.5 (0.1, 1.7) [418.6]
Gastroenteritis	5 (0.3)	< 0.1 (0, 0.2) [5104.3]	0	0 (0, 0.5) [800.7]	0	0 (0, 0.9) [418.6]
Urinary tract infection	5 (0.3)	< 0.1 (0, 0.2) [5105.5]	2 (0.6)	0.3 (0, 0.9) [799.4]	0	0 (0, 0.9) [418.6]
Herpes zoster	10 (0.6)	0.2 (0, 0.4) [5093.9]	0	0 (0, 0.5) [800.7]	0	0 (0, 0.9) [418.6]
Septic shock	3 (0.2)	< 0.1 (0, 0.2) [5106.1]	0	0 (0, 0.9) [800.7]	0	0 (0, 0.9) [418.6]
Pulmonary tuberculosis	2 (0.1)	< 0.1 (0, 0.1) [5106.5]	0	0 (0, 0.5) [800.7]	0	0 (0, 0.9) [418.6]

ADA, adalimumab; csDMARD, conventional synthetic, DMARD; EOW, every other week; MTX, methotrexate; PY, patient-years; QD, once daily; UPA, upadacitinib.

Supplemental Table 4. Exposure-adjusted incidence of adverse events in patients receiving upadacitinib 30 mg from the overall and higher CV risk populations

Event ^b	Overall population UPA 30 mg QD +/- csDMARD(s) ^a (n = 1204)		Higher CV risk population UPA 30 mg QD +/- csDMARD(s) ^a (n = 677)	
	n	n/100 PY (95% CI) [PY]	n	n/100 PY (95% CI) [PY]
Adjudicated MACE ^c	20	0.6 (0.4, 1.0) [3178.0]	18	1.1 (0.6, 1.7) [1686.3]
Malignancies (excluding NMSC)	35	1.1 (0.8, 1.5) [3190.3]	23	1.4 (0.9, 2.0) [1699.0]
NMSC	26	0.8 (0.5, 1.2) [3157.7]	21	1.3 (0.8, 1.9) [1669.9]
Adjudicated VTE ^d	13	0.4 (0.2, 0.7) [3184.6]	9	0.5 (0.2, 1.0) [1695.5]
Serious infection	127	4.1 (3.4, 4.9) [3075.1]	90	5.5 (4.5, 6.8) [1624.5]
Herpes zoster	157	5.3 (4.5, 6.3) [2935.4]	94	6.1 (4.9, 7.4) [1547.3]
Deaths ^e	29	0.9 (0.6, 1.3) [3197.0]	24	1.4 (0.9, 2.1) [1702.5]

ADA, adalimumab; csDMARD, conventional synthetic DMARD; EOW, every other week; MACE, major adverse cardiovascular event; MTX, methotrexate; NMSC, non-melanoma skin cancer; PY, patient-years; QD, once daily; UPA, upadacitinib; VTE, venous thromboembolism.

^aUPA 30 mg data was pooled from four SELECT phase 3 trials that included the 30 mg dose. Baseline disease characteristics and demographics were generally consistent with those reported in Table 1 for the UPA 15 mg group, although fewer patients received background csDMARD(s) on UPA 30 mg. The number of patients on UPA 30 mg who contributed from each of the individual trials are as follows. In the overall population (n = 1204), 240 (19.9%) from SELECT-BEYOND, 332 (27.6%) from SELECT-EARLY, 321 (26.7%) from SELECT-NEXT, and 311 (25.8%) from SELECT-MONOTHERAPY. In the higher CV risk population (n = 677), 147 (21.7%) from SELECT-BEYOND, 170 (25.1%) from SELECT-EARLY, 193 (28.5%) from SELECT-NEXT, and 167 (24.7%) from SELECT-MONOTHERAPY.

^bExcept for deaths, safety results are presented as treatment-emergent outcomes, occurring no more than 30 days after the last dose of upadacitinib.

^cMACE defined as cardiovascular death (includes acute myocardial infarction, sudden cardiac death, heart failure, cardiovascular procedure-related death, death due to cardiovascular hemorrhage, fatal stroke, pulmonary embolism, and other cardiovascular causes), non-fatal myocardial infarction, and non-fatal stroke.

^dVTE events include deep vein thrombosis and pulmonary embolism.

^eIncludes non-treatment-emergent deaths.