Table 10.5. Comparison of Serious Infections between Baricitinib- and TNFi-Treated Patients in Multiple Databases

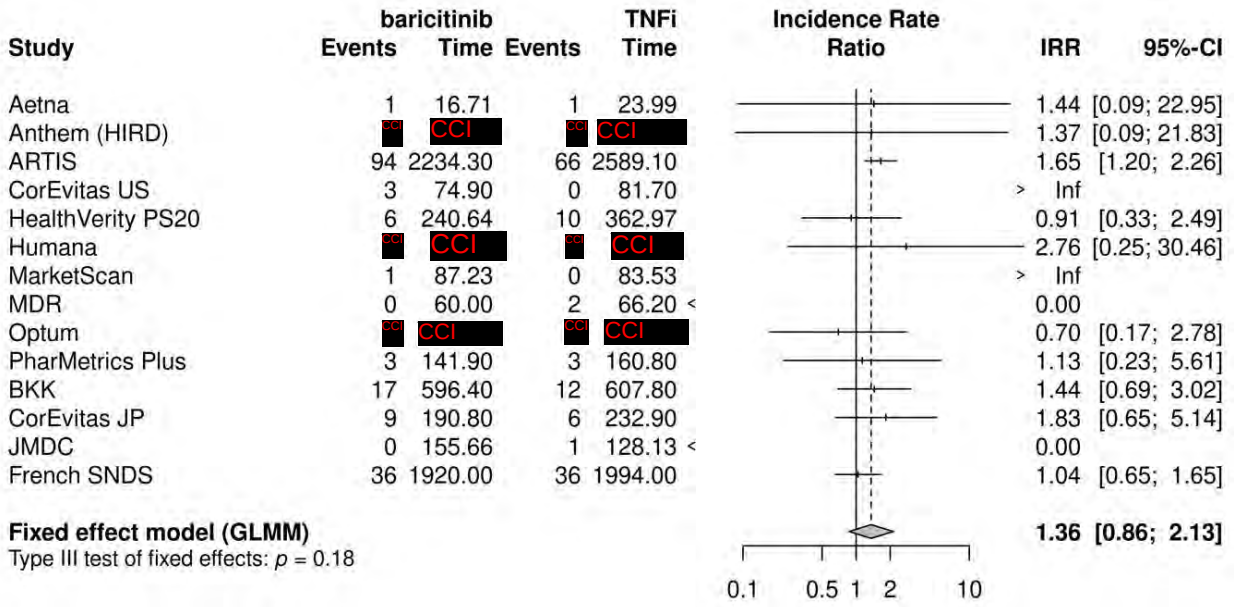
Data Source	Baricitinib **n** [Events, PY]	TNFi **n** [Events, PY]	$IR_{baricitinib}$, IR_{TNFi}, IRD (95% CI) per 100 PY	HR (95% CI)[a]	IRR (95% CI)
All Available Data					
Overall	-	-	**IRD = 0.57 (-0.07, 1.21)**	-	**1.36 (0.86, 2.13)**
US Data					
Aetna /Healthagen	**44** [1, 16.71]	**44** [1, 23.99]	$IR_{baricitinib}$ = 5.98 (0.15, 33.34) IR_{TNFi} = 4.17 (0.11, 23.23) IRD = 1.82 (-12.09, 15.72)	1.71 (0.10, 30.54)	1.44 (0.09, 22.95)
Anthem (HIRD)	**130** [≤10, 73.30]	**130** [≤10, 100.10]	$IR_{baricitinib}$ = 1.36 (0.03, 7.60) IR_{TNFi} = 1.00 (0.03, 5.57) IRD = 0.37 (-2.93, 3.66)	1.22 (0.08, 19.77)	1.37 (0.09, 21.83)
CorEvitas US	**114** [3, 74.9]	**114** [0, 81.7]	$IR_{baricitinib}$ = 4.0 (0.8, 11.7) IR_{TNFi} = 0 (0, 4.5) IRD = 4.01 (-1.00, 9.01)	-	-
HealthVerity PS20	**748** [6, 240.64]	**748** [10, 362.97]	$IR_{baricitinib}$ = 2.49 (0.92, 5.43) IR_{TNFi} = 2.76 (1.05, 4.46) IRD = -0.26 (-2.85, 2.33)	0.86 (0.31, 2.28)	0.91 (0.33, 2.49)
Humana	**53** [[redacted], CCI]	**53** [[redacted], CCI]	$IR_{baricitinib}$ = 10.12 (1.23, 36.54) IR_{TNFi} = 3.66 (0.09, 20.41) IRD = 6.45 (-8.59, 21.50)	2.41 (0.21, 27.25)	2.76 (0.25, 30.46)
MarketScan	**194** [1, 87.23]	**194** [0, 83.53]	$IR_{baricitinib}$ = 1.15 (0.03, 6.39) IR_{TNFi} = 0 (0, 4.42) IRD = 1.15 (-2.01, 4.30)	-	-
MDR	**115** [0, 60.0]	**115** [2, 66.20]	$IR_{baricitinib}$ = 0 (0, 6.15) IR_{TNFi} = 3.0 (0.8, 12.1) IRD = -3.02 (-8.08, 2.04)	-	0
Optum	**300** [[redacted], CCI 8]	**300** [[redacted], CCI]	$IR_{baricitinib}$ = 2.39 (0.49, 7.00) IR_{TNFi} = 3.44 (1.26, 7.49) IRD = -1.05 (-4.85, 2.76)	0.69 (0.17, 2.80)	0.70 (0.17, 2.78)

Data Source	**Baricitinib** **n** [Events, PY]	**TNFi** **n** [Events, PY]	**$IR_{baricitinib}$, $IR_{TNF\ blocker}$, IR Diff.** (95% CI) per 100 PY	HR (95% CI)[a]	**IRR (95% CI)**
All Available Data					
Overall	**-**	**-**	**IRD = 0.57 (-0.07, 1.21)**	**-**	**1.36 (0.86, 2.13)**
US Data					
PharMetrics Plus	**265** [3, 141.90]	**265** [3, 160.8]	$IR_{baricitinib}$ = 2.1 (0.7, 6.6) IR_{TNFi} = 1.9 (0.6, 5.8) IRD = 0.25 (-2.91, 3.41)	1.17 (0.2, 5.8)	1.13 (0.23, 5.61)
OUS Data					
ARTIS	**1683** [94, 2234.3]	**1683** [66, 2589.1]	$IR_{baricitinib}$ = 4.21 (3.44, 5.15) IR_{TNFi} = 2.55 (2.00, 3.24) *RD = 1.66 (0.63, 2.69)	**1.72 (1.24, 2.39)**	**1.65 (1.20, 2.26)**
BKK	**859** [17, 596.40]	**859** [12, 607.80]	$IR_{baricitinib}$ = 2.9 (1.7, 4.6) IR_{TNFi} = 2.0 (1.0, 3.4) IRD = 0.88 (-0.86, 2.61)	1.44 (0.7, 3.0)	1.44 (0.69, 3.02)
CorEvitas JP	**170** [9, 190.8]	**170** [6, 232.90]	$IR_{baricitinib}$ = 4.7 (2.2, 9.0) IR_{TNFi} = 2.6 (0.9, 5.6) IRD = 2.14 (-1.49, 5.77)	1.44 (0.49.4.23)	1.83 (0.65, 5.14)
JMDC	**220** [0, 155.66]	**220** [0, 128.13]	$Ir_{baricitinib}$ = 0 (0, 2.38) IR_{TNFi} = 0.78 (0.02, 4.35) IRD = -0.78 (-2.83, 1.27)	-	0
SNDS (France)	**2979** [36, 1920.00]	**2979** [36, 1994.00]	$IR_{baricitinib}$ = 1.9 (1.3, 2.6) IR_{TNFi} = 1.8 (1.3, 2.5) IRD = 0.07 (-0.77, 0.91)	1.04 (0.65, 1.66)	1.04 (0.65, 1.65)

Abbreviations: ARTIS = Anti-Rheumatic Therapy in Sweden; BKK = Betriebskrankenkasse; CI = confidence interval; HIRD = HealthCore Integrated Research Database; HR = hazard ratio; IR = incidence rate; $IR_{baricitinib}$ = incidence rate for the baricitinib-treated cohort; IR_{TNFi} = incidence rate for the TNFi-treated cohort; IRD = incidence rate difference; IRR = incidence rate ratio; JMDC = Japan Medical Data Center, Inc's claims database; JP = Japan; MDR = Military Data Repository; OUS = outside the United States; PS20 = Healthy Verity Private Source 20; PY = person years; SNDS = Système National des Données de Santé; TNFi = tumour necrosis factor inhibitor; US = United States.

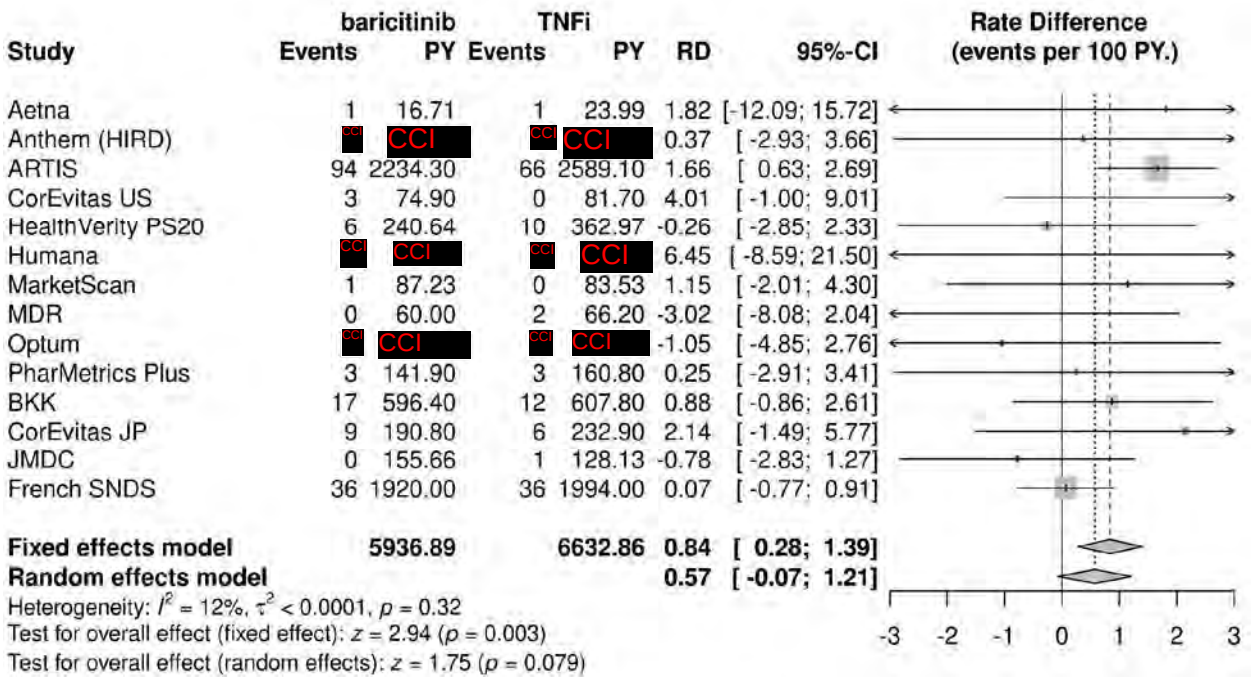
[a] Hazard ratios from base model comparing propensity score-matched treatment cohorts, except for the Anthem HIRD and CorEvitas Japan which report model 1 results to include variables imbalanced after propensity score-matching. This included rheumatologist visits for HIRD (see Table 61_HIRD for detail) and body mass index and smoking for CorEvitas Japan (see Checking that this is an external link.for detail).

Note: Any differences between confidence intervals for the individual incidence rate differences reported here and in Section 10.3 are due to different methods used for the calculation.



Abbreviations: ARTIS = Anti-Rheumatic Therapy in Sweden; BKK = Betriebskrankenkasse; CI = confidence interval; HIRD = HealthCore Integrated Research Database; IRR = incidence rate ratio; GLMM = generalized linear mixed model; JMDC = Japan Medical Data Center, Inc.'s claims database; JP = Japan; MDR = Military Data Repository; PS20 = HealthyVerity Private Source 20; SNDS = Système National des Données de Santé; TNFi = tumour necrosis factor inhibitor.
Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\irr_si_14ds.png

Figure 10.5. Meta-analysis on incidence rate ratios for serious infections comparing baricitinib and TNFi.



Abbreviations: ARTIS = Anti-Rheumatic Therapy in Sweden; BKK = Betriebskrankenkasse; CI = confidence interval; HIRD = HealthCore Integrated Research Database; JMDC = Japan Medical Data Center, Inc.'s claims database; JP = Japan; MDR = Military Data Repository; PS20 = HealthyVerity Private Source 20; PY = person years; RD = incidence rate difference; SNDS = Système National des Données de Santé; TNFi = tumour necrosis factor inhibitor; US = United States.
Note: Any differences between confidence intervals for the individual IRD reported here and in Section 10.3 are due to different methods used for the calculation.
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Figure 10.6. Meta-analysis on incidence rate differences in serious infections comparing baricitinib and TNFi.

10.1.6. Tuberculosis results

A secondary objective of this study was to describe the risk of TB requiring hospitalization among patients with RA. In the 9,013 eligible baricitinib-treated patients identified across all data sources included in this study (Table 10.1), there were zero events of hospitalised TB. The only hospitalizations due to TB were identified within the TNFi cohort of the French SNDS data, where 3 cases were found in the unmatched eligible TNFi cohort and 1of those was included in the matched TNFi cohort (see Table 64 in Annex 16). As no TB events requiring hospitalization were found among baricitinib-treated patients included in this study, no further results are presented.

10.2. Descriptive data

This section provides descriptive information for all individual data sources. It is organized by geography (US data sources, followed by European and Japanese data sources), then within each data source, descriptive information is provided for the matched analytic cohorts for each respective outcome: VTE, MACE, serious infection in order. The analytic cohorts are generated by propensity score matching baricitinib-treated patients with patients treated with TNFi, separately for each respective outcome and data source.

Important note regarding the table numbering for results in this section: As described in Section 9.9, the protocol and SAP were shared with each individual data partner. Results were generated for each data source, as applicable, and the tables generated follow the same numbering structure. For example, "Table 1" from each data source is the baseline demographics in the unmatched VTE cohorts, "Table 2" from each data source is the baseline characteristics in the matched VTE cohorts, and so on. To prevent duplication, each table has the respective data source appended to the Table number as a suffix, eg, Table 2_Aetna. Any table generated that is not included in the body of this report may be found in the respective Annex of "Additional Results" for the data source. If the table is not in the body nor the Annex, the table was not generated for that data source. All other tables throughout the document follow the naming convention of sequential numbering with a suffix for the respective section, eg, Table 10.1.

Comparisons should not be made between individual baricitinib dose groups and the TNFi cohort, or between the dose groups themselves, or any groups other than the intended baricitinib and TNFi comparison cohorts. The dose subgroups have not been propensity score-matched with each other or the TNFi cohort. The treatment groups themselves have also been modified by the propensity score-matching process. Thus, the characteristics of these subgroups may not reflect the underlying patients receiving these doses (or medications) and may differ in important ways that have not been controlled for. An understanding of the characteristics of patients treated with each baricitinib dose is best provided by inspection of the unmatched eligible patient populations (eg, Table 1 and Table 6 for patients in the unmatched eligible treatment cohorts for the VTE analyses in ARTIS and SNDS, data available in Annex 11 and Annex 16, respectively).

10.2.1. US data sources

10.2.1.1. Aetna (Healthagen)

There were 69 eligible patients treated with baricitinib and 289 eligible TNFi patients in the Aetna database. Demographic and clinical characteristics for these unmatched cohorts are in Annex 2. From these unmatched cohorts, the number of patients included in analyses of VTE, MACE, or serious infection after 1:1 matching varies. Details of these analysis-specific cohorts follow.

10.2.1.1.1. VTE cohort

After propensity score matching, there were a total of 74 patients (37 each in the baricitinib and TNFi cohorts) included in the analysis of VTE (Table 2_Aetna). The small size of the analysis cohort limited the ability to evaluate the characteristics of the treatment groups at baseline. On

average, patients analysed were aged 55.91 years at baseline (range 26 to 79 years) and were almost all (91.9%) female. Based on standardised differences >0.10 after propensity score matching, patients treated with baricitinib were younger (mean 54.24 years vs 57.57 years, respectively) and slightly less likely to be female (89.2% and 94.6%) than those treated with TNFi.

Clinical characteristics of patients at baseline are described in Table 7_Aetna. The most commonly observed conditions with at least 10 total cases were dyslipidaemia (baricitinib 29.7%, TNFi 51.4%), hypertension (baricitinib 40.5%, TNFi 35.1%), and obesity (baricitinib 21.6%, TNFi 16.2%). Smoking was also prevalent (13.5% for baricitinib and TNFi each, respectively) With regard to RA severity, the CIRAS score was slightly elevated among the baricitinib compared to the TNFi cohort (baricitinib 4.68, TNFi 4.44), but it's not clear that this is a meaningful difference.

RA treatment received prior to the index medication is described in Table 7_Aetna. Over half of patients used cDMARDs (baricitinib 56.8%, TNFi 64.9%), with methotrexate recorded most frequently (baricitinib 40.5%, TNFi 43.2%). Patients treated with baricitinib were more likely to have >1 cDMARD concomitantly than those treated with TNFi (baricitinib 24.3%, TNFi 8.1%). Prior use of bDMARDs was observed in almost 30% (n = 11) of the baricitinib cohort in contrast to the TNFi cohort (97.3%, n = 36). Note that the high prevalence of bDMARD use in the TNFi cohort is due to the eligibility requirement for the TNFi patients in US claims data. This is to better align TNFi use in the comparison group with the USPI for baricitinib. Etanercept (45.9%) was the most frequently recorded prior bDMARD used by the TNFi cohort.

Baseline healthcare resource utilisation was not dissimilar across the baricitinib and TNF cohorts (Table 12B_Aetna). As a group, baricitinib patients had slightly more rheumatologist visits over the 6-month baseline but were less likely to have inpatient visits than patients within the TNFi cohort. Note that Table 12B_Aetna reports visit days per patient (ie, at most 1 visit per day), but the propensity scores model actually controlled for the total number of visits during the period (ie, more than 1 visit; see Table 12A in Annex 2) could occur per day.

Table 2_Aetna Baseline Demographics VTE Cohorts, Matched [Aetna]

Characteristic	Baricitinib			TNFi (N = 37)	Std. Diff. (Any vs TNFi)	Total (N = 74)
	Any (N = 37)	4 mg (N = 0)	2 mg (N = 37)			
Age (yrs)						
N	37	-	37	37		74
Mean (SD)	54.24 (13.11)	-	54.24 (13.11)	57.57 (11.72)	0.27	55.91 (12.46)
Median [IQR]	57.00 [43.00, 64.50]	-	57.00 [43.00, 64.50]	58.00 [49.00, 65.50]		57.50 [46.75, 65.00]
Min, Max	26.0, 76.0	-	26.0, 76.0	33.0, 79.0		26.0, 79.0
≥65 years	9 (24.3%)	-	9 (24.3%)	11 (29.7%)	0.12	20 (27.0%)
Sex						
Male	4 (10.8%)	-	4 (10.8%)	2 (5.4%)	0.20	6 (8.1%)
Female	33 (89.2%)	-	33 (89.2%)	35 (94.6%)	0.20	68 (91.9%)

Abbreviations: IQR = interquartile range; max = maximum; min = minimum; N = number of patients within specified category; SD = standard deviation; Std. Diff. = standardised difference; TNFi = tumour necrosis factor inhibitor; vs = versus; VTE = venous thromboembolism; yrs = years.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\AETNA\7. Table 6.2. - Baseline Demographics VTE Cohorts, Matched [Healthagen].docx

Table 7_Aetna Clinical Characteristics Primary VTE Cohorts, Matched [Aetna]

Characteristic[a,b]	Baricitinib[c] (N = 37)	TNFi (N = 37)	Std. Diff.
Clinical Conditions during baseline			
Cancer	5 (13.5%)	3 (8.1%)	0.18
NMSC	1 (2.7%)	0 (0.0%)	0.24
Chronic lung disease	3 (8.1%)	5 (13.5%)	0.18
Cardiovascular conditions			
Atrial arrhythmia/fibrillation	1 (2.7%)	2 (5.4%)	0.14
Cardiovascular revascularization	0 (0.0%)	0 (0.0%)	-
Congestive heart failure, hospitalized	0 (0.0%)	0 (0.0%)	-
Coronary artery disease	0 (0.0%)	1 (2.7%)	0.24
Ischemic heart disease	0 (0.0%)	1 (2.7%)	0.24
Unstable angina	0 (0.0%)	1 (2.7%)	0.24
Ventricular arrhythmia	0 (0.0%)	2 (5.4%)	0.34
Diabetes Mellitus	3 (8.1%)	5 (13.5%)	0.18
Type I	2 (5.4%)	0 (0.0%)	0.34
Type II	3 (8.1%)	5 (13.5%)	0.18
Dyslipidaemia	11 (29.7%)	19 (51.4%)	0.45
Hypertension	15 (40.5%)	13 (35.1%)	0.11
Immune disorders	7 (18.9%)	4 (10.8%)	0.23
AIDS/HIV	0 (0.0%)	0 (0.0%)	-
Antiphospholipid syndrome	1 (2.7%)	0 (0.0%)	0.24
SLE	4 (10.8%)	1 (2.7%)	0.33

Characteristic[a,b]	Baricitinib[c] (N = 37)	TNFi (N = 37)	Std. Diff.
Primary Sjögren syndrome	3 (8.1%)	3 (8.1%)	0.00
Liver disorder	2 (5.4%)	0 (0.0%)	0.34
Obesity	8 (21.6%)	6 (16.2%)	0.14
Pregnancy	0 (0.0%)	0 (0.0%)	-
RA severity (CIRAS Index), mean (SD)	4.68 (1.43)	4.44 (1.31)	0.18
Smoking	5 (13.5%)	5 (13.5%)	0.00
Surgery, trauma & hospitalization, recent	1 (2.7%)	4 (10.8%)	0.33
TIA	0 (0.0%)	0 (0.0%)	-
DMARDs			
cDMARDs, during baseline			
n, total	21 (56.8%)	24 (64.9%)	0.17
Mean (SD)	0.89 (0.84)	0.78 (0.67)	0.14
Median	1.00 [0.00, 1.50]	1.00 [0.00, 1.00]	-
Min, Max	0.0, 3.0	0.0, 3.0	-
>1 cDMARD concomitantly	9 (24.3%)	3 (8.1%)	0.45
Hydroxychloroquine	6 (16.2%)	5 (13.5%)	0.08
Leflunomide	7 (18.9%)	2 (5.4%)	0.42
Methotrexate	15 (40.5%)	16 (43.2%)	0.06
Minocycline	0 (0.0%)	0 (0.0%)	-
Sulfasalazine	2 (5.4%)	2 (5.4%)	0.00
bDMARDs, during baseline[a]			
n, total	11 (29.7%)	36 (97.3%)	1.97
Mean (SD)	0.32 (0.53)	1.30 (0.52)	1.85
Median	0.00 [0.00, 1.00]	1.00 [1.00, 2.00]	-
Min, Max	0.0, 2.0	1.0, 3.0	-
cDMARDs, concomitant	5 (13.5%)	19 (51.4%)	0.88
abatacept	3 (8.1%)	3 (8.1%)	0.00
adalimumab[d]	2 (5.4%)	6 (16.2%)	0.35
anakinra	0 (0.0%)	0 (0.0%)	-
certolizumab pegol[d]	1 (2.7%)	5 (13.5%)	0.40
etanercept[d]	0 (0.0%)	17 (45.9%)	1.30
golimumab[d]	0 (0.0%)	3 (8.1%)	0.42
infliximab[d]	0 (0.0%)	8 (21.6%)	0.74
rituximab	1 (2.7%)	0 (0.0%)	0.24
sarilumab	3 (8.1%)	0 (0.0%)	0.42
tocilizumab	1 (2.7%)	1 (2.7%)	0.00
Other Prescription Medications			
Antibiotics	17 (45.9%)	17 (45.9%)	0.00
Antidiabetic agents	3 (8.1%)	6 (16.2%)	0.25
Insulins	1 (2.7%)	1 (2.7%)	0.00
Non-insulins	2 (5.4%)	6 (16.2%)	0.35
Aspirin	1 (2.7%)	0 (0.0%)	0.24
Cardiovascular			
Anticoagulant	1 (2.7%)	2 (5.4%)	0.14
Antihypertensives	15 (40.5%)	17 (45.9%)	0.11
Antiplatelet	1 (2.7%)	3 (8.1%)	0.24
Nitrates	0 (0.0%)	1 (2.7%)	0.24

Characteristic[a,b]	Baricitinib[c] (N = 37)	TNFi (N = 37)	Std. Diff.
Hormonal			
HRT	1 (2.7%)	4 (10.8%)	0.33
Oral Contraceptives	1 (2.7%)	3 (8.1%)	0.24
SERMs	0 (0.0%)	0 (0.0%)	-
Lipid-lowering agents			
Bile acid binding	0 (0.0%)	0 (0.0%)	-
Cholesterol absorption inhibitor	0 (0.0%)	0 (0.0%)	-
Fibrates	1 (2.7%)	0 (0.0%)	0.24
Niacin	0 (0.0%)	0 (0.0%)	-
Omega-3 fatty acids	0 (0.0%)	0 (0.0%)	-
Statins	4 (10.8%)	14 (37.8%)	0.66
Rheumatoid arthritis-related			
Cox-2 inhibitor	5 (13.5%)	1 (2.7%)	0.40
Glucocorticosteroid	21 (56.8%)	20 (54.1%)	0.05
Vaccinations	7 (18.9%)	14 (37.8%)	0.43

Abbreviations: AIDS = acquired immunodeficiency syndrome; bDMARDs = biologic disease-modifying antirheumatic drugs; CIRAS = claims-based index for RA severity; cDMARDs = conventional disease-modifying antirheumatic drugs; Chronic lung disease = asthma, chronic obstructive lung disease, interstitial lung disease, pulmonary fibrosis; HIV = human immunodeficiency virus; HRT = hormone replacement therapy; Max = maximum; Min = minimum; N = number of patients within specified category; NMSC = non-melanoma skin cancer; RA = rheumatoid arthritis; SD = standard deviation; SERMs = selective oestrogen receptor modulators; SLE = systemic lupus erythematosus; Std. Diff. = standardised difference; TIA = transient ischemic attack; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism.

[a] All conditions and characteristics, except for bDMARDs, are measured during the 6 months prior to initiation of study medication including the date at which the qualifying exposure of baricitinib or TNFi occurs (index date). bDMARDs are measured from the 6 months prior to the initiation of study medication until the day prior to baricitinib or the index TNFi exposure, excluding the index date.

[b] Many characteristics of the cohort are included in this table, but propensity score matching is only expected to balance those risk factors listed in Table 4 (see Section 8.3.3, Annex 19) for each outcome (eg, hospitalized congestive heart failure) for VTE. Other factors are included for descriptive purposes only, may not be balanced across treatment groups but do not contribute to confounding bias (eg, Type I diabetes) for VTE.

[c] Both 2- and 4-mg baricitinib doses are included when the 4-mg dose is available. Alternatively, additional columns may be added for each dose when numbers of patients are sufficient to warrant separate reporting.

[d] TNF inhibitors.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\AETNA\ 7. Table 6.7. - Clinical Characteristics Primary VTE Cohorts, Matched [Healthagen].docx

Table 12B_Aetna Baseline Healthcare Resource Utilisation Primary VTE Cohorts, Matched [Aetna], Count at Most One Visit Per Day

Type of Resource Use	Baricitinib (N = 37)	TNFi (N = 37)	Std. Diff.
Physician Office Visits[a]			
n, patients	32 (86.5%)	32 (86.5%)	0.00
n, events	201	180	
Mean (SD)	5.43 (4.14)	4.86 (4.47)	0.13
Median	5.00 [2.50, 8.00]	4.00 [1.50, 6.00]	
Min, Max	0.0, 16.0	0.0, 22.0	
Rheumatologist Visits[a]			
n, patients	29 (78.4%)	27 (73.0%)	0.13
n, events	91	92	
Mean (SD)	2.46 (2.05)	2.49 (2.71)	0.01
Median	2.00 [1.00, 4.00]	2.00 [0.00, 4.00]	
Min, Max	0.0, 8.0	0.0, 12.0	
Other Outpatient Visits[a]			
n, patients	34 (91.9%)	31 (83.8%)	0.25
n, events	158	128	
Mean (SD)	4.27 (3.80)	3.46 (2.94)	0.24
Median	2.00 [1.00, 6.50]	3.00 [1.00, 5.50]	
Min, Max	0.0, 14.0	0.0, 11.0	
Inpatient Visits[a]			
n, patients	3 (8.1%)	5 (13.5%)	0.18
n, events	12	14	
Mean (SD)	0.32 (1.40)	0.38 (1.38)	0.04
Median	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	
Min, Max	0.0, 8.0	0.0, 8.0	
ED Visits[a]			
n, patients	4 (10.8%)	6 (16.2%)	0.16
n, events	12	14	
Mean (SD)	0.32 (1.03)	0.38 (0.95)	0.06
Median	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	
Min, Max	0.0, 5.0	0.0, 4.0	

Abbreviations: ED = emergency department; Max = maximum; Min = minimum; N = number of patients within specified category; PS = propensity score;
SD = standard deviation; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor;
VTE = venous thromboembolism.

Note: Physician office visits do not include rheumatologist visits.

a In this table, results describe utilisation of healthcare where a maximum of 1 event was allowed per day. In the PS-matching analyses, multiple claims on the same day were allowed to capture additional information on the amount of services received in a given visit. These results are presented in Table 12A_Aetna in Annex 2.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\AETNA\7. Table 6.12B (count at most 1 visit per day). Baseline Healthcare Resource Utilisation Primary VTE Cohorts, Matched [Healthagen (RA)].docx

10.2.1.1.2. MACE cohort

After propensity score matching, there were 86 patients (43 each in the baricitinib and TNFi cohorts) included in the analysis of MACE (Table 3_Aetna). The small size of the analysis cohort limits the ability to evaluate the characteristics of the treatment groups at baseline. On average, patients analysed were 56.67 years at baseline (range 25 to 80 years) and were almost all (91.9%) female. Based on standardised differences >0.10 after propensity score matching, patients treated with baricitinib were slightly less likely to be female than those treated with TNFi (88.4% and 95.3%, respectively).

Clinical characteristics of patients at baseline are described in Table 8_Aetna. The most commonly observed conditions with at least 10 total cases were dyslipidaemia (baricitinib 30.2%, TNFi 27.9%), hypertension (baricitinib 39.5%, TNFi 44.2%), obesity (baricitinib 20.9%, TNFi 20.9%), and chronic lung disease (baricitinib 18.6%, TNFi 11.6%). Smoking was also prevalent in both treatment cohorts (baricitinib 11.6%, TNFi 18.6%). With regard to RA severity, the CIRAS score was slightly elevated among the baricitinib compared to the TNFi cohort (baricitinib 4.49, TNFi 4.33), but it's not clear that this is a meaningful difference.

RA treatment received prior to the index medication is described in Table 8_Aetna. Use of cDMARDs prior to index was common in both patients treated with baricitinib (60.5%) and TNFi (48.8%). Methotrexate was the most frequently recorded cDMARD (baricitinib 41.9%, TNFi 32.6%). Patients treated with baricitinib were more likely to have >1 cDMARD concomitantly than those treated with TNFi (baricitinib 20.9%, TNFi 14%). Prior use of bDMARDs was observed in 37.2% (n = 16) of the baricitinib cohort in contrast to the TNFi cohort (93%). Note that the high prevalence of bDMARD use in the TNFi cohort is due to the eligibility requirement for the TNFi patients in US claims data. Etanercept (32.6%) was the most frequently recorded prior bDMARD used by the TNFi cohort.

Baseline healthcare resource utilisation is approximately consistent across the baricitinib and TNF cohorts (Table 13B_Aetna); however, baricitinib patients had more rheumatologist visits than patients in the TNFi cohort. Note that Table 13B_Aetna reports with visits for each patient (ie, at most 1 visit per day), but the propensity score model controlled for the total number of visits during the period (ie, more than 1 visit; see Table 13A in Annex 2) could occur per day.

Table 3_Aetna Baseline Demographics MACE Cohorts, Matched [Aetna]

	Baricitinib			TNFi (N = 43)	Std. Diff. (Any vs TNFi)	Total (N = 86)
	Any (N = 43)	4 mg (N = 0)	2 mg (N = 43)			
Age [yrs]						
n	43	-	43	43		86
Mean (SD)	56.53 (12.81)	-	56.53 (12.81)	56.81 (14.00)	0.02	56.67 (13.34)
Median	60.00 [48.00, 68.00]	-	60.00 [48.00, 68.00]	59.00 [46.00, 65.00]		59.50 [46.75, 65.75]
Min, Max	26.0, 80.0	-	26.0, 80.0	25.0, 80.0		25.0, 80.0
≥65 years	12 (27.9%)	-	12 (27.9%)	11 (25.6%)	0.05	23 (26.7%)
Sex						
Male	5 (11.6%)	-	5 (11.6%)	2 (4.7%)	0.26	7 (8.1%)
Female	38 (88.4%)	-	38 (88.4%)	41 (95.3%)	0.26	79 (91.9%)

Abbreviations: MACE = major adverse cardiovascular event, defined based on primary hospital discharge diagnosis codes for acute myocardial infarction, ischemic or haemorrhagic stroke; Max = maximum; Min = minimum; N = number of patients in the specific category; n = number of patients within specified category; SD = standard deviation; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor; vs = versus; yrs = years.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\AETNA\ 7. Table 6.3 - Baseline Demographics MACE Cohorts, Matched [Healthagen].docx

Table 8_Aetna Clinical Characteristics MACE Cohorts, Matched [Aetna]

Characteristic[a,b]	Baricitinib[c] (N = 43)	TNFi (N = 43)	Std. Diff.
Clinical Conditions during baseline			
Cancer	6 (14.0%)	2 (4.7%)	0.32
NMSC	1 (2.3%)	0 (0.0%)	0.22
Chronic lung disease	8 (18.6%)	5 (11.6%)	0.20
Cardiovascular conditions			
Atrial arrhythmia/fibrillation	1 (2.3%)	0 (0.0%)	0.22
Cardiovascular revascularization	0 (0.0%)	0 (0.0%)	-
Congestive heart failure, hospitalized	0 (0.0%)	0 (0.0%)	-
Coronary artery disease	0 (0.0%)	3 (7.0%)	0.39
Ischemic heart disease	0 (0.0%)	3 (7.0%)	0.39
Unstable angina	1 (2.3%)	0 (0.0%)	0.22
Ventricular arrhythmia	1 (2.3%)	1 (2.3%)	0.00
Diabetes Mellitus	5 (11.6%)	2 (4.7%)	0.26
Type I	2 (4.7%)	0 (0.0%)	0.31
Type II	5 (11.6%)	2 (4.7%)	0.26
Dyslipidaemia	13 (30.2%)	12 (27.9%)	0.05
Hypertension	17 (39.5%)	19 (44.2%)	0.09
Immune disorders	6 (14.0%)	11 (25.6%)	0.30
AIDS/HIV	0 (0.0%)	0 (0.0%)	-
Antiphospholipid syndrome	0 (0.0%)	0 (0.0%)	-

Characteristic[a,b]	Baricitinib[c] (N = 43)	TNFi (N = 43)	Std. Diff.
SLE	3 (7.0%)	5 (11.6%)	0.16
Primary Sjögren syndrome	4 (9.3%)	6 (14.0%)	0.15
Liver disorder	1 (2.3%)	1 (2.3%)	0.00
Obesity	9 (20.9%)	9 (20.9%)	0.00
Pregnancy	0 (0.0%)	1 (2.3%)	0.22
RA severity (CIRAS Index), mean (SD)	4.49 (1.35)	4.33 (1.15)	0.13
Smoking	5 (11.6%)	8 (18.6%)	0.20
Surgery, trauma & hospitalization, recent	5 (11.6%)	5 (11.6%)	0.00
TIA	0 (0.0%)	0 (0.0%)	-
DMARDs			
cDMARDs, during baseline			
n, total	26 (60.5%)	21 (48.8%)	0.24
Mean (SD)	0.88 (0.79)	0.65 (0.78)	0.30
Median	1.00 [0.00, 1.00]	0.00 [0.00, 1.00]	-
Min, Max	0.0, 3.0	0.0, 3.0	-
>1 cDMARD concomitantly	9 (20.9%)	6 (14.0%)	0.19
Hydroxychloroquine	6 (14.0%)	6 (14.0%)	0.00
Leflunomide	9 (20.9%)	2 (4.7%)	0.50
Methotrexate	18 (41.9%)	14 (32.6%)	0.19
Minocycline	0 (0.0%)	1 (2.3%)	0.22
Sulfasalazine	2 (4.7%)	1 (2.3%)	0.13
bDMARDs, during baseline[a]			
n, total	16 (37.2%)	40 (93.0%)	1.45
Mean (SD)	0.42 (0.59)	1.33 (0.52)	1.63
Median	0.00 [0.00, 1.00]	1.00 [1.00, 2.00]	-
Min, Max	0.0, 2.0	1.0, 3.0	-
cDMARDs, concomitant	7 (16.3%)	17 (39.5%)	0.54
abatacept	3 (7.0%)	5 (11.6%)	0.16
adalimumab[d]	2 (4.7%)	6 (14.0%)	0.32
anakinra	0 (0.0%)	0 (0.0%)	-
certolizumab pegol[d]	3 (7.0%)	8 (18.6%)	0.35
etanercept[d]	1 (2.3%)	14 (32.6%)	0.87
golimumab[d]	1 (2.3%)	3 (7.0%)	0.22
infliximab[d]	0 (0.0%)	8 (18.6%)	0.68
rituximab	2 (4.7%)	0 (0.0%)	0.31
sarilumab	2 (4.7%)	1 (2.3%)	0.13
tocilizumab	3 (7.0%)	4 (9.3%)	0.09
Other Prescription Medications			
Antibiotics	21 (48.8%)	24 (55.8%)	0.14
Antidiabetic agents	6 (14.0%)	1 (2.3%)	0.44
Insulins	2 (4.7%)	0 (0.0%)	0.31
Non-insulins	5 (11.6%)	1 (2.3%)	0.37
Aspirin	1 (2.3%)	1 (2.3%)	0.00
Cardiovascular			
Anticoagulant	2 (4.7%)	1 (2.3%)	0.13
Antihypertensives	18 (41.9%)	22 (51.2%)	0.19
Antiplatelet	2 (4.7%)	3 (7.0%)	0.10

Characteristic[a,b]	Baricitinib[c] (N = 43)	TNFi (N = 43)	Std. Diff.
Nitrates	1 (2.3%)	0 (0.0%)	0.22
Hormonal			
HRT	4 (9.3%)	0 (0.0%)	0.45
Oral Contraceptives	1 (2.3%)	1 (2.3%)	0.00
SERMs	0 (0.0%)	0 (0.0%)	-
Lipid-lowering agents			
Bile acid binding	0 (0.0%)	0 (0.0%)	-
Cholesterol absorption inhibitor	0 (0.0%)	0 (0.0%)	-
Fibrates	1 (2.3%)	0 (0.0%)	0.22
Niacin	0 (0.0%)	0 (0.0%)	-
Omega-3 fatty acids	0 (0.0%)	0 (0.0%)	-
Statins	9 (20.9%)	8 (18.6%)	0.06
Rheumatoid arthritis-related			
Cox-2 Inhibitor	4 (9.3%)	1 (2.3%)	0.30
Glucocorticosteroid	25 (58.1%)	25 (58.1%)	0.00
Vaccinations	8 (18.6%)	13 (30.2%)	0.27

Abbreviations: AIDS = acquired immunodeficiency syndrome; bDMARDs = biologic disease-modifying antirheumatic drugs; CIRAS = claims-based index for RA severity; cDMARDs = conventional synthetic disease-modifying antirheumatic drugs; DMARDs = disease-modifying antirheumatic drugs; HIV = human immunodeficiency virus; HRT = hormone replacement therapy; Max = maximum; Min = minimum; MACE = major adverse cardiovascular event, defined based on primary hospital discharge diagnosis codes for acute myocardial infarction, ischemic or haemorrhagic stroke; N = number of patients in the specified category; NMSC = non-melanoma skin cancer; RA = rheumatoid arthritis; SD = standard deviation; SERMs = selective oestrogen receptor modulators; SLE = systemic lupus erythematosus; Std. Diff = standardised difference; TIA = transient ischemic attack; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism.

[a] All conditions and characteristics, except for bDMARDs, are measured during the 6 months prior to initiation of study medication including the date at which the qualifying exposure of baricitinib or TNFi occurs (index date). bDMARDs are measured from the 6 months prior to the initiation of study medication until the day prior to baricitinib or the index TNFi exposure, excluding the index date.

[b] Many characteristics of the cohort are included in this table, but propensity score matching is only expected to balance those risk factors listed in Table 4 (see Section 8.3.3, Annex 19) for each outcome (eg, hospitalized congestive heart failure) for VTE. Other factors are included for descriptive purposes only, may not be balanced across treatment groups but do not contribute to confounding bias (eg, Type I diabetes) for VTE.

[c] Both 2- and 4-mg baricitinib doses are included when the 4-mg dose is available. Alternatively, additional columns may added be for each dose when numbers of patients are sufficient to warrant separate reporting.

[d] TNF inhibitors.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\AETNA\7. Table 6.8. - Clinical Characteristics MACE Cohorts, Matched [Healthagen RA].docx

Table 13B_Aetna Baseline Healthcare Resource Utilisation MACE Cohorts, Matched [Aetna], Count at Most One Visit Per Day

Type of Resource Use	Baricitinib (N = 43)	TNFi (N = 43)	Std. Diff.
Physician Office Visits[a]			
n, patients	38 (88.4%)	38 (88.4%)	0.00
n, events	235	188	
Mean (SD)	5.47 (4.25)	4.37 (3.74)	0.27
Median	4.00 [2.00, 8.00]	4.00 [1.00, 6.00]	
Min, Max	0.0, 16.0	0.0, 14.0	
Rheumatologist Visits[a]			
n, patients	36 (83.7%)	31 (72.1%)	0.28
n, events	127	104	
Mean (SD)	2.95 (2.17)	2.42 (2.24)	0.24
Median	3.00 [1.00, 4.00]	2.00 [0.00, 4.00]	
Min, Max	0.0, 8.0	0.0, 8.0	
Other Outpatient Visits[a]			
n, patients	39 (90.7%)	39 (90.7%)	0.00
n, events	233	243	
Mean (SD)	5.42 (5.67)	5.65 (6.45)	0.04
Median	4.00 [2.00, 7.00]	3.00 [2.00, 7.00]	
Min, Max	0.0, 31.0	0.0, 29.0	
Inpatient Visits[a]			
n, patients	5 (11.6%)	4 (9.3%)	0.08
n, events	17	9	
Mean (SD)	0.40 (1.42)	0.21 (0.74)	0.17
Median	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	
Min, Max	0.0, 8.0	0.0, 4.0	
ED Visits[a]			
n, patients	7 (16.3%)	6 (14.0%)	0.07
n, events	19	12	
Mean (SD)	0.44 (1.10)	0.28 (0.73)	0.17
Median	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	
Min, Max	0.0, 5.0	0.0, 3.0	

Abbreviations: ED = emergency department; MACE = major adverse cardiovascular event, defined based on primary hospital discharge diagnosis codes for acute myocardial infarction, ischemic or haemorrhagic stroke; Max = maximum; Min = minimum; N = number of patients in the specified category; n = number of patients within each specific category; SD = standard deviation; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor.

Note: Physician office visits do not include rheumatologist visits.

[a] In this table, results describe utilisation of healthcare where a maximum of 1 event was allowed per day. In the PS-matching analyses, multiple claims on the same day were allowed to capture additional information on the amount of services received in a given visit. These results are presented in Table 13A_Aetna.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\AETNA\7. Table 6.13B (count at most 1 visit per day). Baseline Healthcare Resource Utilisation MACE Cohorts, Matched [Healthagen (RA)].docx

10.2.1.1.3. Serious infection cohort

After propensity score matching, there were a total of 88 patients (44 each in the baricitinib and TNFi cohorts) included in the analysis of serious infection (Annex 2, Table 4). Similar to the VTE and MACE cohorts described above, the small size of the analysis cohort limits ability to evaluate the characteristics of the treatment groups at baseline. On average, patients analysed were aged 55.16 years (range 19 to 80 years) and almost all (86.4%) were female. Based on standardised differences >0.10 after propensity score matching, patients treated with baricitinib were slightly more likely to be female than those treated with TNFi (88.6% and 84.1%, respectively).

Clinical characteristics of patients at baseline are described in Annex 2, Table 9. The most commonly observed conditions with at least 10 total cases were dyslipidaemia (baricitinib 31.8%, TNFi 29.5%), hypertension (baricitinib 43.2%, TNFi 34.1%), cancer (baricitinib 13.6%, TNFi 9.1%) and obesity (baricitinib 20.5%, TNFi 15.9%). The CIRAS score was similar across the baricitinib and TNFi cohorts (4.53 and 4.47, respectively).

RA treatment received prior to the index medication is described in Annex 2, Table 9. Over half of patients used cDMARDs (56.8% in each cohort) and methotrexate was the most frequently recorded cDMARD (baricitinib 40.9%, TNFi 34.1%). A similar proportion of patients in the baricitinib and TNFi cohorts received >1 cDMARD concomitantly (baricitinib 20.5%, TNFi 18.2%). All patients in the TNFi cohort received a bDMARD in baseline (most frequently etanercept or adalimumab) whereas 34.1% of baricitinib cohort received a bDMARD in baseline.

10.2.1.2. Anthem (HIRD)

There were 255 eligible patients treated with baricitinib and 1,304 eligible TNFi patients in the unmatched VTE cohort in the HIRD. Demographic and clinical characteristics for these unmatched cohorts are in Annex 3. From these unmatched cohorts, the number of patients included in analyses of VTE, MACE, or serious infection after 1:1 matching varies. Details of these analysis-specific cohorts follow.

10.2.1.2.1. VTE

After propensity score matching, there were a total of 246 patients (123 each in the baricitinib and TNFi cohorts) included in the analysis of VTE (Table 2_HIRD). The small size of the analysis cohort limits the ability to evaluate the characteristics of the treatment groups at baseline. Further, Anthem protects members' privacy by reporting "≤10" where patients counts are between 1 and 10. Thus, data is not presented for all characteristics. On average, patients analysed were aged 55.9 years at baseline (range 21 to 88 years) and most were female (83.3%). Based on standardised differences >0.10 after propensity score matching, patients treated with baricitinib were younger, as measured by the proportion of patients ≥65 years old (baricitinib 16.3%, TNFi 23.6%).

Clinical characteristics of patients at baseline are described in Table 7_HIRD. The most commonly observed conditions with at least 10 total cases were dyslipidaemia (baricitinib 31.7%, TNFi 26.8%), hypertension (baricitinib 28.5%, TNFi 39.0%), obesity (baricitinib 17.1%, TNFi 14.6%), and chronic lung disease (baricitinib 17.1%, TNFi 12.2%). Smoking was also

prevalent (baricitinib 12.2%, ≤10 patients in TNFi). With regard to RA severity, the mean CIRAS score was nearly identical in the two cohorts (baricitinib 3.7, TNFi 3.6).

RA treatment received prior to the index medication is described in Table 7_HIRD. Approximately half of the patients used cDMARDs (baricitinib 48.8%, TNFi 59.3%), with methotrexate recorded most frequently (baricitinib 26.8%, TNFi 29.3%). Within the baricitinib cohort, ≤10 patients were concomitantly treated with >1 cDMARD in baseline and 11 patients (8.9%) of patients in the TNFi cohort had record of >1 concomitant cDMARD. Prior use of bDMARDs was observed in all patients in both cohorts. Adalimumab (42.3%) was the most frequently recorded prior bDMARD used by the TNFi cohort and abatacept (22.8%) was most frequently recorded prior bDMARD in baricitinib cohort.

Baseline healthcare resource utilisation was not dissimilar across the baricitinib and TNF cohorts (Table 12_HIRD). Slightly more baricitinib patients recorded rheumatologist visits than TNFi patients. However, the baricitinib patients had approximately same number of visits as the TNFi cohort patients.

Table 2_HIRD Baseline Demographics VTE Cohorts, Matched [HIRD]

	Baricitinib (N = 123)	TNFi (N = 123)	Std. Diff. (Any vs. TNFi)	Total (N = 246)
Age [yrs]				
n	123	123		246
Mean (SD)	56.0 (11.4)	55.8 (12.5)	0.02	55.9 (11.9)
Median	56.0	56.0		56.0
Min, Max	21.0, 88.0	27.0, 88.0		21.0, 88.0
≥65 years	20 (16.3%)	29 (23.6%)	-0.18	49 (19.9%)
Sex				
Male	22 (17.9%)	19 (15.4%)	0.07	41 (16.7%)
Female	101 (82.1%)	104 (84.6%)		205 (83.3%)

Abbreviations: HIRD = HealthCore Integrated Research Database; N = number of patients in the specified category; SD = standard deviation; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor; vs = versus; VTE = venous thromboembolism; yrs = years.

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Table 7_HIRD Clinical Characteristics Primary VTE Cohorts, Matched [HIRD]

Characteristic[a,b]	Baricitinib (N = 123)	TNFi (N = 123)	Std. Diff.
Clinical Conditions during baseline			
Cancer	≤ 10	13 (10.6%)	-0.08
NMSC	≤ 10	≤ 10	0.13
Chronic lung disease	21 (17.1%)	15 (12.2%)	0.14
Cardiovascular conditions			
Atrial arrhythmia/fibrillation	≤ 10	≤ 10	-0.13
Cardiovascular revascularization	0 (0.0%)	0 (0.0%)	NA
Congestive heart failure, hospitalized	≤ 10	0 (0.0%)	NA
Coronary artery disease	≤ 10	≤ 10	0.10

Characteristic[a,b]	Baricitinib (N = 123)	TNFi (N = 123)	Std. Diff.
Ischemic heart disease	≤ 10	≤ 10	0.07
Unstable angina	0 (0.0%)	0 (0.0%)	NA
Ventricular arrhythmia	≤ 10	≤ 10	0.00
Diabetes Mellitus	18 (14.6%)	16 (13.0%)	0.05
Type I	≤ 10	≤ 10	-0.07
Type II	17 (13.8%)	14 (11.4%)	0.07
Dyslipidaemia	39 (31.7%)	33 (26.8%)	0.11
Hypertension	35 (28.5%)	48 (39.0%)	-0.22
Immune disorders	14 (11.4%)	≤ 10	0.14
AIDS/HIV	0 (0.0%)	0 (0.0%)	NA
Antiphospholipid syndrome	≤ 10	≤ 10	0.00
SLE	≤ 10	≤ 10	0.04
Primary Sjögren syndrome	≤ 10	≤ 10	0.14
Liver disorder	≤ 10	0 (0.0)	NA
Obesity	21 (17.1%)	18 (14.6%)	0.07
Pregnancy	≤ 10	≤ 10	-0.07
RA Severity (CIRAS Index), mean (SD)	3.7 (1.4)	3.6 (1.4)	0.03
Smoking	15 (12.2%)	≤ 10	0.16
Surgery, trauma & hospitalization, recent	≤ 10	≤ 10	0.04
TIA	0 (0.0%)	≤ 10	NA
DMARDs			
cDMARDs, during baseline			
n, total	60 (48.8%)	73 (59.3%)	-0.21
Mean (SD)	0.6 (0.7)	0.7 (0.7)	-0.17
Median	0.0	1.0	NA
Min, Max	0.0, 2.0	0.0, 3.0	NA
>1 cDMARD concomitantly	≤ 10	11 (8.9%)	-0.13
Hydroxychloroquine	16 (13.0%)	21 (17.1%)	-0.11
Leflunomide	17 (13.8%)	16 (13.0%)	0.02
Methotrexate	33 (26.8%)	36 (29.3%)	-0.05
Minocycline	0 (0.0%)	0 (0.0%)	NA
Sulfasalazine	≤ 10	≤ 10	-0.03
bDMARDs, during baseline			
n, total	123 (100.0%)	123 (100.0%)	NA
Mean (SD)	1.1 (0.3)	1.1 (0.3)	0.03
Median	1.0	1.0	NA
Min, Max	1.0, 3.0	1.0, 2.0	NA
cDMARDs, concomitant	36 (29.3%)	42 (34.1%)	-0.10
abatacept	28 (22.8%)	≤ 10	0.68
adalimumab[d]	18 (14.6%)	52 (42.3%)	-0.64
anakinra	≤ 10	0 (0.0%)	NA
certolizumab pegol[d]	12 (9.8%)	16 (13.0%)	-0.10
etanercept[d]	12 (9.8%)	27 (22.0%)	-0.34
golimumab[d]	13 (10.6%)	13 (10.6%)	0.00
infliximab[d]	≤ 10	20 (16.3%)	-0.38
rituximab	≤ 10	0 (0.0%)	NA
sarilumab	20 (16.3%)	≤ 10	0.53

Characteristic[a,b]	Baricitinib (N = 123)	TNFi (N = 123)	Std. Diff.
tocilizumab	14 (11.4%)	≤ 10	0.45
Other Prescription Medications			
Antibiotics	≤ 10	≤ 10	-0.09
Antidiabetic agents	11 (8.9%)	13 (10.6%)	-0.05
Insulins	≤ 10	≤ 10	0.15
Non-insulins	≤ 10	12 (9.8%)	-0.09
Aspirin	0 (0.0%)	≤ 10	NA
Cardiovascular			
Anticoagulant	≤ 10	0 (0.0%)	NA
Antihypertensives	50 (40.7%)	51 (41.5%)	-0.02
Antiplatelet	≤ 10	≤ 10	-0.05
Nitrates	≤ 10	≤ 10	0.00
Hormonal			
HRT	≤ 10	≤ 10	0.04
Oral Contraceptives	≤ 10	≤ 10	-0.11
SERMs	≤ 10	≤ 10	0.00
Lipid-lowering agents			
Bile acid binding	≤ 10	≤ 10	0.00
Cholesterol absorption inhibitor	0 (0.0%)	0 (0.0%)	NA
Fibrates	0 (0.0%)	≤ 10	NA
Niacin	0 (0.0%)	0 (0.0%)	NA
Omega-3 fatty acids	≤ 10	0 (0.0%)	NA
Statins	31 (25.2%)	28 (22.8%)	0.06
Rheumatoid arthritis-related			
Cox-2 Inhibitor	≤ 10	12 (9.8%)	-0.19
Glucocorticosteroid	90 (73.2%)	89 (72.4%)	0.02
Vaccinations	32 (26.0%)	33 (26.8%)	-0.02

Abbreviations: AIDS = acquired immunodeficiency syndrome; bDMARDs = biologic disease-modifying antirheumatic drugs; CIRAS = claims-based index for RA severity; cDMARDs = conventional synthetic disease-modifying antirheumatic drugs; Chronic lung disease = asthma, chronic obstructive lung disease, interstitial lung disease, pulmonary fibrosis; DMARDs = disease-modifying antirheumatic drugs; HIRD = HealthCore Integrated Research Database; HIV = human immunodeficiency virus; HRT = hormone replacement therapy; Max = maximum; Min = minimum; N = number of patients in the specified category; NMSC = non-melanoma skin cancer; RA = rheumatoid arthritis; SD = standard deviation; SERMs = selective oestrogen receptor modulators; SLE = systemic lupus erythematosus; Std. Diff. = standardised difference; TIA = transient ischemic attack; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism.

Note: Anthem protects members' privacy by reporting "≤10" where patients counts are between 1 and 10.

[a] All conditions and characteristics are measured during the 6 months prior to initiation of study medication until and including the day of cohort entry, with the exception of baseline bDMARDs.

[b] Many characteristics of the cohort are included in this table, but propensity score matching is only expected to balance those risk factors listed in Table 4 (see Section 8.3.3, Annex 19) for each outcome (eg, hospitalized congestive heart failure) for VTE. Other factors are included for descriptive purposes only and may not be balanced across treatment groups but do not contribute to confounding bias (eg, Type I diabetes) for VTE.

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Table 12_HIRD Baseline Healthcare Resource Utilisation Primary VTE Cohorts, Matched [HIRD]

Type of Resource Use	Baricitinib (N = 123)	TNFi (N = 123)	Std. Diff.
Physician Office Visits			
n, patient	108 (87.8%)	114 (92.7%)	-0.16
n, events			
Mean (SD)	6.1 (5.7)	5.9 (4.8)	0.05
Median	4.0	4.0	NA
Min, Max	1.0, 37.0	1.0, 23.0	NA
Rheumatologist Visits			
n, patient	112 (91.1%)	105 (85.4%)	0.18
n, events			
Mean (SD)	2.5 (1.3)	2.4 (1.4)	0.03
Median	2.0	2.0	NA
Min, Max	1.0, 7.0	1.0, 10.0	NA
Other Outpatient Visits			
n, patient	121 (98.4%)	119 (96.7%)	0.11
n, events			
Mean (SD)	13.9 (14.7)	13.9 (14.3)	-0.01
Median	9.0	10.0	NA
Min, Max	1.0, 84.0	1.0, 108.0	NA
Inpatient Visits			
n, patient	≤ 10	≤ 10	0.10
n, events			
Mean (SD)	1.2 (0.4)	1.2 (0.4)	0.13
Median	1.0	1.0	NA
Min, Max	1.0, 2.0	1.0, 2.0	NA
ED Visits			
n, patient	17 (13.8%)	15 (12.2%)	0.05
n, events			
Mean (SD)	1.4 (0.9)	1.0 (0.0)	0.67
Median	1.0	1.0	NA
Min, Max	1.0, 4.0	1.0, 1.0	NA

Abbreviations: ED = emergency department; HIRD = HealthCore Integrated Research Database; Max = maximum; Min = minimum; N = number of patients in the specified category; NA = not applicable; SD = standard deviation; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism.

Note: Physician office visits do not include rheumatologist visits.

Note: Anthem protects members' privacy by reporting "≤10" where patients counts are between 1 and 10.

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10.2.1.2.2. MACE

After propensity score matching, there were 246 patients (123 each in the baricitinib and TNFi cohorts) included in the analysis of MACE (Table 3_HIRD). The small size of the analysis cohort limits the ability to evaluate the characteristics of the treatment groups at baseline. On average, patients analysed were 55.7 years at baseline (range 18 to 88 years) and most were

female (86.2%). Based on standardised differences >0.10 after propensity score matching, patients treated with baricitinib were less likely to be female than those treated with TNFi (82.1% and 90.2%, respectively).

Clinical characteristics of patients at baseline are described in Table 8_HIRD. The most commonly observed conditions with at least 10 total cases were dyslipidaemia (baricitinib 31.7%, TNFi 26.8%), hypertension (baricitinib 28.5%, TNFi 28.5%), obesity (baricitinib 17.1%, TNFi 21.1%), and chronic lung disease (baricitinib 17.1%, TNFi 8.9%). Smoking was also prevalent in both treatment cohorts (baricitinib 12.2%, TNFi 15.4%). Regarding RA severity, the mean CIRAS score was slightly lower among the baricitinib compared to the TNFi cohort (baricitinib 3.7, TNFi 3.9), but it is unclear that this is a meaningful difference.

RA treatment received prior to the index medication is described in Table 8_HIRD. Use of cDMARDs prior to index was common in both patients treated with baricitinib (48.8%) and TNFi (57.7%). Methotrexate was the most frequently recorded cDMARD (baricitinib 26.8%, TNFi 35.0%). Fewer than or equal to 10 patients treated with baricitinib recorded >1 cDMARD concomitantly and 11 patients (8.9%) treated with TNFi recorded >1 cDMARD. Prior use of bDMARDs was recorded in all patients in both cohorts. Adalimumab (40.7%) was the most frequently recorded prior bDMARD used by the TNFi cohort and abatacept (22.8%) was most frequently recorded prior bDMARD in baricitinib cohort.

Baseline healthcare resource utilisation is approximately consistent across the baricitinib and TNF cohorts (Table 13_HIRD). There were small differences based on absolute value of the standardised differences >0.1, yet these are of uncertain clinical relevance.

Table 3_HIRD Baseline Demographics MACE Cohorts, Matched [HIRD]

	Baricitinib (N = 123)	TNFi (N = 123)	Std. Diff. (Any vs. TNFi)	Total (N = 246)
Age [yrs]				
n	123	123		246
Mean (SD)	56.0 (11.4)	55.3 (13.0)	0.06	55.7 (12.2)
Median	56.0	56.0		56.0
Min, Max	21.0, 88.0	18.0, 84.0		18.0, 88.0
≥65 years	20 (16.3%)	23 (18.7%)	-0.06	43 (17.5%)
Sex				
Male	22 (17.9%)	12 (9.8%)	0.24	34 (13.8%)
Female	101 (82.1%)	111 (90.2%)		212 (86.2%)

Abbreviations: HIRD = HealthCore Integrated Research Database; MACE = major adverse cardiovascular event, defined based on primary hospital discharge diagnosis codes for acute myocardial infarction, ischemic or haemorrhagic stroke; N = number of patients in the specific category; n = number of patients within specified category; SD = standard deviation; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor; vs = versus; yrs = years.

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Table 8_HIRD Clinical Characteristics MACE Cohorts, Matched [HIRD]

Characteristic[a,b]	Baricitinib[c] (N = 123)	TNFi[d] (N = 123)	Std. Diff.
Clinical Conditions during baseline			
Cancer	≤ 10	≤ 10	0.13
NMSC	≤ 10	≤ 10	0.13
Chronic lung disease	21 (17.1%)	11 (8.9%)	0.24
Cardiovascular conditions			
Atrial arrhythmia/fibrillation	≤ 10	0 (0.0%)	NA
Cardiovascular revascularization	0 (0.0%)	0 (0.0%)	NA
Congestive heart failure, hospitalized	≤ 10	0 (0.0%)	NA
Coronary artery disease	≤ 10	≤ 10	0.14
Ischemic heart disease	≤ 10	≤ 10	0.14
Unstable angina	0 (0.0%)	0 (0.0%)	NA
Ventricular arrhythmia	≤ 10	≤ 10	0.06
Diabetes Mellitus	18 (14.6%)	17 (13.8%)	0.02
Type I	≤ 10	≤ 10	-0.17
Type II	17 (13.8%)	14 (11.4%)	0.07
Dyslipidaemia	39 (31.7%)	33 (26.8%)	0.11
Hypertension	35 (28.5%)	35 (28.5%)	0.00
Immune disorders	14 (11.4%)	14 (11.4%)	0.00
AIDS/HIV	0 (0.0%)	0 (0.0%)	NA
Antiphospholipid syndrome	≤ 10	≤ 10	0.00
SLE	≤ 10	≤ 10	0.00
Primary Sjögren syndrome	≤ 10	≤ 10	0.00
Liver disorder	≤ 10	≤ 10	-0.07
Obesity	21 (17.1%)	26 (21.1%)	-0.10
Pregnancy	≤ 10	≤ 10	-0.07
RA Severity (CIRAS Index), mean (SD)	3.7 (1.4)	3.9 (1.5)	-0.13
Smoking	15 (12.2%)	19 (15.4%)	-0.09
Surgery, trauma & hospitalization, recent	≤ 10	≤ 10	0.08
TIA	0 (0.0%)	0 (0.0%)	NA
DMARDs			
cDMARDs, during baseline			
n, total	60 (48.8%)	71 (57.7%)	-0.18
Mean (SD)	0.6 (0.7)	0.8 (0.8)	-0.17
Median	0.0	1.0	NA
Min, Max	0.0, 2.0	0.0, 3.0	NA
>1 cDMARD concomitantly	≤ 10	11 (8.9%)	-0.13
Hydroxychloroquine	16 (13.0%)	20 (16.3%)	-0.09
Leflunomide	17 (13.8%)	14 (11.4%)	0.07
Methotrexate	33 (26.8%)	43 (35.0%)	-0.18
Minocycline	0 (0.0%)	0 (0.0%)	NA
Sulfasalazine	≤ 10	≤ 10	-0.10
bDMARDs, during baseline			
n, total	123 (100.0%)	123 (100.0%)	NA
Mean (SD)	1.1 (0.3)	1.1 (0.3)	0.03
Median	1.0	1.0	NA

Characteristic[a,b]	Baricitinib[c] (N = 123)	TNFi[d] (N = 123)	Std. Diff.
Min, Max	1.0, 3.0	1.0, 2.0	NA
cDMARDs, concomitant	36 (29.3%)	41 (33.3%)	-0.09
abatacept	28 (22.8%)	≤ 10	0.47
adalimumab[d]	18 (14.6%)	50 (40.7%)	-0.61
anakinra	≤ 10	0 (0.0%)	NA
certolizumab pegol[d]	12 (9.8%)	17 (13.8%)	-0.13
etanercept[d]	12 (9.8%)	28 (22.8%)	-0.36
golimumab[d]	13 (10.6%)	≤ 10	0.15
infliximab[d]	≤ 10	20 (16.3%)	-0.38
rituximab	≤ 10	0 (0.0%)	NA
sarilumab	20 (16.3%)	≤ 10	0.58
tocilizumab	14 (11.4%)	≤ 10	0.45
Other Prescription Medications			
Antibiotics	≤ 10	≤ 10	-0.05
Antidiabetic agents	11 (8.9%)	15 (12.2%)	-0.11
Insulins	≤ 10	≤ 10	-0.04
Non-insulins	≤ 10	≤ 10	0.00
Aspirin	0 (0.0%)	0 (0.0%)	NA
Cardiovascular			
Anticoagulant	≤ 10	≤ 10	-0.17
Antihypertensives	50 (40.7%)	57 (46.3%)	-0.11
Antiplatelet	≤ 10	0 (0.0%)	NA
Nitrates	≤ 10	0 (0.0%)	NA
Hormonal			
HRT	≤ 10	12 (9.8%)	-0.23
Oral Contraceptives	≤ 10	≤ 10	0.04
SERMs	≤ 10	≤ 10	0.07
Lipid-lowering agents			
Bile acid binding	≤ 10	0 (0.0%)	NA
Cholesterol absorption inhibitor	0 (0.0%)	0 (0.0%)	NA
Fibrates	0 (0.0%)	≤ 10	NA
Niacin	0 (0.0%)	0 (0.0%)	NA
Omega-3 fatty acids	≤ 10	0 (0.0%)	NA
Statins	31 (25.2%)	26 (21.1%)	0.10
Rheumatoid arthritis-related			
Cox-2 Inhibitor	≤ 10	11 (8.9%)	-0.16
Glucocorticosteroid	90 (73.2%)	93 (75.6%)	-0.06
Vaccinations	32 (26.0%)	32 (26.0%)	0.00

Abbreviations: AIDS = acquired immunodeficiency syndrome; bDMARDs = biologic disease-modifying antirheumatic drugs; CIRAS = claims-based index for RA severity; cDMARDs = conventional disease-modifying antirheumatic drugs; Chronic lung disease = asthma, chronic obstructive lung disease, interstitial lung disease, pulmonary fibrosis; DMARDs = disease-modifying antirheumatic drugs; HIRD = HealthCore Integrated Research Database; HIV = human immunodeficiency virus; HRT = hormone replacement therapy; MACE = major adverse cardiovascular event, defined based on primary hospital discharge diagnosis codes for acute myocardial infarction, ischemic or haemorrhagic stroke; Max = maximum; Min = minimum; N = counts of patients in the specified category; NMSC = non-melanoma skin cancer; RA = rheumatoid arthritis; SD = standard deviation; SERMs = selective oestrogen receptor modulators; SLE = systemic lupus erythematosus; Std. Diff. = standardised difference; TIA = transient ischemic attack; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism.

Note: Anthem protects members' privacy by reporting "≤10" where patients counts are between 1 and 10.

[a] All conditions and characteristics are measured during the 6 months prior to initiation of study medication until and including the day of cohort entry, with the exception of baseline bDMARDs.

[b] Many characteristics of the cohort are included in this table, but propensity score matching is only expected to balance those risk factors listed in Table 4 (see Section 8.3.3, Annex 19) for each outcome (eg, hospitalized congestive heart failure) for VTE. Other factors are included for descriptive purposes only and may not be balanced across treatment groups but do not contribute to confounding bias (eg, Type I diabetes) for VTE.

[c] Both 2- and 4 mg baricitinib doses are included when the 4 mg dose is available. Alternatively, columns may be added for each dose where numbers of patients are sufficient to warrant separate reporting.

[d] TNF inhibitors.

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Table 13_HIRD Baseline Healthcare Resource Utilisation MACE Cohorts, Matched [HIRD]

Type of Resource Use	Baricitinib (N = 123)	TNFi (N = 123)	Std. Diff.
Physician Office Visits			
n, patient	108 (87.8%)	114 (92.7%)	-0.16
n, events			
Mean (SD)	6.1 (5.7)	6.0 (4.7)	0.01
Median	4.0	5.0	NA
Min, Max	1.0, 37.0	1.0, 24.0	NA
Rheumatologist Visits			
n, patient	112 (91.1%)	110 (89.4%)	0.05
n, events			
Mean (SD)	2.5 (1.3)	2.8 (1.7)	-0.22
Median	2.0	2.0	NA
Min, Max	1.0, 7.0	1.0, 10.0	NA
Other Outpatient Visits			
n, patient	121 (98.4%)	123 (100.0%)	-0.18
n, events			
Mean (SD)	13.9 (14.7)	15.0 (12.7)	-0.09
Median	9.0	11.0	NA
Min, Max	1.0, 84.0	1.0, 68.0	NA
Inpatient Visits			
n, patient	≤ 10	≤ 10	0.10
n, events			
Mean (SD)	1.2 (0.4)	1.3 (0.5)	-0.23
Median	1.0	1.0	NA
Min, Max	1.0, 2.0	1.0, 2.0	NA
ED Visits			
n, patient	17 (13.8%)	16 (13.0%)	0.02
n, events			
Mean (SD)	1.4 (0.9)	1.3 (0.6)	0.13
Median	1.0	1.0	NA
Min, Max	1.0, 4.0	1.0, 3.0	NA

Abbreviations: ED = emergency department; HIRD = HealthCore Integrated Research Database; MACE = major adverse cardiovascular event, defined based on primary hospital discharge diagnosis codes for acute myocardial infarction, ischemic or haemorrhagic stroke; Max = maximum; Min = minimum; N = count of patients in the specified category; SD = standard deviation; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor.

Note: Physician office visits do not include rheumatologist visits.

Note: Anthem protects members' privacy by reporting "≤10" where patients counts are between 1 and 10.

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10.2.1.2.3. Serious infections

After propensity score matching, a total of 260 patients (130 each in the baricitinib and TNFi cohorts) were included in the analysis of serious infection (Annex 3, Table 4). Like the VTE and MACE cohorts, the small size of the analysis cohort limited the ability to evaluate the

characteristics of the treatment groups at baseline. On average, patients included in analyses were aged 56 years (range 19 to 91 years) and the large majority were female (80.8%). Based on absolute value of standardised differences >0.10 after propensity score matching, patients treated with baricitinib were slightly less likely to be ≥65 years old than those treated with TNFi (16.2% and 21.5%, respectively).

Clinical characteristics of patients at baseline are described in Annex 3, Table 9. The most observed conditions with at least 10 cases were dyslipidaemia (baricitinib 33.8%, TNFi 32.3%), hypertension (baricitinib 31.5%, TNFi 39.2%), diabetes (baricitinib 14.6%, TNFi 17.7%), chronic lung disease (baricitinib 17.7%, TNFi 19.2%) and obesity (baricitinib 19.2%, TNFi 26.2%). The mean CIRAS score was similar across the baricitinib and TNFi cohorts (3.7 and 3.6, respectively).

RA treatment received prior to the index medication is described in Annex 3, Table 9. Approximately half of patients used cDMARDs (baricitinib 49.2%, TNFi 66.9%) and methotrexate was the most frequently recorded cDMARD (baricitinib 26.9%, TNFi 40.0%). Of the 130 patients in each cohort, ≤10 patients from each cohort reported baseline use of >1 concomitant cDMARD. Prior use of bDMARDs was recorded in all patients in both cohorts. Adalimumab (33.8%) was the most frequently recorded prior bDMARD used by the TNFi cohort and abatacept (22.3%) was most frequently recorded prior bDMARD in baricitinib cohort.

10.2.1.3. CorEvitas US

There were 118 eligible patients treated with baricitinib and 1,897 eligible TNFi patients in the CorEvitas US registry. Demographic and clinical characteristics for these unmatched cohorts are in Annex 4. From these unmatched cohorts, the number of patients included in analyses of VTE, MACE, or serious infection after 1:1 matching varies. Details of these analysis-specific cohorts follow.

10.2.1.3.1. VTE

After propensity score matching, there were a total of 224 patients (112 each in the baricitinib and TNFi cohorts) included in the analysis of VTE (Table 2_Cor_US). The small size of the analysis cohort limits the ability to evaluate the characteristics of the treatment groups at baseline. On average, patients analysed were aged 59.7 years at baseline (range 27 to 90 years) and the majority (77.7%) were female. Based on the average BMI (29.7), patients enrolled in the CorEvitas US registry were on average overweight and 54.0% were current or former smokers. Patients in the baricitinib cohort reported alcohol use less often than patients in TNFi cohort (baricitinib 34.8%; 46.4%), and fewer attained college/university level education (baricitinib 49.1%; TNFi 60%).

Clinical characteristics of patients at baseline are described in Table 7_Cor_US. The most common conditions ever reported by physicians were hypertension (baricitinib 41.1%, TNFi 36.6%), obesity (baricitinib 37.3%, TNFi 37.0%), other immune disorders (secondary Sjogren syndrome) (baricitinib 25.9%%, TNFi 27.7%), hyperlipidaemia (baricitinib 20.5%, TNFi 17.9%), and diabetes (baricitinib 10.7%, TNFi 14.3%). Regarding RA severity, the CDAI score

was slightly lower in the baricitinib cohort compared to the TNFi cohort (baricitinib 18.8, TNFi 20.2).

RA treatment received prior to the index medication is described in Table 7_Cor_US. Almost all (97.3%) patients in CorEvitas US registry have a history of using at least 1 cDMARD; methotrexate was used by 91.1% of patients. Over half of patients reported concomitant use of cDMARD at baseline (baricitinib 61.6%, TNFi 68.8%). Prior use of bDMARDs was reported in almost all patients (baricitinib 86.6%, TNFi 84.8%).

Table 2_Cor_US Baseline Demographics, VTE Cohorts, Matched [COR_US]

	Baricitinib (N = 112)	TNFi (N = 112)	Std. Diff.	Total (N = 224)
Age [yrs]				
n	112	112	0.015	224
Mean ± SD	59.8 ±11.4	59.6 ±12.7		59.7 ±12.1
Median	60.5	59.5		60.0
Min, Max	27.0, 81.0	30.0, 90.0		27.0, 90.0
≥65 years	40 (35.7%)	43 (38.4%)	0.055	83 (37.1%)
Gender				
Male	27 (24.1%)	23 (20.5%)	0.086	50 (22.3%)
Female	85 (75.9%)	89 (79.5%)		174 (77.7%)
BMI				
n	110	108	0.118	218
Mean ± SD	30.2 ± 7.6	29.3 ± 6.9		29.7 ± 7.3
Median	28.9	28.2		28.7
Min, Max	16.1, 50.9	16.8, 57.9		16.1, 57.9
Smoking (current/former)	62 (55.4%)	59 (52.7%)	0.054	121 (54.0%)
Alcohol use	39 (34.8%)	52 (46.4%)	0.238	91 (40.6%)
Education				
College/university	52 (49.1%)	66 (60.0%)	0.221	118 (54.6%)

Abbreviations: Cor_US = CorEvitas United States; Max = maximum; Min = minimum; N = count of patients in specified category; SD = standard deviation; Std Diff = absolute value of the standardised difference; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism; yrs = years.

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Table 7_Cor_US Clinical Characteristics Primary VTE Cohorts, Matched [COR_US]

	Baricitinib (N = 112)	TNFi (N = 112)	Std. Diff.	Total (N = 224)
History of MD-reported comorbidities (ever experienced)				
Cancer, Non-NMSC	6 (5.4%)	8 (7.1%)	0.074	14 (6.3%)
Cancer, NMSC only	10 (8.9%)	7 (6.3%)	0.101	17 (7.6%)
Chronic Lung Disease (COPD, pulmonary fibrosis, asthma, interstitial lung disease)	11 (9.8%)	14 (12.5%)	0.085	25 (11.2%)
CVD-VTE risk (hospitalized congestive heart failure, ventricular or atrial arrhythmia)	4 (3.6%)	7 (6.3%)	0.124	11 (4.9%)
CVD-MACE risk (unstable angina, hospitalized congestive heart failure, ventricular arrhythmia, cardiovascular revascularization, coronary artery disease TIA)	8 (7.1%)	9 (8.0%)	0.034	17 (7.6%)
Cardiovascular revascularization	2 (1.8%)	5 (4.5%)	0.154	7 (3.1%)
Congestive heart failure (hospitalized & non-hospitalized)	2 (1.8%)	4 (3.6%)	0.111	6 (2.7%)
Coronary artery disease	5 (4.5%)	5 (4.5%)	0.000	10 (4.5%)
Ischemic heart disease	6 (5.4%)	7 (6.3%)	0.038	13 (5.8%)
TIA	1 (0.9%)	1 (0.9%)	0.000	2 (0.9%)
Unstable angina	0 (0.0%)	1 (0.9%)	0.134	1 (0.4%)
Ventricular arrhythmia	0 (0.0%)	0 (0.0%)		0 (0.0%)
Diabetes mellitus	12 (10.7%)	16 (14.3%)	0.108	28 (12.5%)
Hyperlipidaemia	23 (20.5%)	20 (17.9%)	0.068	43 (19.2%)
Hypertension (hospitalized & non-hospitalized)	46 (41.1%)	41 (36.6%)	0.092	87 (38.8%)
Immune disorders	29 (25.9%)	31 (27.7%)	0.040	60 (26.8%)
Secondary Sjogren Syndrome	29 (25.9%)	31 (27.7%)	0.040	60 (26.8%)
Liver disorder (hepatic event hospitalized & hepatic event non-hospitalized)	4 (3.6%)	4 (3.6%)	0.000	8 (3.6%)
Obesity, current	41 (37.3%)	40 (37.0%)	0.005	81 (37.2%)
Pregnancy, recent (current or since last visit)	0 (0.0%)	0 (0.0%)		0 (0.0%)
RA severity (CDAI)				
n	112	112	0.100	224
Mean±SD	18.8 ±11.6	20.2 ±15.3		19.5 ±13.6
Median	16.5	18.1		17.5
25th percentile, 75th percentile	10.8, 25.0	7.9, 28.9		9.4, 26.6
Min, Max	0.8, 51.2	0.0, 72.5		0.0, 72.5
Prevalent outcomes				
VTE (at any time in the past)	3 (2.7%)	2 (1.8%)	0.060	5 (2.2%)

	Baricitinib (N = 112)	TNFi (N = 112)	Std. Diff.	Total (N = 224)
MACE (at any time in the past)	2 (1.8%)	5 (4.5%)	0.154	7 (3.1%)
Myocardial infarction	2 (1.8%)	3 (2.7%)	0.060	5 (2.2%)
Stroke	0 (0.0%)	2 (1.8%)	0.191	2 (0.9%)
Serious infection (at any time in the past)	10 (8.9%)	16 (14.3%)	0.168	26 (11.6%)
TB, hospitalized (at any time in the past)	0 (0.0%)	0 (0.0%)		0 (0.0%)
DMARD history				
Number of cDMARDs used (ever)				
0	3 (2.7%)	3 (2.7%)	0.000	6 (2.7%)
1	38 (33.9%)	35 (31.3%)	0.057	73 (32.6%)
2+	71 (63.4%)	74 (66.1%)	0.056	145 (64.7%)
Methotrexate (prior use)	102 (91.1%)	102 (91.1%)	0.000	204 (91.1%)
Number of bDMARDs used (ever)				
0	15 (13.4%)	17 (15.2%)	0.051	32 (14.3%)
1	19 (17.0%)	14 (12.5%)	0.126	33 (14.7%)
2+	78 (69.6%)	81 (72.3%)	0.059	159 (71.0%)
Prior bDMARD use[a]	97 (86.6%)	95 (84.8%)	0.051	192 (85.7%)
Prior TNFi bDMARD use	94 (83.9%)	90 (80.4%)	0.093	184 (82.1%)
Prior non-TNFi bDMARD use	66 (58.9%)	64 (57.1%)	0.036	130 (58.0%)
DMARD, current (baseline)				
cDMARD, concomitant use at baseline	69 (61.6%)	77 (68.8%)	0.150	146 (65.2%)
Methotrexate, concomitant use at baseline	50 (44.6%)	54 (48.2%)	0.072	104 (46.4%)
Prescription medication use, current (baseline)				
Other prescription medications				
Cardiovascular medications				
Anticoagulant (coumadin/warfarin; patient-reported)	0 (0.0%)	0 (0.0%)		0 (0.0%)
Antihypertensives (blood pressure lowering medication(s); patient-reported)	51 (45.5%)	54 (48.2%)	0.054	105 (46.9%)
Antiplatelet (Plavix; patient-reported)	2 (1.8%)	4 (3.6%)	0.111	6 (2.7%)
Nitrates (angina/nitrate medications; patient-reported)	2 (1.8%)	4 (3.6%)	0.111	6 (2.7%)
Hormonal Medication HRT (in RA US only)	0 (0.0%)	1 (0.9%)	0.134	1 (0.4%)
Lipid-lowering agents (cholesterol medication; patient-reported)	26 (23.2%)	31 (27.7%)	0.103	57 (25.4%)
RA-related				
Aspirin (includes non-prescription)	18 (16.1%)	18 (16.1%)	0.000	36 (16.1%)
Celebrex (in RA US only)	11 (9.8%)	11 (9.8%)	0.000	22 (9.8%)

	Baricitinib (N = 112)	TNFi (N = 112)	Std. Diff.	Total (N = 224)
Prednisone	39 (34.8%)	32 (28.6%)	0.135	71 (31.7%)
Vaccinations				
Influenza (baseline) (in RA US only)	44 (46.3%)	38 (37.3%)	0.184	82 (41.6%)
Pneumonia (ever) (in RA US only)	25 (25.8%)	23 (21.5%)	0.101	48 (23.5%)
Shingles (ever)	22 (22.0%)	21 (19.3%)	0.068	43 (20.6%)

Abbreviations: bDMARDs = biologic disease-modifying antirheumatic drugs; CDAI = clinical disease activity index; cDMARDs = conventional disease-modifying antirheumatic drugs; COPD = chronic obstructive pulmonary disease; Cor_US = CorEvitas United States; CVD = cardiovascular disease; DMARDs = disease-modifying antirheumatic drugs; HRT = hormone replacement therapy; MACE = major adverse cardiovascular event; Max = maximum; Min = minimum; N = count of patients in specified category; NMSC = non-melanoma skin cancer; RA = rheumatoid arthritis; SD = standard deviation; Std Diff = absolute value of the standardised difference; TB = tuberculosis; TIA = transient ischemic attack; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism.

Note: Many characteristics of the cohort are included in this table but propensity score matching is only expected to balance those risk factors listed in Table 4 (see Section 8.3.3, Annex 19) for each outcome eg, congestive heart failure for VTE. Other factors are included for descriptive purposes only and may not be balanced across treatment groups but do not contribute to confounding bias eg, diabetes for VTE.

[a] Per CorEvitas' contractual obligations, reports on individual drugs are subject to review by individual market authorization holders who are also subscribers to CorEvitas' RA Registry and have therefore not been included in this table.

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10.2.1.3.2. MACE

After propensity score matching, there were a total of 228 patients (114 each in the baricitinib and TNFi cohorts) included in the analysis of MACE (Table 3_Cor_US). The small size of the analysis cohort limits the ability to evaluate the characteristics of the treatment groups at baseline. On average, patients analysed were aged 59.3 years at baseline (range 21 to 81 years) and the majority (76.8%) were female. Based on the average BMI (30.3), patients enrolled in the CorEvitas US registry were on average obese and 54.4% were current or former smokers. Approximately a third (33.8%) of patients reported alcohol use. A slightly lower proposition of patients in the baricitinib cohort attained college/university level education compared to those in the TNFi cohort (baricitinib 49.1%; TNFi 63.4%).

Clinical characteristics of patients at baseline are described in Table 8_Cor_US. The most common conditions ever reported by physicians were hypertension (baricitinib 41.2%, TNFi 42.2%), obesity (baricitinib 37.5%, TNFi 40.4%), other immune disorders (secondary Sjogren syndrome) (baricitinib 26.3%, TNFi 29.8%), hyperlipidaemia (baricitinib 21.9%, TNFi 18.4%), and diabetes (baricitinib 10.5%, TNFi 9.6%). Regarding RA severity, the CDAI score was similar in the baricitinib and TNFi cohorts (baricitinib 18.8, TNFi 19.6).

RA treatment received prior to the index medication is described in Table 8_Cor_US. Almost all (96.5%) patients in CorEvitas US registry has history of using at least 1 cDMARD; methotrexate was used by 89.9% of patients. Over half of patients reported concomitant use of cDMARD at baseline (baricitinib 62.3%, TNFi 57.9%). Prior use of bDMARDs was reported in almost all patients (baricitinib 86.8%, TNFi 86.8%).

Table 3_Cor_US Baseline Demographics MACE Cohorts, Matched [COR_US]

	Baricitinib (N = 114)	TNFi (N = 114)	Std. Diff.	Total (N = 228)
Age [yrs]				
n	114	114	0.070	228
Mean ± SD	59.7 ±11.3	58.9 ±12.7		59.3 ±12.0
Median	60.0	59.5		60.0
Min, Max	27.0, 81.0	21.0, 81.0		21.0, 81.0
≥65 years	40 (35.1%)	41 (36.0%)	0.018	81 (35.5%)
Gender				
Male	27 (23.7%)	26 (22.8%)	0.021	53 (23.2%)
Female	87 (76.3%)	88 (77.2%)		175 (76.8%)
BMI				
n	112	114	0.032	226
Mean ± SD	30.2 ± 7.6	30.4 ± 7.3		30.3 ± 7.4
Median	28.9	28.5		28.8
Min, Max	16.1, 50.9	18.2, 57.4		16.1, 57.4
Smoking (current or former)	63 (55.3%)	61 (53.5%)	0.035	124 (54.4%)
Alcohol use	40 (35.1%)	37 (32.5%)	0.056	77 (33.8%)
Education				
College/university	53 (49.1%)	71 (63.4%)	0.292	124 (56.4%)

Abbreviations: BMI = body mass index; Cor_US = CorEvitas United States; MACE = major adverse cardiovascular event; Max = maximum; Min = minimum; N = count of patients in the specified category; SD = standard deviation; Std Diff = absolute value of the standardised difference; TNFi = tumour necrosis factor inhibitor; yrs = years.

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Table 8_Cor_US Clinical Characteristics MACE Cohorts, Matched [COR_US]

	Baricitinib (N = 114)	TNFi (N = 114)	Std. Diff.	Total (N = 228)
History of MD-reported comorbidities (ever experienced)				
Cancer, Non-NMSC	6 (5.3%)	4 (3.5%)	0.086	10 (4.4%)
Cancer, NMSC only	10 (8.8%)	6 (5.3%)	0.138	16 (7.0%)
Chronic Lung Disease (COPD, pulmonary fibrosis, asthma, interstitial lung disease)	11 (9.6%)	15 (13.2%)	0.111	26 (11.4%)
CVD-VTE risk (hospitalized congestive heart failure, ventricular or atrial arrhythmia)	5 (4.4%)	2 (1.8%)	0.153	7 (3.1%)
CVD-MACE risk (unstable angina, hospitalized congestive heart failure, ventricular arrhythmia, cardiovascular revascularization, coronary artery disease TIA)	9 (7.9%)	9 (7.9%)	0.000	18 (7.9%)
Cardiovascular revascularization	2 (1.8%)	6 (5.3%)	0.192	8 (3.5%)
Congestive heart failure (hospitalized & non-hospitalized)	2 (1.8%)	3 (2.6%)	0.060	5 (2.2%)
Coronary artery disease	5 (4.4%)	7 (6.1%)	0.079	12 (5.3%)
Ischemic heart disease	6 (5.3%)	9 (7.9%)	0.106	15 (6.6%)
TIA	1 (0.9%)	2 (1.8%)	0.077	3 (1.3%)
Unstable angina	0 (0.0%)	0 (0.0%)		0 (0.0%)
Ventricular arrhythmia	1 (0.9%)	0 (0.0%)	0.133	1 (0.4%)
Diabetes mellitus	12 (10.5%)	11 (9.6%)	0.029	23 (10.1%)
Hyperlipidaemia	25 (21.9%)	21 (18.4%)	0.088	46 (20.2%)
Hypertension (hospitalized & non-hospitalized)	47 (41.2%)	48 (42.1%)	0.018	95 (41.7%)
Immune disorders	30 (26.3%)	34 (29.8%)	0.078	64 (28.1%)
Secondary Sjogren Syndrome	30 (26.3%)	34 (29.8%)	0.078	64 (28.1%)
Liver disorder (hepatic event hospitalized & hepatic event non-hospitalized)	4 (3.5%)	6 (5.3%)	0.086	10 (4.4%)
Obesity, current	42 (37.5%)	46 (40.4%)	0.058	88 (38.9%)
Pregnancy, recent (current or since last visit)	0 (0.0%)	1 (0.9%)	0.138	1 (0.5%)
RA severity (CDAI)				
n	114	114	0.061	228
Mean±SD	18.8 ±11.5	19.6 ±14.2		19.2 ±12.9
Median	16.8	17.9		17.6
25th percentile, 75th percentile	11.0, 25.0	7.5, 30.5		9.2, 26.9
Min, Max	0.8, 51.2	0.0, 63.0		0.0, 63.0
Prevalent outcomes				
VTE (at any time in the past)	5 (4.4%)	3 (2.6%)	0.095	8 (3.5%)
MACE (at any time in the past)	2 (1.8%)	4 (3.5%)	0.110	6 (2.6%)

	Baricitinib (N = 114)	TNFi (N = 114)	Std. Diff.	Total (N = 228)
Myocardial infarction	2 (1.8%)	3 (2.6%)	0.060	5 (2.2%)
Stroke	0 (0.0%)	1 (0.9%)	0.133	1 (0.4%)
Serious infection (at any time in the past)	10 (8.8%)	14 (12.3%)	0.115	24 (10.5%)
TB, hospitalized (at any time in the past)	0 (0.0%)	0 (0.0%)		0 (0.0%)
DMARD history				
Number of cDMARDs used (ever)				
0	3 (2.6%)	5 (4.4%)	0.095	8 (3.5%)
1	39 (34.2%)	38 (33.3%)	0.019	77 (33.8%)
2+	72 (63.2%)	71 (62.3%)	0.018	143 (62.7%)
Methotrexate (prior use)	104 (91.2%)	101 (88.6%)	0.087	205 (89.9%)
Number of bDMARDs used (ever)				
0	15 (13.2%)	15 (13.2%)	0.000	30 (13.2%)
1	19 (16.7%)	18 (15.8%)	0.024	37 (16.2%)
2+	80 (70.2%)	81 (71.1%)	0.019	161 (70.6%)
Prior bDMARD use[a]	99 (86.8%)	99 (86.8%)	0.000	198 (86.8%)
Prior TNFi bDMARD use	96 (84.2%)	92 (80.7%)	0.092	188 (82.5%)
Prior non-TNFi bDMARD use	68 (59.6%)	68 (59.6%)	0.000	136 (59.6%)
DMARD, current (baseline)				
cDMARD, concomitant use at baseline	71 (62.3%)	66 (57.9%)	0.090	137 (60.1%)
Methotrexate, concomitant use at baseline	51 (44.7%)	40 (35.1%)	0.198	91 (39.9%)
Prescription medication use, current (baseline)				
Other prescription medications				
Cardiovascular medications				
Anticoagulant (coumadin/warfarin; patient-reported)	0 (0.0%)	0 (0.0%)		0 (0.0%)
Antihypertensives (blood pressure lowering medication(s); patient-reported)	53 (46.5%)	53 (46.5%)	0.000	106 (46.5%)
Antiplatelet (Plavix; patient-reported)	2 (1.8%)	1 (0.9%)	0.077	3 (1.3%)
Nitrates (angina/nitrate medications; patient-reported)	2 (1.8%)	2 (1.8%)	0.000	4 (1.8%)
Hormonal Medication HRT (in RA US only)	0 (0.0%)	0 (0.0%)		0 (0.0%)
Lipid-lowering agents (cholesterol medication; patient-reported)	28 (24.6%)	26 (22.8%)	0.041	54 (23.7%)
RA-related				
Aspirin (includes non-prescription)	18 (15.8%)	17 (14.9%)	0.024	35 (15.4%)
Celebrex (in RA US only)	12 (10.5%)	12 (10.5%)	0.000	24 (10.5%)
Prednisone	40 (35.1%)	42 (36.8%)	0.037	82 (36.0%)

	Baricitinib (N = 114)	TNFi (N = 114)	Std. Diff.	Total (N = 228)
Vaccinations				
Influenza (baseline) (in RA US only)	45 (46.4%)	38 (36.2%)	0.208	83 (41.1%)
Pneumonia (ever) (in RA US only)	27 (27.3%)	26 (23.9%)	0.078	53 (25.5%)
Shingles (ever)	22 (21.6%)	19 (17.4%)	0.105	41 (19.4%)

Abbreviations: bDMARDs = biologic disease-modifying antirheumatic drugs; CDAI = clinical disease activity index; cDMARDs = conventional disease-modifying antirheumatic drugs; COPD = chronic obstructive pulmonary disease; Cor_US = CorEvitas United States; CVD = cardiovascular disease; DMARDs = classical disease-modifying antirheumatic drugs; HRT = hormone replacement therapy; MACE = major adverse cardiovascular event; Max = maximum; Min = minimum; N = count of patients in the specified category; NMSC = non-melanoma skin cancer; RA = rheumatoid arthritis; SD = standard deviation; Std Diff = absolute value of the standardised difference; TB = tuberculosis; TIA = transient ischemic attack; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism.

[a] Per CorEvitas' contractual obligations reports on individual drugs are subject to review by individual market authorization holders who are also subscribers to CorEvitas' RA Registry and have therefore not been included in this table.

Note: Many characteristics of the cohort are included in this table but propensity score matching is only expected to balance those risk factors listed in Table 4 (see Section 8.3.3, Annex 19) for each outcome (eg, congestive heart failure) for VTE. Other factors are included for descriptive purposes only and may not be balanced across treatment groups but do not contribute to confounding bias (eg, diabetes) for VTE.

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10.2.1.3.3. Serious infections

After propensity score matching, there were a total of 228 patients (114 each in the baricitinib and TNFi cohorts) included in the analysis of serious infections (Annex 4, Table 4). The small size of the analysis cohort limits the ability to evaluate the characteristics of the treatment groups at baseline. On average, patients analysed were aged 60.8 years at baseline (range 23 to 84 years) and the majority (75.9%) were female. Based on the average BMI (29.4), patients enrolled in the CorEvitas US registry were on average overweight and 53.9% were current or former smokers. Patients in the baricitinib cohort reported alcohol use less often than patients in TNFi cohort (baricitinib 34.2%; TNFi 42.1%), and fewer attained college/university level education (baricitinib 50%; TNFi 61.8%).

Clinical characteristics of patients at baseline are described in Annex 4, Table 9. The most common conditions ever reported by physicians were hypertension (baricitinib 39.5%, TNFi 32.5%), obesity (baricitinib 35.7%, TNFi 35.5%), other immune disorders (secondary Sjogren syndrome) (baricitinib 26.3%%, TNFi 27.2%), hyperlipidaemia (baricitinib 21.9%, TNFi 18.4%), diabetes (baricitinib 10.5%, TNFi 11.4%), and chronic lung disease (baricitinib 9.6%, TNFi 13.2%). Regarding RA severity, the CDAI score was slightly higher in the baricitinib cohort compared to the TNFi cohort (baricitinib 19.2, TNFi 17.6).

RA treatment received prior to the index medication is described in Annex 4, Table 9. Almost all (97.4%) patients in CorEvitas US registry have a history of using at least 1 cDMARD; methotrexate was used by 90.4% of patients. Over half of patients reported concomitant use of cDMARD at baseline (baricitinib 62.3%, TNFi 70.2%). Prior use of bDMARDs was reported in almost all patients (baricitinib 86.8%, TNFi 84.2%).

10.2.1.4. Humana

There were 89 eligible patients treated with baricitinib and 154 eligible TNFi patients in the Humana data. Demographic and clinical characteristics for these unmatched cohorts are in Annex 5. From these unmatched cohorts, the number of patients included in analyses of VTE, MACE, or serious infection after 1:1 matching varies. Details of these analysis-specific cohorts follow.

10.2.1.4.1. VTE

After propensity score matching, there were a total of 98 patients (49 each in the baricitinib and TNFi cohorts) included in the analysis of VTE (Table 2_HUM). The small size of the analysis cohort limits the ability to evaluate the characteristics of the treatment groups at baseline. On average, patients analysed were aged 63.05 years at baseline (range 29 to 80 years) and were almost all (88.8%) female. Based on standardised differences >0.10 after propensity score matching, patients treated with baricitinib were less likely to be ≥65 years of age (44.9% and 53.1%) than those treated with TNFi.

Clinical characteristics of patients at baseline are described in Table 7_HUM. The most commonly observed conditions with at least 10 total cases were dyslipidaemia (baricitinib 51%, TNFi 49%), hypertension (baricitinib 49%, TNFi 65.3%), diabetes (baricitinib 28.6%, TNFi

30.6%), chronic lung disease (baricitinib 20.4%, TNFi 18.4%) and obesity (baricitinib 30.6%, TNFi 30.6%). Smoking was also prevalent (baricitinib 18.4%, TNFi 16.3%). Regarding RA severity, the CIRAS score was the same across the cohorts (baricitinib 4.00, TNFi 4.03).

RA treatment received prior to the index medication is described in Table 7_HUM. Over half of patients used cDMARDs (baricitinib 59.2%, TNFi 53.1%), with methotrexate recorded most frequently (baricitinib 28.6%, TNFi 24.5%). Patients treated with baricitinib were less likely to have >1 cDMARD concomitantly than those treated with TNFi (baricitinib 6.1%, TNFi 16.3%). Prior use of bDMARDs was observed in almost CCI% (n = CCI) of the baricitinib cohort in contrast to the TNFi cohort (98%, n = 48). Note that the high prevalence of bDMARD use in the TNFi cohort is due to the eligibility requirement for the TNFi patients in US claims data. This is to better align TNFi use in the comparison group with the USPI for baricitinib. Adalimumab (32.7%) was the most frequently recorded prior bDMARD used by the TNFi cohort.

Baseline healthcare resource utilisation was generally consistent between the patients treated with baricitinib and TNFi (Table 12B_HUM); however, the patients treated with baricitinib had more inpatient visits than patients in the TNFi cohort. Note that Table 12B_HUM reports visit days per patient (ie, at most 1 visit per day), but the propensity scores model controlled for the total number of visits during the period (ie, more than 1 visit; see Table 12A in Annex 5) could occur per day.

Table 2_HUM Baseline Demographics VTE Cohorts, Matched [HUM]

	Baricitinib			TNFi (N = 49)	Std. Diff. (Any vs TNFi)	Total (N = 98)
	Any (N = 49)	4 mg (N)	2 mg (N = 49)			
Age [yrs]						
n	49	-	49	49		98
Mean (SD)	62.53 (10.98)	-	62.53 (10.98)	63.57 (11.58)	0.09	63.05 (11.23)
Median	64.00 [56.00, 71.00]	-	64.00 [56.00, 71.00]	66.00 [54.50, 73.00]		64.00 [55.00, 72.00]
Min, Max	29.0, 78.0	-	29.0, 78.0	38.0, 80.0		29.0, 80.0
≥65 years	22 (44.9%)	-	22 (44.9%)	26 (53.1%)	0.16	48 (49.0%)
Sex						
Male	CCI	-	CCI	CCI	0.07	11 (11.2%)
Female	CCI	-	CCI	CCI	0.07	87 (88.8%)

Abbreviations: HUM = Humana; Max = maximum; Min = minimum; N = number of patients in specified category; n = number of patients within specified category; SD = standard deviation; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor; vs = versus; VTE = venous thromboembolism.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\humana_HUM\5. Table 6.2 - Baseline Demographics VTE Cohorts, Matched [Humana 1179 Curated (RA) - Rheumatoid Arthritis].docx

Table 7_HUM Clinical Characteristics Primary VTE Cohorts, Matched [HUM]

Characteristic[a,b]	Baricitinib[c] (N = 49)	TNFi (N = 49)	Std. Diff.
Clinical Conditions during baseline			
Cancer	CCI	CCI	0.07
NMSC	CCI	0 (0.0%)	0.20
Chronic lung disease	CCI	CCI	0.05
Cardiovascular conditions			
Atrial arrhythmia/fibrillation	CCI	CCI	0.00
Cardiovascular revascularization	0 (0.0%)	0 (0.0%)	-
Congestive heart failure, hospitalized	0 (0.0%)	0 (0.0%)	-
Coronary artery disease	CCI	CCI	0.28
Ischemic heart disease	CCI	CCI	0.28
Unstable angina	0 (0.0%)	0 (0.0%)	-
Ventricular arrhythmia	CCI	CCI	0.09
Diabetes Mellitus	14 (28.6%)	15 (30.6%)	0.05
Type I	0 (0.0%)	0 (0.0%)	-
Type II	14 (28.6%)	15 (30.6%)	0.05
Dyslipidaemia	25 (51.0%)	24 (49.0%)	0.04
Hypertension	24 (49.0%)	32 (65.3%)	0.33
Immune disorders	CCI	CCI	0.06
AIDS/HIV	0 (0.0%)	0 (0.0%)	-
Antiphospholipid syndrome	0 (0.0%)	CCI	0.20
SLE	CCI	CCI	0.30
Primary Sjögren syndrome	CCI	CCI	0.21
Liver disorder	0 (0.0%)	CCI	0.20
Obesity	15 (30.6%)	15 (30.6%)	0.00
Pregnancy	0 (0.0%)	0 (0.0%)	-
RA severity (CIRAS Index), mean (SD)	4.00 (1.15)	4.03 (1.26)	0.03
Smoking	CCI	CCI	0.05
Surgery, trauma & hospitalization, recent	CCI	0 (0.0%)	0.00
TIA	0 (0.0%)	CCI	0.20
DMARDs			
cDMARDs, during baseline			
n, total	29 (59.2%)	26 (53.1%)	0.12
Mean (SD)	0.65 (0.60)	0.71 (0.79)	0.09
Median	1.00 [0.00, 1.00]	1.00 [0.00, 1.00]	-
Min, Max	0.0, 2.0	0.0, 3.0	-
>1 cDMARD concomitantly	CCI	CCI	0.33
Hydroxychloroquine	CCI	CCI	0.22
Leflunomide	CCI	CCI	0.12
Methotrexate	14 (28.6%)	12 (24.5%)	0.09
Minocycline	CCI	0 (0.0%)	0.42
Sulfasalazine	CCI)	CCI	0.09

Characteristic[a,b]	Baricitinib[c] (N = 49)	TNFi (N = 49)	Std. Diff.
bDMARDs, during baseline[a]			
n, total	CCI	48 (98.0%)	2.57
Mean (SD)	0.20 (0.41)	1.16 (0.43)	2.30
Median	0.00 [0.00, 0.00]	1.00 [1.00, 1.00]	-
Min, Max	0.0, 1.0	1.0, 3.0	-
cDMARDs, concomitant	CCI	22 (44.9%)	0.84
abatacept	CCI	CCI	0.28
adalimumab[d]	0 (0.0%)	16 (32.7%)	0.99
anakinra	0 (0.0%)	0 (0.0%)	-
certolizumab pegol[d]	0 (0.0%)	CCI	0.48
etanercept[d]	CCI	12 (24.5%)	0.70
golimumab[d]	0 (0.0%)	CCI	0.53
infliximab[d]	0 (0.0%)	CCI	0.67
rituximab	0 (0.0%)	0 (0.0%)	-
sarilumab	CCI	CCI	0.07
tocilizumab	CCI	0 (0.0%)	0.36
Other Prescription Medications			
Antibiotics	29 (59.2%)	24 (49.0%)	0.21
Antidiabetic agents	13 (26.5%)	CCI	0.20
Insulins	CCI	CCI	0.08
Non-insulins	CCI	CCI	0.11
Aspirin	0 (0.0%)	0 (0.0%)	-
Cardiovascular			
Anticoagulant	0 (0.0%)	0 (0.0%)	-
Antihypertensives	31 (63.3%)	31 (63.3%)	0.00
Antiplatelet	CCI	CCI	0.00
Nitrates	0 (0.0%)	CCI	0.29
Hormonal			
HRT	CCI	CCI	0.15
Oral Contraceptives	0 (0.0%)	0 (0.0%)	-
SERMs	0 (0.0%)	0 (0.0%)	-
Lipid-lowering agents			
Bile acid binding	CCI	0 (0.0%)	0.29
Cholesterol absorption inhibitor	0 (0.0%)	0 (0.0%)	-
Fibrates	CCI	CCI	0.00
Niacin	0 (0.0%)	0 (0.0%)	-
Omega-3 fatty acids	0 (0.0%)	CCI	0.20
Statins	14 (28.6%)	19 (38.8%)	0.22
Rheumatoid arthritis-related			
Cox-2 Inhibitor	CCI	CCI	0.15
Glucocorticosteroid	31 (63.3%)	28 (57.1%)	0.13
Vaccinations	13 (26.5%)	23 (46.9%)	0.43

Abbreviations: AIDS = acquired immunodeficiency syndrome; bDMARDs = biologic disease-modifying antirheumatic drugs; cDMARDs = conventional disease-modifying antirheumatic drugs; CIRAS = claims-based index for RA severity; DMARDs = disease-modifying antirheumatic drugs; HIV = human immunodeficiency virus; HUM = Humana; Max = maximum; Min = minimum; N = number of patients in the specified category; NMSC = non-melanoma skin cancer; RA = rheumatoid arthritis; SERMs = selective oestrogen receptor modulators; SD = standard deviation; Std. Diff = standardised difference; SLE = systemic lupus erythematosus; TIA = transient ischemic attack; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism.

[a] All conditions and characteristics, except for bDMARDs, are measured during the 6 months prior to initiation of study medication including the date at which the qualifying exposure of baricitinib or TNFi occurs (index date). bDMARDs are measured from the 6 months prior to the initiation of study medication until the day prior to baricitinib or the index TNFi exposure, excluding the index date.

[b] Many characteristics of the cohort are included in this table, but propensity score matching is only expected to balance those risk factors listed in Table 4 (see Section 8.3.3, Annex 19) for each outcome (eg, hospitalized congestive heart failure) for VTE. Other factors are included for descriptive purposes only, may not be balanced across treatment groups but do not contribute to confounding bias (eg, Type I diabetes) for VTE.

[c] Both 2- and 4-mg baricitinib doses are included when the 4-mg dose is available. Alternatively, additional columns may be added for each dose when numbers of patients are sufficient to warrant separate reporting.

[d] TNF inhibitors.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\humana_HUM\5. Table 6.7. - Clinical Characteristics Primary VTE Cohorts, Matched [Humana 1179 Curated (RA) - Rheumatoid Arthritis].docx

Table 12B_HUM Baseline Healthcare Resource Utilisation Primary VTE Cohorts, Matched [HUM], Count at Most 1 Visit per Day

Type of Resource Use	Baricitinib (N = 49)	TNFi (N = 49)	Std. Diff.
Physician Office Visits[a]			
n, patients	43 (87.8%)	46 (93.9%)	0.21
n, events	343	351	
Mean (SD)	7.00 (7.66)	7.16 (5.89)	0.02
Median	4.00 [2.00, 10.00]	7.00 [2.00, 10.00]	
Min, Max	0.0, 31.0	0.0, 29.0	
Rheumatologist Visits[a]			
n, patients	39 (79.6%)	41 (83.7%)	0.11
n, events	126	143	
Mean (SD)	2.57 (1.88)	2.92 (2.37)	0.16
Median	3.00 [1.00, 4.00]	2.00 [2.00, 4.00]	
Min, Max	0.0, 8.0	0.0, 10.0	
Other Outpatient Visits[a]			
n, patients	48 (98.0%)	49 (100.0%)	0.20
n, events	291	353	
Mean (SD)	5.94 (5.40)	7.20 (4.77)	0.25
Median	5.00 [3.00, 7.50]	6.00 [4.00, 9.00]	
Min, Max	0.0, 29.0	1.0, 26.0	
Inpatient Visits[a]			
n, patients	CCI	CCI	0.17
n, events	40	10	
Mean (SD)	0.82 (3.28)	0.20 (1.17)	0.25
Median	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	
Min, Max	0.0, 17.0	0.0, 8.0	
ED Visits[a]			
n, patients	CCI)	CCI	0.00
n, events	20	14	
Mean (SD)	0.41 (1.14)	0.29 (0.68)	0.13
Median	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	
Min, Max	0.0, 6.0	0.0, 3.0	

Abbreviations: ED = emergency department; HUM = Humana; Max = maximum; Min = minimum; N = count of patients in the specified category; PS = propensity score; SD = standard deviation; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism.

Note: Physician office visits do not include rheumatologist visits.

[a] In this table, results describe utilisation of healthcare where a maximum of 1 event was allowed per day. In the PS-matching analyses, multiple claims on the same day were allowed to capture additional information on the amount of services received in a given visit. These results are presented in Table 12A_HUM in Annex 5.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\humana_HUM\5. Table 6.12B (count at most 1 visit per day). Baseline Healthcare Resource Utilisation Primary VTE Cohorts, Matched [Humana 1179 Curated (RA) - Rheumatoid Arthritis].docx

10.2.1.4.2. MACE

After propensity score matching, there were 102 patients (51 each in the baricitinib and TNFi cohorts) included in the analysis of MACE (Table 3_HUM). The small size of the analysis cohort limits the ability to evaluate the characteristics of the treatment groups at baseline. On average, patients analysed were 62.84 years at baseline (range 29 to 80 years) and were almost all (86.3%) female. Based on standardised differences >0.10 after propensity score matching, patients treated with baricitinib were slightly more likely to be female than those treated with TNFi (88.2% and 84.3%, respectively).

Clinical characteristics of patients at baseline are described in Table 8_HUM. The most commonly observed conditions with at least 10 total cases were dyslipidaemia (baricitinib 49%, TNFi 49%), hypertension (baricitinib 58.8%, TNFi 62.7%), diabetes (baricitinib 23.5%, TNFi 31.4%), chronic lung disease (baricitinib 19.6%, TNFi 21.6%), obesity (baricitinib 31.4%, TNFi 35.3%), and cancer (baricitinib CCI %, TNFi CCI %). Smoking was also prevalent in both treatment cohorts (baricitinib 19.6%, TNFi CCI %). Regarding RA severity, the CIRAS score was not dissimilar among the baricitinib and TNFi cohorts (baricitinib 3.91, TNFi 4.07).

RA treatment received prior to the index medication is described in Table 8_HUM. Over half of patients in both the baricitinib (62.7%) and TNFi (58.8%) cohorts used cDMARDs prior to index. Methotrexate was the most frequently recorded cDMARD (baricitinib 33.3%, TNFi 43.1%). Patients treated with baricitinib were more likely to have >1 cDMARD concomitantly than those treated with TNFi (baricitinib CCI %, TNFi CCI %). Prior use of bDMARDs was observed in CCI % (n = CCI) of the baricitinib cohort in contrast to the almost all patients in the TNFi cohort (94.1%). Note that the high prevalence of bDMARD use in the TNFi cohort is due to the eligibility requirement for the TNFi patients in US claims data. Etanercept (35.3%) was the most frequently recorded prior bDMARD used by the TNFi cohort.

Baseline healthcare resource utilisation is approximately consistent between the baricitinib and TNF cohorts (Table 13B_HUM); however, patients treated with baricitinib had on average more emergency department visits. Note that Table 13B_HUM reports visit days per patient (ie, at most 1 visit per day), but the propensity scores model controlled for the total number of visits during the period (ie, more than 1 visit; see Table 13A in Annex 5) could occur per day.

Table 3_HUM Baseline Demographics MACE Cohorts, Matched [HUM]

	Baricitinib			TNFi (N = 51)	Std. Diff. (Any vs TNFi)	Total (N = 102)
	Any (N = 51)	4 mg (N = 0)	2 mg (N = 51)			
Age [yrs]						
n	51	-	51	51		102
Mean (SD)	62.55 (10.89)	-	62.55 (10.89)	63.14 (10.46)	0.06	62.84 (10.63)
Median	64.00 [56.00, 71.00]	-	64.00 [56.00, 71.00]	64.00 [55.00, 72.00]		64.00 [55.75, 71.25]
Min, Max	29.0, 78.0	-	29.0, 78.0	41.0, 80.0		29.0, 80.0
≥65 years	23 (45.1%)	-	23 (45.1%)	24 (47.1%)	0.04	47 (46.1%)
Sex						
Male	CCI	-	CCI	CCI	0.11	14 (13.7%)
Female	CCI	-	CCI	CCI	0.11	88 (86.3%)

Abbreviations: HUM = Humana; MACE = major adverse cardiovascular event, defined based on primary hospital discharge diagnosis codes for acute myocardial infarction, ischemic or haemorrhagic stroke; Max = maximum; Min = minimum; N = count of patients in the specified category; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor; vs = versus; yrs = years.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\humana_HUM\5. Table 6.3- Baseline Demographics MACE Cohorts, Matched [Humana 1179 Curated (RA) - Rheumatoid Arthritis].docx

Table 8_HUM Clinical Characteristics MACE Cohorts, Matched [HUM]

Characteristic[a,b]	Baricitinib[c] (N = 51)	TNFi (N = 51)	Std. Diff.
Clinical Conditions during baseline			
Cancer	[redacted]	[redacted]	0.13
NMSC	[redacted]	0 (0.0%)	0.20
Chronic lung disease	[redacted]	11 (21.6%)	0.05
Cardiovascular conditions			
Atrial arrhythmia/fibrillation	[redacted]	0 (0.0%)	0.29
Cardiovascular revascularization	0 (0.0%)	0 (0.0%)	-
Congestive heart failure, hospitalized	0 (0.0%)	0 (0.0%)	-
Coronary artery disease	[redacted]	[redacted]	0.07
Ischemic heart disease	[redacted]	[redacted]	0.07
Unstable angina	0 (0.0%)	0 (0.0%)	-
Ventricular arrhythmia	[redacted]	[redacted]	0.20
Diabetes Mellitus	12 (23.5%)	16 (31.4%)	0.18
Type I	0 (0.0%)	0 (0.0%)	-
Type II	12 (23.5%)	16 (31.4%)	0.18
Dyslipidaemia	25 (49.0%)	25 (49.0%)	0.00
Hypertension	30 (58.8%)	32 (62.7%)	0.08
Immune disorders	[redacted]	[redacted]	0.06
AIDS/HIV	0 (0.0%)	0 (0.0%)	-
Antiphospholipid syndrome	0 (0.0%)	[redacted]	0.20
SLE	[redacted]	[redacted]	0.34
Primary Sjögren syndrome	0 (0.0%)	[redacted]	0.41
Liver disorder	0 (0.0%)	0 (0.0%)	-
Obesity	16 (31.4%)	18 (35.3%)	0.08
Pregnancy	0 (0.0%)	0 (0.0%)	-
RA severity (CIRAS Index), mean (SD)	3.91 (1.16)	4.07 (1.04)	0.15
Smoking	[redacted]	[redacted]	0.05
Surgery, trauma & hospitalization, recent	[redacted]	[redacted]	0.09
TIA	0 (0.0%)	[redacted]	0.20
DMARDs			
cDMARDs, during baseline			
n, total	32 (62.7%)	30 (58.8%)	0.08
Mean (SD)	0.82 (0.82)	0.75 (0.77)	0.10
Median	1.00 [0.00, 1.00]	1.00 [0.00, 1.00]	-
Min, Max	0.0, 3.0	0.0, 3.0	-
>1 cDMARD concomitantly	[redacted]	[redacted]	0.06
Hydroxychloroquine	[redacted]	[redacted]	0.11
Leflunomide	[redacted]	[redacted]	0.25
Methotrexate	17 (33.3%)	22 (43.1%)	0.20
Minocycline	[redacted]	0 (0.0%)	0.35
Sulfasalazine	[redacted]	[redacted]	0.15

Characteristic[a,b]	Baricitinib[c] (N = 51)	TNFi (N = 51)	Std Diff
bDMARDs, during baseline[a]			
n, total	[redacted]	48 (94.1%)	2.41
Mean (SD)	0.18 (0.39)	1.18 (0.43)	2.44
Median	0.00 [0.00, 0.00]	1.00 [1.00, 1.00]	-
Min, Max	0.0, 1.0	1.0, 3.0	-
cDMARDs, concomitant	[redacted]	24 (47.1%)	1.06
abatacept	[redacted]	[redacted]	0.28
adalimumab[d]	[redacted]	[redacted]	0.55
anakinra	0 (0.0%)	0 (0.0%)	-
certolizumab pegol[d]	[redacted]	[redacted]	0.45
etanercept[d]	0 (0.0%)	18 (35.3%)	1.04
golimumab[d]	0 (0.0%)	[redacted]	0.52
infliximab[d]	[redacted]	[redacted]	0.35
rituximab	0 (0.0%)	0 (0.0%)	-
sarilumab	[redacted]	[redacted]	0.23
tocilizumab	[redacted]	0 (0.0%)	0.29
Other Prescription Medications			
Antibiotics	31 (60.8%)	24 (47.1%)	0.28
Antidiabetic agents	[redacted]	11 (21.6%)	0.10
Insulins	[redacted]	[redacted]	0.12
Non-insulins	[redacted]	[redacted]	0.16
Aspirin	0 (0.0%)	0 (0.0%)	-
Cardiovascular			
Anticoagulant	0 (0.0%)	[redacted]	0.20
Antihypertensives	34 (66.7%)	29 (56.9%)	0.20
Antiplatelet	[redacted]	[redacted]	0.12
Nitrates	[redacted]	[redacted]	0.00
Hormonal			
HRT	[redacted]	[redacted]	0.28
Oral Contraceptives	0 (0.0%)	0 (0.0%)	-
SERMs	0 (0.0%)	0 (0.0%)	-
Lipid-lowering agents			
Bile acid binding	[redacted]	[redacted]	0.00
Cholesterol absorption inhibitor	[redacted]	[redacted]	0.00
Fibrates	[redacted]	[redacted]	0.00
Niacin	0 (0.0%)	0 (0.0%)	-
Omega-3 fatty acids	0 (0.0%)	0 (0.0%)	-
Statins	16 (31.4%)	15 (29.4%)	0.04

Characteristic[a,b]	Baricitinib[c] (N = 51)	TNFi (N = 51)	Std. Diff.
Rheumatoid arthritis-related			
Cox-2 Inhibitor	[redacted] ([redacted]%)	[redacted] ([redacted]%)	0.15
Glucocorticosteroid	35 (68.6%)	36 (70.6%)	0.04
Vaccinations	16 (31.4%)	21 (41.2%)	0.21

Abbreviations: AIDS = acquired immunodeficiency syndrome; bDMARDs = biologic disease-modifying antirheumatic drugs; cDMARDs = conventional disease-modifying antirheumatic drugs; CIRAS = claims-based index for RA severity; DMARDs = disease-modifying antirheumatic drugs; HIV = human immunodeficiency virus; HRT = hormone replacement therapy; HUM = Humana; MACE = major adverse cardiovascular event, defined based on primary hospital discharge diagnosis codes for acute myocardial infarction, ischemic or haemorrhagic stroke; N = count of patients in the specified category; NMSC = non-melanoma skin cancer; RA = rheumatoid arthritis; SD = standard deviation;
SERMs = selective oestrogen receptor modulators; SLE = systemic lupus erythematosus; Std. Diff = standardised difference; TIA = transient ischemic attack; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism.

a All conditions and characteristics, except for bDMARDs, are measured during the 6 months prior to initiation of study medication including the date at which the qualifying exposure of baricitinib or TNFi occurs (index date). bDMARDs are measured from the 6 months prior to the initiation of study medication until the day prior to baricitinib or the index TNFi exposure, excluding the index date.

b Many characteristics of the cohort are included in this table, but propensity score matching is only expected to balance those risk factors listed in Table 4 (see Section 8.3.3, Annex 19) for each outcome (eg, hospitalized congestive heart failure) for VTE. Other factors are included for descriptive purposes only, may not be balanced across treatment groups but do not contribute to confounding bias (eg, Type I diabetes) for VTE.

c Both 2- and 4-mg baricitinib doses are included when the 4-mg dose is available. Alternatively, additional columns may be added for each dose when numbers of patients are sufficient to warrant separate reporting.

d TNF inhibitors.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\humana_HUM\5. Table 6.8. - Clinical Characteristics MACE Cohorts, Matched [Humana 1179 Curated RA].docx

Table 13B_HUM Baseline Healthcare Resource Utilisation MACE Cohorts, Matched [HUM], Count at Most 1 Visit Per Day

Type of Resource Use	Baricitinib (N = 51)	TNFi (N = 51)	Std. Diff.
Physician Office Visits[a]			
n, patients	45 (88.2%)	48 (94.1%)	0.21
n, events	366	382	
Mean (SD)	7.18 (7.40)	7.49 (7.15)	0.04
Median	6.00 [2.00, 10.00]	6.00 [3.00, 10.00]	
Min, Max	0.0, 31.0	0.0, 33.0	
Rheumatologist Visits[a]			
n, patients	40 (78.4%)	42 (82.4%)	0.10
n, events	136	145	
Mean (SD)	2.67 (3.99)	2.84 (2.19)	0.06
Median	2.00 [1.00, 3.00]	3.00 [1.00, 4.00]	
Min, Max	0.0, 28.0	0.0, 9.0	
Other Outpatient Visits[a]			
n, patients	50 (98.0%)	49 (96.1%)	0.12
n, events	342	360	
Mean (SD)	6.71 (8.73)	7.06 (5.68)	0.05
Median	4.00 [3.00, 7.00]	6.00 [4.00, 7.00]	
Min, Max	0.0, 55.0	0.0, 25.0	
Inpatient Visits[a]			
n, patients	[redacted] (CCI %)	[redacted] (CCI %)	0.00
n, events	40	37	
Mean (SD)	0.78 (3.22)	0.73 (3.14)	0.02
Median	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	
Min, Max	0.0, 17.0	0.0, 18.0	
ED Visits[a]			
n, patients	12 (23.5%)	[redacted] (CCI %)	0.15
n, events	25	13	
Mean (SD)	0.49 (1.16)	0.25 (0.69)	0.25
Median	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	
Min, Max	0.0, 6.0	0.0, 4.0	

Abbreviations: ED = emergency department; HUM = Humana; MACE = major adverse cardiovascular event, defined based on primary hospital discharge diagnosis codes for acute myocardial infarction, ischemic or haemorrhagic stroke; Max = maximum; Min = minimum; N = number of patients in the specified category; SD = standard deviation; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor.

Note: Physician office visits do not include rheumatologist visits.

[a] In this table, results describe utilisation of healthcare where a maximum of 1 event was allowed per day. In the PS-matching analyses, multiple claims on the same day were allowed to capture additional information on the amount of services received in a given visit. These results are presented in Table 13A_HUM in Annex 5.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\humana_HUM\5. Table 6.13B (count at most 1 visit per day). Baseline Healthcare Resource Utilisation MACE Cohorts, Matched [Humana 1179 Curated (RA) - Rheumatoid Arthritis].docx

10.2.1.4.3. Serious infections

After propensity score matching, there were a total of 106 patients (53 each in the baricitinib and TNFi cohorts) included in the analysis of serious infection (Annex 5, Table 4). Like the VTE and MACE cohorts described above, the small size of the analysis cohort limits ability to evaluate the characteristics of the treatment groups at baseline. On average, patients analysed were aged 64.84 years (range 29 to 86 years) and almost all (CCI%) were female. Based on standardised differences >0.10 after propensity score matching, patients treated with baricitinib were on average slightly younger (64.17 vs 65.51 years) and less likely to be female than those treated with TNFi (CCI% and CCI%, respectively).

Clinical characteristics of patients at baseline are described in Annex 5, Table 9. The most commonly observed conditions with at least 10 total cases were dyslipidaemia (baricitinib 52.8%, TNFi 45.3%), hypertension (baricitinib 64.2%, TNFi 60.4%), diabetes (baricitinib 35.8%, TNFi 32.1%), chronic lung disease (baricitinib 22.6%, TNFi 20.8%), obesity (baricitinib 34.0%, TNFi 35.8%), and cancer (baricitinib CCI%, TNFi CCI%). Smoking was also prevalent in both treatment cohorts (baricitinib CCI%, TNFi 22.6%). Regarding RA severity, the CIRAS score was the same in the baricitinib and TNFi cohorts (baricitinib 3.97, TNFi 3.98).

RA treatment received prior to the index medication is described in Annex 5, Table 9. Over half of patients used cDMARDs (baricitinib 64.2%, TNFi 66%) and methotrexate was the most frequently recorded cDMARD (baricitinib 30.2%, TNFi 47.2%). Patients treated with baricitinib were less likely to have >1 cDMARD concomitantly than those treated with TNFi (baricitinib CCI%, TNFi 24.5%). Almost all patients in the TNFi cohort received a bDMARD in baseline (96.2%, most frequently adalimumab) whereas CCI% of baricitinib cohort received a bDMARD in baseline.

10.2.1.5. MarketScan

There were 257 eligible patients treated with baricitinib and 1,599 eligible TNFi patients in the MarketScan database. Demographic and clinical characteristics for these unmatched cohorts are in Annex 6. From these unmatched cohorts, the number of patients included in analyses of VTE, MACE, or serious infection after 1:1 matching varies. Details of these analysis-specific cohorts follow.

10.2.1.5.1. VTE

After propensity score matching, there were a total of 370 patients (185 each in the baricitinib and TNFi cohorts) included in the analysis of VTE (Table 2_MTSCN). The small size of the analysis cohort limits the ability to evaluate the characteristics of the treatment groups at baseline. On average, patients analysed were aged 51.3 years at baseline (range 20 to 85 years) and were almost all (84.3%) female. After propensity score matching, baseline demographics of patients treated with baricitinib were not dissimilar of patients treated with TNFi (standardised differences <0.10).

Clinical characteristics of patients at baseline are described in Table 7_MTSCN. The most frequently observed conditions were dyslipidaemia (baricitinib 29.2%, TNFi 23.2%), hypertension (baricitinib 31.4%, TNFi 32.4%), obesity (baricitinib 23.2%, TNFi 24.3%),

diabetes (baricitinib 14.6%, TNFi 13%), cancer (baricitinib 7%, TNFi 11.4%), and chronic lung disease (baricitinib 7%, 13%). Smoking was also prevalent (baricitinib 5.9%, TNFi 6.5%). Regarding RA severity, the CIRAS score was nearly identical in the two cohorts (baricitinib 4.88, TNFi 4.89).

RA treatment received prior to the index medication is described in Table 7_MTSCN. Approximately half of the patients used cDMARDs (baricitinib 57.3%, TNFi 54.6%), with methotrexate recorded most frequently (baricitinib 36.8%, TNFi 34.1%). Concomitant use of >1 cDMARD in baseline was recorded in slightly more baricitinib patients compared to TNFi (21.6% vs. 15.1%, respectively). Prior use of bDMARDs was observed in all patients in the TNFi cohort; adalimumab (35.1%) and etanercept (31.9%) were the most frequently recorded bDMARDs within the TNFi cohort. Within the baricitinib cohort, 46.5% of patients used a bDMARD in baseline period.

Baseline healthcare resource utilisation was not dissimilar across the baricitinib and TNF cohorts (Table 12B_MTSCN). Slightly more baricitinib patients recorded rheumatologist visits than TNFi patients. However, the baricitinib patients had approximately same number of rheumatologist visits as the TNFi cohort patients. Note that Table 12B_MTSCN reports visit days per patient (ie, at most 1 visit per day), but the propensity scores model controlled for the total number of visits during the period (ie, more than 1 visit; see Table 12A in Annex 6) could occur per day.

Table 2_MTSCN Baseline Demographics VTE Cohorts, Matched [MTSCN]

	Baricitinib					
	Any (N = 185)	4 mg (N = 0)	2 mg (N = 185)	TNFi (N = 185)	Std. Diff. (Any vs TNFi)	Total (N = 370)
Age [yrs]						
n	185	-	185	185	370	
Mean (SD)	50.99 (9.70)	-	50.99 (9.70)	51.61 (11.34)	0.06	51.30 (10.54)
Median	52.00 [45.50, 59.00]	-	52.00 [45.50, 59.00]	53.00 [45.00, 60.00]		52.50 [45.00, 59.25]
Min, Max	24.0, 70.0	-	24.0, 70.0	20.0, 85.0		20.0, 85.0
≥65 years	7 (3.8%)	-	7 (3.8%)	8 (4.3%)	0.03	15 (4.1%)
Sex						
Male	30 (16.2%)	-	30 (16.2%)	28 (15.1%)	0.03	58 (15.7%)
Female	155 (83.8%)	-	155 (83.8%)	157 (84.9%)	0.03	312 (84.3%)

Abbreviations: Max = maximum; Min = minimum; MTSCN = MarketScan; N = count of patients in the specified category; SD = standard deviation; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor; vs = versus; VTE = venous thromboembolism; yrs = years.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\marketscan_MKTSN\1. Table 6.2. - Baseline Demographics VTE Cohorts, Matched [IBM MarketScan RA].docx

Table 7_MTSCN Clinical Characteristics Primary VTE Cohorts, Matched [MTSCN]

Characteristic[a,b]	Baricitinib[c] (N = 185)	TNFi (N = 185)	Std. Diff.
Clinical Conditions during baseline			
Cancer	13 (7.0%)	21 (11.4%)	0.15
NMSC	2 (1.1%)	2 (1.1%)	0.00
Chronic lung disease	13 (7.0%)	24 (13.0%)	0.20
Cardiovascular conditions			
Atrial arrhythmia/fibrillation	2 (1.1%)	1 (0.5%)	0.06
Cardiovascular revascularization	1 (0.5%)	0 (0.0%)	0.10
Congestive heart failure, hospitalized	0 (0.0%)	0 (0.0%)	-
Coronary artery disease	7 (3.8%)	8 (4.3%)	0.03
Ischemic heart disease	7 (3.8%)	8 (4.3%)	0.03
Unstable angina	0 (0.0%)	0 (0.0%)	-
Ventricular arrhythmia	1 (0.5%)	2 (1.1%)	0.06
Diabetes Mellitus	27 (14.6%)	24 (13.0%)	0.05
Type I	2 (1.1%)	2 (1.1%)	0.00
Type II	26 (14.1%)	24 (13.0%)	0.03
Dyslipidaemia	54 (29.2%)	43 (23.2%)	0.14
Hypertension	58 (31.4%)	60 (32.4%)	0.02
Immune disorders	16 (8.6%)	21 (11.4%)	0.09
AIDS/HIV	0 (0.0%)	1 (0.5%)	0.10
Antiphospholipid syndrome	0 (0.0%)	0 (0.0%)	-
SLE	11 (5.9%)	5 (2.7%)	0.16
Primary Sjögren syndrome	6 (3.2%)	16 (8.6%)	0.23
Liver disorder	3 (1.6%)	4 (2.2%)	0.04
Obesity	43 (23.2%)	45 (24.3%)	0.02
Pregnancy	0 (0.0%)	0 (0.0%)	-
RA severity (CIRAS Index), mean (SD)	4.88 (1.26)	4.89 (1.32)	0.01
Smoking	11 (5.9%)	12 (6.5%)	0.02
Surgery, trauma & hospitalization, recent	4 (2.2%)	5 (2.7%)	0.03
TIA	0 (0.0%)	1 (0.5%)	0.10
DMARDs			
cDMARDs, during baseline			
n, total	106 (57.3%)	101 (54.6%)	0.05
Mean (SD)	0.84 (0.82)	0.75 (0.79)	0.11
Median	1.00 [0.00, 1.00]	1.00 [0.00, 1.00]	-
Min, Max	0.0, 3.0	0.0, 3.0	-
>1 cDMARD concomitantly	40 (21.6%)	28 (15.1%)	0.17
Hydroxychloroquine	45 (24.3%)	30 (16.2%)	0.20
Leflunomide	18 (9.7%)	22 (11.9%)	0.07
Methotrexate	68 (36.8%)	63 (34.1%)	0.06
Minocycline	0 (0.0%)	0 (0.0%)	-
Sulfasalazine	8 (4.3%)	11 (5.9%)	0.07

Characteristic[a,b]	Baricitinib[c] (N = 185)	TNFi (N = 185)	Std. Diff.
bDMARDs, during baseline[a]			
n, total	86 (46.5%)	185 (100.0%)	1.52
Mean (SD)	0.52 (0.56)	1.50 (0.58)	1.71
Median	0.00 [0.00, 1.00]	1.00 [1.00, 2.00]	-
Min, Max	0.0, 2.0	1.0, 3.0	-
cDMARDs, concomitant	48 (25.9%)	79 (42.7%)	0.36
abatacept	11 (5.9%)	40 (21.6%)	0.47
adalimumab[d]	13 (7.0%)	65 (35.1%)	0.73
anakinra	0 (0.0%)	0 (0.0%)	-
certolizumab pegol[d]	7 (3.8%)	22 (11.9%)	0.31
etanercept[d]	10 (5.4%)	59 (31.9%)	0.72
golimumab[d]	8 (4.3%)	28 (15.1%)	0.37
infliximab[d]	4 (2.2%)	24 (13.0%)	0.42
rituximab	8 (4.3%)	4 (2.2%)	0.12
sarilumab	13 (7.0%)	12 (6.5%)	0.02
tocilizumab	16 (8.6%)	8 (4.3%)	0.18
Other Prescription Medications			
Antibiotics	92 (49.7%)	93 (50.3%)	0.01
Antidiabetic agents	26 (14.1%)	26 (14.1%)	0.00
Insulins	9 (4.9%)	8 (4.3%)	0.03
Non-insulins	23 (12.4%)	22 (11.9%)	0.02
Aspirin	2 (1.1%)	2 (1.1%)	0.00
Cardiovascular			
Anticoagulant	3 (1.6%)	2 (1.1%)	0.05
Antihypertensives	82 (44.3%)	78 (42.2%)	0.04
Antiplatelet	2 (1.1%)	1 (0.5%)	0.06
Nitrates	3 (1.6%)	3 (1.6%)	0.00
Hormonal			
HRT	15 (8.1%)	13 (7.0%)	0.04
Oral Contraceptives	17 (9.2%)	13 (7.0%)	0.08
SERMs	4 (2.2%)	2 (1.1%)	0.09
Lipid-lowering agents			
Bile acid binding	1 (0.5%)	1 (0.5%)	0.00
Cholesterol absorption inhibitor	5 (2.7%)	2 (1.1%)	0.12
Fibrates	5 (2.7%)	3 (1.6%)	0.07
Niacin	1 (0.5%)	0 (0.0%)	0.10
Omega-3 fatty acids	2 (1.1%)	0 (0.0%)	0.15
Statins	43 (23.2%)	35 (18.9%)	0.11
Rheumatoid arthritis-related			
Cox-2 Inhibitor	17 (9.2%)	14 (7.6%)	0.06
Glucocorticosteroid	118 (63.8%)	114 (61.6%)	0.05
Vaccinations	50 (27.0%)	58 (31.4%)	0.10

Abbreviations: AIDS = acquired immunodeficiency syndrome; bDMARDs = biologic disease-modifying antirheumatic drugs; CDAI = clinical disease activity index; cDMARDs = conventional disease-modifying antirheumatic drugs; CIRAS = claims-based index for RA severity; DMARDs = disease-modifying antirheumatic drugs; HIV = human immunodeficiency virus; HRT = hormone replacement therapy; Max = maximum; Min = minimum; MTSCN = MarketScan; N = count of patients in the specified category; NMSC = non-melanoma skin cancer; RA = rheumatoid arthritis; SD = standard deviation; SERMs = selective oestrogen receptor modulators; SLE = systemic lupus erythematosus; Std. Diff = standardised difference; TIA = transient ischemic attack; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism.

[a] All conditions and characteristics, except for bDMARDs, are measured during the 6 months prior to initiation of study medication including the date at which the qualifying exposure of baricitinib or TNFi occurs (index date). bDMARDs are measured from the 6 months prior to the initiation of study medication until the day prior to baricitinib or the index TNFi exposure, excluding the index date.

[b] Many characteristics of the cohort are included in this table, but propensity score matching is only expected to balance those risk factors listed in Table 4 (see Section 8.3.3, Annex 19) for each outcome (eg, hospitalized congestive heart failure) for VTE. Other factors are included for descriptive purposes only, may not be balanced across treatment groups but do not contribute to confounding bias (eg, Type I diabetes) for VTE.

[c] Both 2- and 4-mg baricitinib doses are included when the 4-mg dose is available. Alternatively, additional columns may be added for each dose when numbers of patients are sufficient to warrant separate reporting.

[d] TNF inhibitors.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\marketscan_MKTSN\1. Table 6.7. - Clinical Characteristics Primary VTE Cohorts, Matched [IBM MarketScan]_.docx

Table 12B_MTSCN Baseline Healthcare Resource Utilisation Primary VTE Cohorts, Matched [MTSCN], Count at Most 1 Visit per Day

Type of Resource Use	Baricitinib (N = 185)	TNFi (N = 185)	Std. Diff.
Physician Office Visits[a]			
n, patients	174 (94.1%)	174 (94.1%)	0.00
n, events	1,452	1,449	
Mean (SD)	7.85 (7.04)	7.83 (7.35)	0.00
Median	6.00 [3.00, 10.00]	6.00 [3.00, 11.00]	
Min, Max	0.0, 31.0	0.0, 54.0	
Rheumatologist Visits[a]			
n, patients	139 (75.1%)	128 (69.2%)	0.13
n, events	400	405	
Mean (SD)	2.16 (2.06)	2.19 (2.27)	0.02
Median	2.00 [0.50, 3.00]	2.00 [0.00, 3.00]	
Min, Max	0.0, 16.0	0.0, 9.0	
Other Outpatient Visits[a]			
n, patients	167 (90.3%)	167 (90.3%)	0.00
n, events	951	820	
Mean (SD)	5.14 (13.43)	4.43 (4.20)	0.07
Median	3.00 [2.00, 5.50]	4.00 [2.00, 5.00]	
Min, Max	0.0, 179.0	0.0, 23.0	
Inpatient Visits [a]			
n, patients	6 (3.2%)	5 (2.7%)	0.03
n, events	6	6	
Mean (SD)	0.03 (0.18)	0.03 (0.16)	0.03
Median	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	
Min, Max	0.0, 1.0	0.0, 1.0	
ED Visits[a]			
n, patients	26 (14.1%)	26 (14.1%)	0.00
n, events	35	33	
Mean (SD)	0.19 (0.58)	0.18 (0.56)	0.01
Median	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	
Min, Max	0.0, 5.0	0.0, 5.0	

Abbreviations: ED = emergency department; Max = maximum; Min = minimum; MTSCN = MarketScan; N = number of patients in the specified category; PS = propensity score; SD = standard deviation; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism.

Note: Physician office visits do not include rheumatologist visits.

[a] In this table, results describe utilisation of healthcare where a maximum of 1 event was allowed per day. In the PS-matching analyses, multiple claims on the same day were allowed to capture additional information on the amount of services received in a given visit. These results are presented in Table 12A.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\marketscan_MKTSN\1. Table 6.12B (count at most one visit per day). Baseline Healthcare Resource Utilisation Primary VTE Cohorts, Matched [IBM Marketscan RA].docx

10.2.1.5.2. MACE

After propensity score matching, there were a total of 384 patients (192 each in the baricitinib and TNFi cohorts) included in the analysis of MACE (Table 3_MTSCN). The small size of the analysis cohort limits the ability to evaluate the characteristics of the treatment groups at baseline. On average, patients analysed were aged 51.62 years at baseline (range 18 to 85 years) and were almost all (83.3%) female. After propensity score matching, baseline demographics of patients treated with baricitinib were not dissimilar of patients treated with TNFi (standardised differences <0.10).

Clinical characteristics of patients at baseline are described in Table 8_MTSCN. The most frequently observed conditions were dyslipidaemia (baricitinib 27.1%, TNFi 29.7%), hypertension (baricitinib 33.3%, TNFi 34.4%), obesity (baricitinib 21.4%, TNFi 26.6%), diabetes (baricitinib 15.1%, TNFi 17.7%), cancer (baricitinib 10.4%, TNFi 9.4%), and chronic lung disease (baricitinib 8.9%, 11.5%). Smoking was also prevalent (baricitinib 6.8%, TNFi 7.3%). Regarding RA severity, the CIRAS score was nearly identical in the two cohorts (baricitinib 4.76, TNFi 4.81).

RA treatment received prior to the index medication is described in Table 8_MTSCN. Approximately half of the patients used cDMARDs (baricitinib 54.2%, TNFi 57.3%), with methotrexate recorded most frequently (baricitinib 33.3%, TNFi 34.4%). Concomitant use of >1 cDMARD in baseline was recorded in slightly more baricitinib patients compared to TNFi (19.8% vs. 15.1%, respectively). Prior use of bDMARDs was observed in all patients in the TNFi cohort; adalimumab (32.3%) and etanercept (39.1%) were the most frequently recorded bDMARDs within the TNFi cohort. Within the baricitinib cohort, 46.4% of patients used a bDMARD in baseline period.

Baseline healthcare resource utilisation was approximately similar across the baricitinib and TNF cohorts (Table 13B_MTSCN). Note that Table 13B_MTSCN reports visit days per patient (ie, at most 1 visit per day), but the propensity scores model controlled for the total number of visits during the period (ie, more than 1 visit; see Table 13A in Annex 6) could occur per day.

Table 3_MTSCN Baseline Demographics MACE Cohorts, Matched [MTSCN]

	Baricitinib			TNFi (N = 192)	Std. Diff. (Any vs TNFi)	Total (N = 384)
	Any (N = 192)	4 mg (N = 0)	2 mg (N = 192)			
Age [yrs]						
n	192	-	192	192		384
Mean (SD)	51.56 (9.62)	-	51.56 (9.62)	51.69 (10.59)	0.01	51.62 (10.10)
Median	53.00 [46.00, 59.00]	-	53.00 [46.00, 59.00]	53.00 [45.00, 59.00]		53.00 [45.25, 59.00]
Min, Max	18.0, 70.0	-	18.0, 70.0	21.0, 85.0		18.0, 85.0
≥65 years	9 (4.7%)	-	9 (4.7%)	8 (4.2%)	0.03	17 (4.4%)
Sex						
Male	33 (17.2%)	-	33 (17.2%)	31 (16.1%)	0.03	64 (16.7%)
Female	159 (82.8%)	-	159 (82.8%)	161 (83.9%)	0.03	320 (83.3%)

Abbreviations: MACE = major adverse cardiovascular event, defined based on primary hospital discharge diagnosis codes for acute myocardial infarction, ischemic or haemorrhagic stroke; Max = maximum; Min = minimum; MTSCN = MarketScan; N = number of patients in the specified category; SD = standard deviation; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor; vs = versus; yrs = years.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\marketscan_MKTSN\1. Table 6.3. - Baseline Demographics MACE Cohorts, Matched [IBM MarketScan RA].docx

Table 8_MTSCN Clinical Characteristics MACE Cohorts, Matched [MTSCN]

Characteristic[a,b]	Baricitinib[c] (N = 192)	TNFi (N = 192)	Std. Diff.
Clinical Conditions during baseline			
Cancer	20 (10.4%)	18 (9.4%)	0.04
NMSC	2 (1.0%)	3 (1.6%)	0.05
Chronic lung disease	17 (8.9%)	22 (11.5%)	0.09
Cardiovascular conditions			
Atrial arrhythmia/fibrillation	3 (1.6%)	1 (0.5%)	0.10
Cardiovascular revascularization	0 (0.0%)	0 (0.0%)	-
Congestive heart failure, hospitalized	0 (0.0%)	1 (0.5%)	0.10
Coronary artery disease	8 (4.2%)	6 (3.1%)	0.06
Ischemic heart disease	8 (4.2%)	6 (3.1%)	0.06
Unstable angina	1 (0.5%)	0 (0.0%)	0.10
Ventricular arrhythmia	1 (0.5%)	4 (2.1%)	0.14
Diabetes Mellitus	29 (15.1%)	34 (17.7%)	0.07
Type I	2 (1.0%)	3 (1.6%)	0.05
Type II	28 (14.6%)	32 (16.7%)	0.06
Dyslipidaemia	52 (27.1%)	57 (29.7%)	0.06
Hypertension	64 (33.3%)	66 (34.4%)	0.02
Immune disorders	19 (9.9%)	22 (11.5%)	0.05
AIDS/HIV	0 (0.0%)	1 (0.5%)	0.10
Antiphospholipid syndrome	1 (0.5%)	0 (0.0%)	0.10
SLE	14 (7.3%)	6 (3.1%)	0.19
Primary Sjögren syndrome	7 (3.6%)	16 (8.3%)	0.20
Liver disorder	3 (1.6%)	4 (2.1%)	0.04
Obesity	41 (21.4%)	51 (26.6%)	0.12
Pregnancy	0 (0.0%)	2 (1.0%)	0.15
RA severity (CIRAS Index), mean (SD)	4.76 (1.20)	4.81 (1.24)	0.05
Smoking	13 (6.8%)	14 (7.3%)	0.02
Surgery, trauma & hospitalization, recent	3 (1.6%)	1 (0.5%)	0.08
TIA	0 (0.0%)	0 (0.0%)	-
DMARDs			
cDMARDs, during baseline			
n, total	104 (54.2%)	110 (57.3%)	0.06
Mean (SD)	0.80 (0.83)	0.80 (0.81)	0.00
Median	1.00 [0.00, 1.00]	1.00 [0.00, 1.00]	-
Min, Max	0.0, 3.0	0.0, 3.0	-
>1 cDMARD concomitantly	38 (19.8%)	29 (15.1%)	0.12
Hydroxychloroquine	45 (23.4%)	33 (17.2%)	0.16
Leflunomide	17 (8.9%)	27 (14.1%)	0.16
Methotrexate	64 (33.3%)	66 (34.4%)	0.02
Minocycline	0 (0.0%)	1 (0.5%)	0.10
Sulfasalazine	10 (5.2%)	13 (6.8%)	0.07

Characteristic[a,b]	Baricitinib[c] (N = 192)	TNFi (N = 192)	Std. Diff.
bDMARDs, during baseline[a]			
n, total	89 (46.4%)	192 (100.0%)	1.52
Mean (SD)	0.54 (0.57)	1.51 (0.57)	1.71
Median	0.50 [0.00, 1.00]	1.00 [1.00, 2.00]	-
Min, Max	0.0, 2.0	1.0, 3.0	-
cDMARDs, concomitant	46 (24.0%)	84 (43.8%)	0.43
abatacept	10 (5.2%)	44 (22.9%)	0.53
adalimumab[d]	8 (4.2%)	62 (32.3%)	0.78
anakinra	0 (0.0%)	0 (0.0%)	-
certolizumab pegol[d]	8 (4.2%)	18 (9.4%)	0.21
etanercept[d]	13 (6.8%)	75 (39.1%)	0.83
golimumab[d]	9 (4.7%)	22 (11.5%)	0.25
infliximab[d]	5 (2.6%)	28 (14.6%)	0.44
rituximab	9 (4.7%)	2 (1.0%)	0.22
sarilumab	14 (7.3%)	16 (8.3%)	0.04
tocilizumab	17 (8.9%)	7 (3.6%)	0.22
Other Prescription Medications			
Antibiotics	96 (50.0%)	93 (48.4%)	0.03
Antidiabetic agents	29 (15.1%)	34 (17.7%)	0.07
Insulins	9 (4.7%)	12 (6.2%)	0.07
Non-insulins	26 (13.5%)	31 (16.1%)	0.07
Aspirin	1 (0.5%)	0 (0.0%)	0.10
Cardiovascular			
Anticoagulant	6 (3.1%)	3 (1.6%)	0.10
Antihypertensives	91 (47.4%)	83 (43.2%)	0.08
Antiplatelet	3 (1.6%)	2 (1.0%)	0.05
Nitrates	3 (1.6%)	2 (1.0%)	0.046
Hormonal			
HRT	14 (7.3%)	11 (5.7%)	0.06
Oral Contraceptives	18 (9.4%)	8 (4.2%)	0.21
SERMs	2 (1.0%)	2 (1.0%)	0.00
Lipid-lowering agents			
Bile acid binding	2 (1.0%)	2 (1.0%)	0.00
Cholesterol absorption inhibitor	4 (2.1%)	3 (1.6%)	0.04
Fibrates	4 (2.1%)	4 (2.1%)	0.00
Niacin	1 (0.5%)	0 (0.0%)	0.10
Omega-3 fatty acids	2 (1.0%)	0 (0.0%)	0.15
Statins	44 (22.9%)	44 (22.9%)	0.00

Characteristic[a,b]	Baricitinib[c] (N = 192)	TNFi (N = 192)	Std. Diff.
Rheumatoid arthritis-related			
Cox-2 Inhibitor	17 (8.9%)	16 (8.3%)	0.02
Glucocorticosteroid	123 (64.1%)	123 (64.1%)	0.00
Vaccinations	52 (27.1%)	57 (29.7%)	0.06

Abbreviations: AIDS = acquired immunodeficiency syndrome; bDMARDs = biologic disease-modifying antirheumatic drugs; cDMARDs = conventional disease-modifying antirheumatic drugs; CIRAS = claims-based index for RA severity; DMARDs = disease-modifying antirheumatic drugs; HIV = human immunodeficiency virus; HRT = hormone replacement therapy; MACE = major adverse cardiovascular event, defined based on primary hospital discharge diagnosis codes for acute myocardial infarction, ischemic or haemorrhagic stroke; Max = maximum; Min = minimum; MTSN = MarketScan; N = count of patients in the specified category; NMSC = non-melanoma skin cancer;
RA = rheumatoid arthritis; SD = standard deviation; SERMs = selective oestrogen receptor modulators; SLE = systemic lupus erythematosus; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism.

[a] All conditions and characteristics, except for bDMARDs, are measured during the 6 months prior to initiation of study medication including the date at which the qualifying exposure of baricitinib or TNFi occurs (index date). bDMARDs are measured from the 6 months prior to the initiation of study medication until the day prior to baricitinib or the index TNFi exposure, excluding the index date.

[b] Many characteristics of the cohort are included in this table, but propensity score matching is only expected to balance those risk factors listed in Table 4 (see Section 8.3.3, Annex 19) for each outcome (eg, hospitalized congestive heart failure) for VTE. Other factors are included for descriptive purposes only, may not be balanced across treatment groups but do not contribute to confounding bias (eg, Type I diabetes) for VTE.

[c] Both 2- and 4-mg baricitinib doses are included when the 4-mg dose is available. Alternatively, additional columns may be added for each dose when numbers of patients are sufficient to warrant separate reporting.

[d] TNF inhibitors.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\marketscan_MKTSN\ 1. Table 6.8. - Clinical Characteristics MACE Cohorts, Matched [IBM Marketscan RA].docx

Table 13B_MTSCN Baseline Healthcare Resource Utilisation MACE Cohorts, Matched [MTSCN], Count at Most 1 Visit per Day

Type of Resource Use	Baricitinib (N = 192)	TNFi (N = 192)	Std. Diff.
Physician Office Visits[a]			
n, patients	179 (93.2%)	183 (95.3%)	0.09
n, events	1592	1607	
Mean (SD)	8.29 (7.51)	8.37 (7.82)	0.01
Median	6.00 [3.00, 10.75]	6.00 [3.00, 12.00]	
Min, Max	0.0, 42.0	0.0, 54.0	
Rheumatologist Visits[a]			
n, patients	147 (76.6%)	136 (70.8%)	0.13
n, events	426	436	
Mean (SD)	2.22 (2.08)	2.27 (2.19)	0.02
Median	2.00 [1.00, 3.00]	2.00 [0.00, 3.00]	
Min, Max	0.0, 16.0	0.0, 10.0	
Other Outpatient Visits[a]			
n, patients	174 (90.6%)	178 (92.7%)	0.075
n, events	1087	852	
Mean (SD)	5.66 (13.51)	4.44 (3.79)	0.12
Median	4.00 [2.00, 6.00]	3.00 [2.00, 6.00]	
Min, Max	0.0, 179.0	0.0, 24.0	
Inpatient Visits[a]			
n, patients	5 (2.6%)	5 (2.6%)	0.00
n, events	6	6	
Mean (SD)	0.03 (0.16)	0.03 (0.16)	0.00
Median	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	
Min, Max	0.0, 1.0	0.0, 1.0	
ED Visits[a]			
n, patients	31 (16.1%)	29 (15.1%)	0.029
n, events	44	36	
Mean (SD)	0.23 (0.70)	0.19 (0.56)	0.07
Median	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	
Min, Max	0.0, 5.0	0.0, 5.0	

Abbreviations: ED = emergency department; MACE = major adverse cardiovascular event, defined based on primary hospital discharge diagnosis codes for acute myocardial infarction, ischemic or haemorrhagic stroke; Max = maximum; Min = minimum; N = number of patients in the specified category; PS = propensity score; SD = standard deviation; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor.

[a] In this table, results describe utilisation of healthcare where a maximum of 1 event was allowed per day. In the PS from matching analyses, multiple claims on the same day were allowed to capture additional information on the amount of services received in a given visit. These results are presented in Table 13A in Annex 6.

Note: Physician office visits do not include rheumatologist visits.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\marketscan_MKTSN\1. Table 6.13B (count at most one visit per day). Baseline Healthcare Resource Utilisation MACE Cohorts, Matched [IBM Marketscan RA].docx

10.2.1.5.3. Serious infections

After propensity score matching, there were a total of 388 patients (194 each in the baricitinib and TNFi cohorts) included in the analysis of serious infections (Annex 6, Table 4). The small size of the analysis cohort limits the ability to evaluate the characteristics of the treatment groups at baseline. On average, patients analysed were aged 51.64 years at baseline (range 18 to 85 years) and were almost all (82.0%) female. Based on standardised differences >0.10 after propensity score matching, patients treated with baricitinib were less likely to be ≥65 years of age than those treated with TNFi (4.6% and 7.7%, respectively).

Clinical characteristics of patients at baseline are described in Annex 6, Table 9. The most frequently observed conditions were dyslipidaemia (baricitinib 32.5%, TNFi 26.8%), hypertension (baricitinib 34.5%, TNFi 36.1%), obesity (baricitinib 26.3%, TNFi 25.3%), diabetes (baricitinib 14.9%, TNFi 15.5%), chronic lung disease (baricitinib 9.3%, 7.7%), and cancer (baricitinib 9.8%, TNFi 8.2%). Smoking was also prevalent (baricitinib 6.7%, TNFi 7.2%). Regarding RA severity, the CIRAS score was nearly identical in the two cohorts (baricitinib 4.77, TNFi 4.78).

RA treatment received prior to the index medication is described in Annex 6, Table 9. Approximately half of the patients used cDMARDs (baricitinib 54.6%, TNFi 60.8%), with methotrexate recorded most frequently (baricitinib 34%, TNFi 35.1%). Concomitant use of >1 cDMARD in baseline was similar in both cohorts (baricitinib 19.6%, TNFi 16.5%). Prior use of bDMARDs was observed in all patients in the TNFi cohort and nearly half the patients in the baricitinib cohort (47.4%). Adalimumab (33%) and etanercept (33%) were the most frequently recorded bDMARDs within the TNFi cohort.

10.2.1.6. MDR

There were 188 eligible patients treated with baricitinib and 1,686 eligible TNFi patients in the MDR. Demographic and clinical characteristics for these unmatched cohorts are in Annex 7. From these unmatched cohorts, the number of patients included in analyses of VTE, MACE, or serious infection after 1:1 matching varies. Details of these analysis-specific cohorts follow.

10.2.1.6.1. VTE

After propensity score matching, there were a total of 228 patients (114 each in the baricitinib and TNFi cohorts) included in the analysis of VTE (Table 2_MDR). The small size of the analysis cohort limits the ability to evaluate the characteristics of the treatment groups at baseline. On average, patients analysed were aged 59.9 years at baseline (range 25 to 85 years) and were almost all (86%) female. After propensity score matching, baseline demographics of patients treated with baricitinib were not dissimilar of patients treated with TNFi (standardised differences <0.10).

Clinical characteristics of patients at baseline are described in Table 7_MDR. The most frequently observed conditions with at least 10 total cases were dyslipidaemia (baricitinib 43%, TNFi 33%), hypertension (baricitinib 54%, TNFi 45%), obesity (baricitinib 20%, TNFi 21%), diabetes (baricitinib 14%, TNFi 16%), cancer (baricitinib 11%, TNFi 16%), and chronic lung

disease (baricitinib 23%, TNFi 18%). Smoking was also prevalent (baricitinib 12%, TNFi 10%). Regarding RA severity, the CIRAS score was identical in the two cohorts (baricitinib 4, TNFi 4).

RA treatment received prior to the index medication is described in Table 7_MDR. Over half of the patients used cDMARDs (baricitinib 59%, TNFi 60%), with methotrexate recorded most frequently (baricitinib 30%, TNFi 30%) followed by hydroxychloroquine (baricitinib 23%, TNFi 25%). Concomitant use of >1 cDMARD in baseline was recorded in slightly more baricitinib patients compared to TNFi (10% vs. 6%, respectively). Prior use of bDMARDs was observed in all patients; adalimumab (51%) and etanercept (20%) were the most frequently reported bDMARDs within the TNFi cohort whereas adalimumab (24%) and abatacept (18%) were the most frequently reported bDMARDs within the baricitinib cohort.

Baseline healthcare resource utilisation was generally consistent between the patients treated with baricitinib and TNFi (Table 12_MDR). However, TNFi patients recorded more rheumatologist visits than baricitinib patients while baricitinib patients recorded more physician office visits than TNFi patients. Note that Table 12B_MDR reports visit days per patient (ie, at most 1 visit per day), but the propensity scores model controlled for the total number of visits during the period (ie, more than 1 visit) could occur per day.

Table 2_MDR Baseline Demographics VTE Cohorts, Matched [MDR]

	Baricitinib					
	Any (N = 114)	4 mg (N = 0)	2 mg (N = 114)	TNFi (N = 114)	Std. Diff. (Any vs TNFi)	Total (N = 228)
Age [yrs]						
n	114	0	114	114	-0.1	228
Mean (SD)	59.4 (13)	NA	59.4 (13)	60.5 (15)		59.9 (14)
Median	58.0	NA	58.0	61.0		60.0
Min, Max	25.0, 85.0	NA	25.0, 85.0	25.0, 85.0		25.0, 85.0
≥65 years	35 (31%)	0 (0%)	35 (31%)	44 (39%)		79 (35%)
Sex						
Male	16 (14%)	0 (0%)	16 (14%)	16 (14%)	0.0	32 (14%)
Female	98 (86%)	0 (0%)	98 (86%)	98 (86%)		196 (86%)

Abbreviations: N = count of patients in the specified category; NA = not applicable; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor; vs = versus; VTE = venous thromboembolism; Max = maximum; MDR = Military Health System Data Repository; Min = minimum; SD = standard deviation.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\military health_MDR\Lilly Baricitinib Results_Top-Line_Military Health_v2.0.docx -page 3

Table 7_MDR Clinical Characteristics Primary VTE Cohorts, Matched [MDR]

Characteristic[a,b]	Baricitinib[c] (N = 114)	TNFi (N = 114)	Std. Diff.
Clinical Conditions during baseline			
Cancer	13 (11%)	18 (16%)	-0.1
NMSC	5 (4%)	1 (1%)	0.2
Chronic lung disease	26 (23%)	21 (18%)	0.1
Cardiovascular conditions			
Atrial arrhythmia/fibrillation	3 (3%)	6 (5%)	-0.1
Cardiovascular revascularization	0 (0%)	0 (0%)	0.0
Congestive Heart Failure, hospitalized	1 (1%)	1 (1%)	0.0
Coronary artery disease	7 (6%)	12 (11%)	-0.2
Ischemic heart disease	7 (6%)	13 (11%)	-0.2
Unstable angina	1 (1%)	0 (0%)	0.1
Ventricular arrhythmia	3 (3%)	5 (4%)	-0.1
Diabetes Mellitus	16 (14%)	18 (16%)	0.0
Type I	3 (3%)	0 (0%)	0.2
Type II	16 (14%)	18 (16%)	0.0
Dyslipidaemia	49 (43%)	38 (33%)	0.2
Hypertension	61 (54%)	51 (45%)	0.2
Immune disorders	17 (15%)	15 (13%)	0.1
AIDS/HIV	0 (0%)	0 (0%)	0.0
Antiphospholipid syndrome	0 (0%)	0 (0%)	0.0
SLE	4 (4%)	4 (4%)	0.0
Primary Sjögren Syndrome	16 (14%)	13 (11%)	0.1
Liver Disorder	2 (2%)	3 (3%)	-0.1
Obesity	23 (20%)	24 (21%)	0.0
Pregnancy	0 (0%)	0 (0%)	0.0
RA Severity (CIRAS Index), mean (SD)	4 (1)	4 (2)	0.0
Smoking	14 (12%)	11 (10%)	0.1
Surgery, trauma & hospitalization, recent	4 (4%)	5 (4%)	0.0
TIA	1 (1%)	2 (2%)	-0.1
Genetic Coagulopathies	0 (0%)	1 (1%)	-0.1
DMARDs			
cDMARDs, during baseline			
n, total	67 (59%)	68 (60%)	0.0
Mean (SD)	0.9 (1)	0.7 (1)	0.2
Median	1.0	1.0	
Min, Max	0.0, 3.0	0.0, 3.0	0.0, 3.0

Characteristic[a,b]	Baricitinib[c] (N = 114)	TNFi (N = 114)	Std. Diff.
>1 cDMARD concomitantly	11 (10%)	7 (6%)	0.1
Hydroxychloroquine	26 (23%)	28 (25%)	0.0
Leflunomide	18 (16%)	10 (9%)	0.2
Methotrexate	34 (30%)	34 (30%)	0.0
Minocycline	0 (0%)	0 (0%)	0.0
Sulfasalazine	8 (7%)	8 (7%)	0.0
bDMARDs, during baseline			
n, total	114 (100%)	114 (100%)	0.0
Mean (SD)	1.1 (0)	1.1 (0)	0.2
Median	1.0	1.0	
Min, Max	1.0, 2.0	1.0, 2.0	1.0, 2.0
cDMARDs, concomitant	20 (18%)	35 (31%)	-0.3
abatacept	21 (18%)	6 (5%)	0.4
adalimumab[d]	27 (24%)	58 (51%)	-0.6
anakinra	2 (2%)	0 (0%)	0.2
certolizumab pegol[d]	10 (9%)	16 (14%)	-0.2
etanercept[d]	12 (11%)	23 (20%)	-0.3
golimumab[d]	6 (5%)	8 (7%)	-0.1
infliximab[d]	6 (5%)	9 (8%)	-0.1
rituximab	6 (5%)	1 (1%)	0.3
sarilumab	19 (17%)	0 (0%)	0.6
tocilizumab	19 (17%)	1 (1%)	0.6
Other Prescription Medications			
Antibiotics	6 (5%)	4 (4%)	0.1
Antidiabetic agents	10 (9%)	15 (13%)	-0.1
Insulins	2 (2%)	1 (1%)	0.1
Non-insulins	10 (9%)	14 (12%)	-0.1
Aspirin	0 (0%)	0 (0%)	0.0
Cardiovascular			
Anticoagulant	1 (1%)	2 (2%)	-0.1
Antihypertensives	65 (57%)	58 (51%)	0.1
Antiplatelet	3 (3%)	4 (4%)	-0.1
Nitrates	1 (1%)	2 (2%)	-0.1
Hormonal			
HRT	9 (8%)	15 (13%)	-0.2
Oral Contraceptives	3 (3%)	2 (2%)	0.1
SERMs	1 (1%)	1 (1%)	0.0

Characteristic[a,b]	Baricitinib[c] (N = 114)	TNFi (N = 114)	Std. Diff.
Lipid-lowering agents			
Bile acid binding	2 (2%)	3 (3%)	-0.1
Cholesterol absorption inhibitor	3 (3%)	5 (4%)	-0.1
Fibrates	5 (4%)	3 (3%)	0.1
Niacin	0 (0%)	0 (0%)	0.0
Omega-3 fatty acids	0 (0%)	1 (1%)	-0.1
Statins	32 (28%)	35 (31%)	-0.1
Rheumatoid arthritis-related			
Cox-2 Inhibitor	12 (11%)	5 (4%)	0.2
Glucocorticosteroid	93 (82%)	91 (80%)	0.0
Vaccinations	43 (38%)	43 (38%)	0.0

Abbreviations: AIDS = acquired immunodeficiency syndrome; bDMARDs = biologic disease-modifying antirheumatic drugs; CIRAS = claims-based index for RA severity; cDMARDs = conventional disease-modifying antirheumatic drugs; Chronic lung disease = asthma, chronic obstructive lung disease, interstitial lung disease, pulmonary fibrosis; DMARDs = disease-modifying antirheumatic drugs; HIV = human immunodeficiency virus; HRT = hormone replacement therapy; Max = maximum; MDR = Military Health System Data Repository; Min = minimum; N = count of patients in the specified category; NMSC = non-melanoma skin cancer; RA = rheumatoid arthritis; SD = standard deviation; SERMs = selective oestrogen receptor modulators; SLE = systemic lupus erythematosus; Std. Diff. = standardised difference; TIA = transient ischemic attack; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism.

[a] All conditions and characteristics except for the use of bDMARD and concomitant cDMARD are measured during the 6 months prior to initiation of study medication until and including index day.

[b] Many characteristics of the cohort are included in this table, but propensity score matching is only expected to balance those risk factors listed in Table 4 in protocol Section 8.3.3 (Annex 19) for each outcome (eg, hospitalized congestive heart failure) for VTE. Other factors are included for descriptive purposes only and may not be balanced across treatment groups but do not contribute to confounding bias (eg, Type I diabetes) for VTE.

[c] Both 2- and 4-mg baricitinib doses are included when the 4-mg dose is available. Alternatively, additional columns may be added for each dose where numbers of patients are sufficient to warrant separate reporting.

[d] TNFi.

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Table 12_MDR Baseline Healthcare Resource Utilisation Primary VTE Cohorts, Matched [MDR]

Type of Resource Use	Baricitinib (N = 114)	TNFi (N = 114)	Std. Diff.
Physician Office Visits			
n, patients	114	113	0.1
n, events	1896	1639	

Type of Resource Use	Baricitinib (N = 114)	TNFi (N = 114)	Std. Diff.
Mean (SD)	16.6 (12)	14.4 (13)	0.2
Median	14.0	11.0	
Min, Max	1.0, 56.0	0.0, 77.0	
Rheumatologist Visits			
n, patients	87	92	-0.1
n, events	262	333	
Mean (SD)	2.3 (2)	2.9 (3)	-0.2
Median	2.0	2.0	
Min, Max	0.0, 10.0	0.0, 16.0	
Other Outpatient Visits			
n, patients	74	77	-0.1
n, events	281	256	
Mean (SD)	2.5 (3)	2.2 (3)	0.1
Median	1.0	1.0	
Min, Max	0.0, 12.0	0.0, 11.0	
Inpatient Visits			
n, patients	8	11	-0.1
n, events	8	11	
Mean (SD)	0.1 (0)	0.1 (0)	-0.1
Median	0.0	0.0	
Min, Max	0.0, 1.0	0.0, 1.0	
ED Visits			
n, patients	35	32	0.1
n, events	46	74	
Mean (SD)	0.4 (1)	0.6 (2)	-0.2
Median	0.0	0.0	
Min, Max	0.0, 3.0	0.0, 12.0	

Abbreviations: ED = emergency department; Max = maximum; MDR = Military Health System Data Repository; Min = minimum; N = count of patients in the specified category; SD = standard deviation; Std. Diff = standardised differences; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism.

Note: Physician office visits do not include rheumatologist visits. Other outpatient visits do not include physician office visits or rheumatologist visits.

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10.2.1.6.2. MACE

After propensity score matching, there were a total of 228 patients (114 each in the baricitinib and TNFi cohorts) included in the analysis of MACE (Table 3_MDR). The small size of the analysis cohort limits the ability to evaluate the characteristics of the treatment groups at baseline. On average, patients analysed were aged 59.2 years at baseline (range 21 to 85 years) and were almost all (86%) female. After propensity score matching, baseline demographics of

patients treated with baricitinib were not dissimilar of patients treated with TNFi (standardised differences <0.10).

Clinical characteristics of patients at baseline are described in Table 8_MDR. The most commonly observed conditions with at least 10 total cases were dyslipidaemia (baricitinib 43%, TNFi 42%), hypertension (baricitinib 54%, TNFi 49%), diabetes (baricitinib 14%, TNFi 10%), chronic lung disease (baricitinib 23%, TNFi 17%), obesity (baricitinib 20%, TNFi 19%), immune disorders (baricitinib 15%, TNFi 17%) and cancer (baricitinib 11%, TNFi 10%). Smoking was also prevalent in both treatment cohorts (baricitinib 12%, TNFi 13%). Regarding RA severity, the CIRAS score was not dissimilar among the baricitinib and TNFi cohorts (baricitinib 4.0, TNFi 4.1).

RA treatment received prior to the index medication is described in Table 8_MDR. Over half of patients in both the baricitinib (59%) and TNFi (62%) cohorts used cDMARDs prior to index. Methotrexate was the most frequently recorded cDMARD (baricitinib 30%, TNFi 39%). Patients treated with baricitinib were more likely to have >1 cDMARD concomitantly than those treated with TNFi (baricitinib 10%, TNFi 4%). Prior use of bDMARDs was observed in all patients in both cohorts. Adalimumab was the most frequently recorded prior bDMARD used by the baricitinib cohort (24%) and the TNFi cohort (52%).

Baseline healthcare resource utilisation is approximately consistent between the baricitinib and TNF cohorts (Table 13_MDR); however, TNFi patients recorded more rheumatologist visits than baricitinib patients while baricitinib patients recorded more physician office visits than TNFi patients. Note that Table 13_MDR reports visit days per patient (ie, at most 1 visit per day), but the propensity scores model controlled for the total number of visits during the period (ie, more than 1 visit) could occur per day.

Table 3_MDR Baseline Demographics MACE Cohorts, Matched [MDR]

	Baricitinib			TNFi	Std. Diff.	Total
	Any (N = 114)	4 mg (N = 0)	2 mg (N = 114)	(N = 114)	(Any vs TNFi)	(N = 228)
Age [yrs]						
n	114	0	114	114	0.0	228
Mean (SD)	59.4 (13)	NA	59.4 (13)	59.1 (15)		59.2 (14)
Median	58.0	NA	58.0	61.5		60.0
Min, Max	25.0, 85.0	NA	25.0, 85.0	21.0, 85.0		21.0, 85.0
≥65 years	35 (31%)	0 (0%)	35 (31%)	45 (39%)		80 (35%)
Sex						
Male	16 (14%)	0 (0%)	16 (14%)	15 (13%)	0.0	31 (14%)
Female	98 (86%)	0 (0%)	98 (86%)	99 (87%)		197 (86%)

Abbreviations: MACE = major adverse cardiovascular event, defined based on primary hospital discharge diagnosis codes for acute myocardial infarction, ischemic or haemorrhagic stroke; Max = maximum; MDR = Military Health System Data Repository; Min = minimum; N = count of patients in the specified category; NA = not applicable; SD = standard deviation; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor; vs = versus.

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Table 8_MDR Clinical Characteristics MACE Cohorts, Matched [MDR]

Characteristic[a,b]	Baricitinib (N = 114)	TNFi (N = 114)	Std. Diff.
Clinical Conditions during baseline			
Cancer	13 (11%)	11 (10%)	0.1
NMSC	5 (4%)	3 (3%)	0.1
Chronic lung disease	26 (23%)	19 (17%)	0.2
Cardiovascular conditions			
Atrial arrhythmia/fibrillation	3 (3%)	4 (4%)	-0.1
Cardiovascular revascularization	0 (0%)	0 (0%)	0.0
Congestive Heart Failure, hospitalized	1 (1%)	2 (2%)	-0.1
Coronary artery disease	7 (6%)	7 (6%)	0.0
Ischemic heart disease	7 (6%)	7 (6%)	0.0
Unstable angina	1 (1%)	0 (0%)	0.1
Ventricular arrhythmia	3 (3%)	2 (2%)	0.1
Diabetes Mellitus	16 (14%)	11 (10%)	0.1
Type I	3 (3%)	0 (0%)	0.2
Type II	16 (14%)	11 (10%)	0.1
Dyslipidaemia	49 (43%)	48 (42%)	0.0
Hypertension	61 (54%)	56 (49%)	0.1
Immune disorders	17 (15%)	19 (17%)	0.0

Characteristic[a,b]	Baricitinib (N = 114)	TNFi (N = 114)	Std. Diff.
AIDS/HIV	0 (0%)	1 (1%)	-0.1
Antiphospholipid syndrome	0 (0%)	1 (1%)	-0.1
SLE	4 (4%)	7 (6%)	-0.1
Primary Sjögren Syndrome	16 (14%)	12 (11%)	0.1
Liver Disorder	2 (2%)	0 (0%)	0.2
Obesity	23 (20%)	22 (19%)	0.0
Pregnancy	0 (0%)	0 (0%)	0.0
RA Severity (CIRAS Index), mean (SD)	4.0 (1)	4.1 (2)	-0.1
Smoking	14 (12%)	15 (13%)	0.0
Surgery, trauma & hospitalization, recent	4 (4%)	5 (4%)	0.0
TIA	1 (1%)	1 (1%)	0.0
Genetic Coagulopathies	0 (0%)	0 (0%)	0.0
DMARDs			

Characteristic[a,b]	Baricitinib (N = 114)	TNFi (N = 114)	Std. Diff.
cDMARDs, during baseline			
n, total	67 (59%)	71 (62%)	-0.1
Mean (SD)	0.9 (1)	0.8 (1)	0.2
Median	1.0	1.0	
Min, Max	0.0, 3.0	0.0, 3.0	
>1 cDMARD concomitantly	11 (10%)	5 (4%)	0.2
Hydroxychloroquine	26 (23%)	21 (18%)	0.1
Leflunomide	18 (16%)	11 (10%)	0.2
Methotrexate	34 (30%)	45 (39%)	-0.2
Minocycline	0 (0%)	0 (0%)	0.0
Sulfasalazine	8 (7%)	7 (6%)	0.0
bDMARDs, during baseline			
n, total	114 (100%)	114 (100%)	0.0
Mean (SD)	1.1 (0)	1.0 (0)	0.3
Median	1.0	1.0	
Min, Max	1.0, 2.0	1.0, 2.0	
cDMARDs, concomitant	20 (18%)	35 (31%)	-0.3
abatacept	21 (18%)	1 (1%)	0.6
adalimumab[c]	27 (24%)	59 (52%)	-0.6
anakinra	2 (2%)	0 (0%)	0.2
certolizumab pegol[c]	10 (9%)	12 (11%)	-0.1
etanercept[c]	12 (11%)	20 (18%)	-0.2
golimumab[c]	6 (5%)	9 (8%)	-0.1
infliximab[c]	6 (5%)	16 (14%)	-0.3
rituximab	6 (5%)	0 (0%)	0.3
sarilumab	19 (17%)	0 (0%)	0.6
tocilizumab	19 (17%)	1 (1%)	0.6
Other Prescription Medications			
Antibiotics	6 (5%)	3 (3%)	0.1
Antidiabetic agents	10 (9%)	8 (7%)	0.1
Insulins	2 (2%)	4 (4%)	-0.1
Non-insulins	10 (9%)	8 (7%)	0.1
Aspirin	0 (0%)	0 (0%)	0.0
Cardiovascular			
Anticoagulant	1 (1%)	4 (4%)	-0.2
Antihypertensives	65 (57%)	63 (55%)	0.0
Antiplatelet	3 (3%)	1 (1%)	0.1
Nitrates	1 (1%)	2 (2%)	-0.1

Characteristic[a,b]	Baricitinib (N = 114)	TNFi (N = 114)	Std. Diff.
Hormonal			
HRT	9 (8%)	8 (7%)	0.0
Oral Contraceptives	3 (3%)	4 (4%)	-0.1
SERMs	1 (1%)	1 (1%)	0.0
Lipid-lowering agents			
Bile acid binding	2 (2%)	3 (3%)	-0.1
Cholesterol absorption inhibitor	3 (3%)	0 (0%)	0.2
Fibrates	5 (4%)	4 (4%)	0.0
Niacin	0 (0%)	0 (0%)	0.0
Omega-3 fatty acids	0 (0%)	0 (0%)	0.0
Statins	32 (28%)	30 (26%)	0.0
Rheumatoid arthritis-related			
Cox-2 Inhibitor	12 (11%)	7 (6%)	0.2
Glucocorticosteroid	93 (82%)	89 (78%)	0.1
Vaccinations	43 (38%)	29 (25%)	0.3

Abbreviations: AIDS = acquired immunodeficiency syndrome; bDMARDs = biologic disease-modifying antirheumatic drugs; CIRAS = claims-based index for RA severity; cDMARDs = conventionaldisease-modifying antirheumatic drugs; Chronic lung disease = asthma, chronic obstructive lung disease, interstitial lung disease, pulmonary fibrosis; DMARD = disease-modifying antirheumatic drug; HIV = human immunodeficiency virus; HRT = hormone replacement therapy; MACE = major adverse cardiovascular event, defined based on primary hospital discharge diagnosis codes for acute myocardial infarction, ischemic or haemorrhagic stroke; Max = maximum; MDR = Military Health System Data Repository; Min = minimum; N = count of patients in the specified category; NMSC = non-melanoma skin cancer; RA = rheumatoid arthritis; SD = standard deviation; SERMs = selective oestrogen receptor modulators; SLE = systemic lupus erythematosus; Std. Diff. = standardised differences; TIA = transient ischemic attack; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism.

[a] All conditions and characteristics except for use of bDMARD and concomitant cDMARD are measured during the 6 months prior to initiation of study medication until and including the index date.

[b] Many characteristics of the cohort are included in this table, but propensity score matching is only expected to balance those risk factors listed in Table 4 in protocol Section 8.3.3 (Annex 19) for each outcome (eg, hospitalized congestive heart failure) for VTE. Other factors are included for descriptive purposes only and may not be balanced across treatment groups but do not contribute to confounding bias (eg, Type I diabetes) for VTE.

[c] TNFi.

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Table 13_MDR Baseline Healthcare Resource Utilisation MACE Cohorts, Matched [MDR]

Type of Resource Use	Baricitinib (N = 114)	TNFi (N = 114)	Std. Diff.
Physician Office Visits			
n, patients	114	114	0.0
n, events	1896	1657	
Mean (SD)	16.6 (12)	14.5 (12)	0.2
Median	14.0	11.0	
Min, Max	1.0, 56.0	1.0, 58.0	
Rheumatologist Visits			
n, patients	87	83	0.1
n, events	262	309	
Mean (SD)	2.3 (2)	2.7 (3)	-0.2
Median	2.0	2.0	
Min, Max	0.0, 10.0	0.0, 16.0	
Other Outpatient Visits			
n, patients	74	79	-0.1
n, events	281	242	
Mean (SD)	2.5 (3)	2.1 (3)	0.1
Median	1.0	1.0	
Min, Max	0.0, 12.0	0.0, 15.0	
Inpatient Visits			
n, patients	8	9	0.0
n, events	8	9	
Mean (SD)	0.1 (0)	0.1 (0)	0.0
Median	0.0	0.0	
Min, Max	0.0, 1.0	0.0, 1.0	
ED Visits			
n, patients	35	37	0.0
n, events	46	58	
Mean (SD)	0.4 (1)	0.5 (1)	-0.1
Median	0.0	0.0	
Min, Max	0.0, 3.0	0.0, 6.0	

Abbreviations: ED = emergency department; MACE = major adverse cardiovascular event, defined based on primary hospital discharge diagnosis codes for acute myocardial infarction, ischemic or haemorrhagic stroke; Max = maximum; MDR = Military Health System Data Repository; Min = minimum; N = count of patients in the specified category; SD = standard deviation; Std. Diff = standardised differences; TNFi = tumour necrosis factor inhibitor.

Note: Physician office visits do not include rheumatologist visits. Other outpatient visits do not include physician office visits or rheumatologist visits.

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10.2.1.6.3. Serious infections

After propensity score matching, there were a total of 230 patients (115 each in the baricitinib and TNFi cohorts) included in the analysis of serious infections (Annex 7, Table 4). The small size of the analysis cohort limits the ability to evaluate the characteristics of the treatment groups at baseline. On average, patients analysed were aged 59.1 years at baseline (range 25 to 85 years) and were almost all (86%) female. After propensity score matching, baseline demographics of patients treated with baricitinib were not dissimilar of patients treated with TNFi (standardised differences <0.10).

Clinical characteristics of patients at baseline are described in Annex 7, Table 9. The most commonly observed conditions with at least 10 total cases were dyslipidaemia (baricitinib 43%, TNFi 37%), hypertension (baricitinib 54%, TNFi 48%), diabetes (baricitinib 15%, TNFi 14%), chronic lung disease (baricitinib 23%, TNFi 23%), obesity (baricitinib 20%, TNFi 18%), and cancer (baricitinib 11%, TNFi 5%). Smoking was also prevalent in both treatment cohorts (baricitinib 14%, TNFi 14%). Regarding RA severity, the CIRAS score was similar across the baricitinib and TNFi cohorts (baricitinib 4.0, TNFi 4.2).

RA treatment received prior to the index medication is described in Annex 7, Table 9. Over half of patients used cDMARDs (baricitinib 59%, TNFi 66%) and methotrexate was the most frequently recorded cDMARD (baricitinib 30%, TNFi 39%). Patients treated with baricitinib were more likely to have >1 cDMARD concomitantly than those treated with TNFi (baricitinib 10%, TNFi 5%). All patients in the baricitinib and TNFi cohorts received a bDMARD in baseline, most frequently adalimumab [baricitinib 23%, TNFi 60%]).

10.2.1.7. Optum

There were 348 eligible patients treated with baricitinib and 1,441 eligible TNFi patients in the Optum data. Demographic and clinical characteristics for these unmatched cohorts are in Annex 8. From these unmatched cohorts, the number of patients included in analyses of VTE, MACE, or serious infection after 1:1 matching varies. Details of these analysis-specific cohorts follow.

10.2.1.7.1. VTE

After propensity score matching, there were a total of 586 patients (284 each in the baricitinib and TNFi cohorts) included in the analysis of VTE (Table 2_Optum). On average, patients analysed were aged 58.8 years at baseline (range 19 to 89 years) and were almost all (86.6%) female.

Clinical characteristics of patients at baseline are described in Table 7_Optum. The most commonly observed conditions were dyslipidaemia (baricitinib 34.9%, TNFi 34.5%), hypertension (baricitinib 46.8%, TNFi 39.8%), diabetes (baricitinib 20.1%, TNFi 22.2%), and obesity (baricitinib 24.6%, TNFi 26.4%). Smoking was also prevalent (baricitinib 16.2%, TNFi 15.5%) With regard to RA severity, the CIRAS score was nearly identical (baricitinib 4.21, TNFi 4.23).

RA treatment received prior to the index medication is described in Table 7_Optum. Over half of patients used cDMARDs (baricitinib 62.3%, TNFi 56%), with methotrexate recorded most frequently (baricitinib 30.3%, TNFi 31.3%). Patients treated with baricitinib were slightly more likely to have >1 cDMARD concomitantly than those treated with TNFi (baricitinib 19.7%, TNFi 16.9%). Prior use of bDMARDs was observed in 33.8% of the baricitinib cohort in contrast to 94% in the TNFi cohort. Note that the high prevalence of bDMARD use in the TNFi cohort is due to the eligibility requirement for the TNFi patients in US claims data. This is to better align TNFi use in the comparison group with the USPI for baricitinib. Adalimumab (34.2%) was the most frequently recorded prior bDMARD used by the TNFi cohort.

Baseline healthcare resource utilisation was generally similar across the baricitinib and TNFi cohorts, with slightly more utilisation among patients in the TNFi cohort (Table 12B_Optum). Note that the table reports visit days per patient (ie, at most 1 visit per day), but the propensity scores model controlled for the total number of visits during the period (ie, more than 1 visit; see Table 12A in Annex 8) could occur per day.

Table 2_Optum Baseline Demographics VTE Cohorts, Matched [Optum]

	Baricitinib			TNFi (N = 284)	Std. Diff. (Any vs TNFi)	Total (N = 586)
	Any (N = 284)	4 mg (N = 0)	2 mg (N = 284)			
Age [yrs]						
n	284	-	284	284		568
Mean (SD)	58.69 (11.94)	-	58.69 (11.94)	58.92 (12.59)	0.02	58.80 (12.26)
Median	59.50 [50.00, 67.00]	-	59.50 [50.00, 67.00]	60.00 [50.00, 69.00]		60.00 [50.00, 68.00]
Min, Max	19.0, 89.0	-	19.0, 89.0	28.0, 89.0		19.0, 89.0
≥65 years	96 (33.8%)	-	96 (33.8%)	96 (33.8%)	0.00	192 (33.8%)
Sex						
Male	40 (14.1%)	-	40 (14.1%)	36 (12.7%)	0.04	76 (13.4%)
Female	244 (85.9%)	-	244 (85.9%)	248 (87.3%)	0.04	492 (86.6%)

Abbreviations: Max = maximum; Min = minimum; N = count of patients in the specified category; SD = standard deviation; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor; vs = versus; VTE = venous thromboembolism.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\optum_OPTUM\2. Table 6.2 - Baseline Demographics VTE Cohorts, Matched [Optum CDM RA].docx

Table 7_Optum Clinical Characteristics Primary VTE Cohorts, Matched [Optum]

Characteristic[a,b]	Baricitinib[c] (N = 284)	TNFi (N = 284)	Std. Diff.
Clinical Conditions during baseline			
Cancer	33 (11.6%)	31 (10.9%)	0.02
NMSC	[redacted]	[redacted]	0.11
Chronic lung disease	54 (19.0%)	54 (19.0%)	0.00
Cardiovascular conditions			
Atrial arrhythmia/fibrillation	11 (3.9%)	[redacted]	0.04
Cardiovascular revascularization	0 (0.0%)	0 (0.0%)	-
Congestive heart failure, hospitalized	[redacted]	[redacted]	0.04
Coronary artery disease	28 (9.9%)	20 (7.0%)	0.10
Ischemic heart disease	28 (9.9%)	20 (7.0%)	0.10
Unstable angina	[redacted]	0 (0.0%)	0.08
Ventricular arrhythmia	14 (4.9%)	[redacted]	0.09
Diabetes Mellitus	57 (20.1%)	63 (22.2%)	0.05
Type I	[redacted]	[redacted]	0.16
Type II	56 (19.7%)	61 (21.5%)	0.04
Dyslipidaemia	99 (34.9%)	98 (34.5%)	0.01
Hypertension	133 (46.8%)	113 (39.8%)	0.14
Immune disorders	32 (11.3%)	32 (11.3%)	0.00
AIDS/HIV	[redacted]	0 (0.0%)	0.08
Antiphospholipid syndrome	[redacted]	[redacted]	0.00
SLE	14 (4.9%)	11 (3.9%)	0.05
Primary Sjögren syndrome	18 (6.3%)	23 (8.1%)	0.07
Liver disorder	[redacted]	6 (2.1%)	0.00
Obesity	70 (24.6%)	75 (26.4%)	0.04
Pregnancy	0 (0.0%)	0 (0.0%)	-
RA severity (CIRAS Index), mean (SD)	4.21 (1.28)	4.23 (1.28)	0.01
Smoking	46 (16.2%)	44 (15.5%)	0.02
Surgery, trauma & hospitalization, recent	13 (4.6%)	15 (5.3%)	0.03
TIA	[redacted]	[redacted]	0.05
DMARDs			
cDMARDs, during baseline			
n, total	177 (62.3%)	159 (56.0%)	0.13
Mean (SD)	0.90 (0.84)	0.77 (0.77)	0.17
Median	1.00 [0.00, 1.00]	1.00 [0.00, 1.00]	-
Min, Max	0.0, 4.0	0.0, 3.0	-
>1 cDMARD concomitantly	56 (19.7%)	48 (16.9%)	0.07
Hydroxychloroquine	60 (21.1%)	41 (14.4%)	0.18
Leflunomide	57 (20.1%)	39 (13.7%)	0.17
Methotrexate	86 (30.3%)	89 (31.3%)	0.02
Minocycline	[redacted]	[redacted]	0.08
Sulfasalazine	24 (8.5%)	30 (10.6%)	0.07
bDMARDs, during baseline[a]			

Characteristic[a,b]	Baricitinib[c] (N = 284)	TNFi (N = 284)	Std. Diff.
n, total	96 (33.8%)	267 (94.0%)	1.61
Mean (SD)	0.47 (0.57)	1.48 (0.57)	1.71
Median	0.00 [0.00, 1.00]	1.00 [1.00, 2.00]	-
Min, Max	0.0, 2.0	1.0, 3.0	-
cDMARDs, concomitant	50 (17.6%)	132 (46.5%)	0.65
abatacept	19 (6.7%)	28 (9.9%)	0.12
adalimumab[d]	18 (6.3%)	97 (34.2%)	0.74
anakinra	0 (0.0%)	0 (0.0%)	-
certolizumab pegol[d]	CCI (CCI%)	40 (14.1%)	0.38
etanercept[d]	13 (4.6%)	46 (16.2%)	0.39
golimumab[d]	CCI (CCI%)	43 (15.1%)	0.44
infliximab[d]	CCI (CCI%)	46 (16.2%)	0.58
rituximab	CCI (CCI%)	CCI (CCI%)	0.04
sarilumab	CCI (CCI%)	CCI (CCI%)	0.02
tocilizumab	17 (6.0%)	12 (4.2%)	0.08
Other Prescription Medications			
Antibiotics	132 (46.5%)	141 (49.6%)	0.06
Antidiabetic agents	48 (16.9%)	50 (17.6%)	0.02
Insulins	11 (3.9%)	12 (4.2%)	0.02
Non-insulins	46 (16.2%)	46 (16.2%)	0.00
Aspirin	0 (0.0%)	0 (0.0%)	-
Cardiovascular			
Anticoagulant	CCI (CCI%)	CCI (CCI%)	0.04
Antihypertensives	155 (54.6%)	148 (52.1%)	0.05
Antiplatelet	CCI (CCI%)	CCI (CCI%)	0.02
Nitrates	CCI (CCI%)	CCI (CCI%)	0.03
Hormonal			
HRT	22 (7.7%)	19 (6.7%)	0.04
Oral Contraceptives	CCI (CCI%)	10 (3.5%)	0.06
SERMs	CCI (CCI%)	CCI (CCI%)	0.05
Lipid-lowering agents			
Bile acid binding	CCI (CCI%)	CCI (CCI%)	0.03
Cholesterol absorption inhibitor	CCI (CCI%)	CCI (CCI%)	0.03
Fibrates	CCI (CCI%)	CCI (CCI%)	0.04
Niacin	0 (0.0%)	CCI (CCI%)	0.08
Omega-3 fatty acids	CCI (CCI%)	CCI (CCI%)	0.04
Statins	71 (25.0%)	82 (28.9%)	0.09
Rheumatoid arthritis-related			
Cox-2 Inhibitor	27 (9.5%)	20 (7.0%)	0.09
Glucocorticosteroid	172 (60.6%)	175 (61.6%)	0.02
Vaccinations	98 (34.5%)	92 (32.4%)	0.05

Abbreviations: AIDS = acquired immunodeficiency syndrome; bDMARD = biologic disease-modifying antirheumatic drug; cDMARD = conventional disease-modifying antirheumatic drug; CIRAS = Claims-Based Index for RA Severity; HIV = human immunodeficiency virus; HRT = hormone replacement therapy; Max = maximum; Min = minimum; N = count of patients in the specified category; NMSC = non-melanoma skin cancer; RA = rheumatoid arthritis; SD = standard deviation; SERM = selective oestrogen receptor modifier; SLE = systemic lupus erythematosus; Std. Diff = standardised difference; TIA = transient ischemic attack; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism.

[a] All conditions and characteristics, except for bDMARDs, are measured during the 6 months prior to initiation of study medication including the date at which the qualifying exposure of baricitinib or TNFi occurs (index date). bDMARDs are measured from the 6 months prior to the initiation of study medication until the day prior to baricitinib or the index TNFi exposure, excluding the index date.

[b] Many characteristics of the cohort are included in this table, but propensity score matching is only expected to balance those risk factors listed in Table 4 (see Section 8.3.3, Annex 19) for each outcome (eg, hospitalized congestive heart failure) for VTE. Other factors are included for descriptive purposes only and may not be balanced across treatment groups but do not contribute to confounding bias (eg, Type I diabetes) for VTE.

[c] Both 2- and 4-mg baricitinib doses are included when the 4-mg dose is available. Alternatively, additional columns may be for each dose where numbers of patients are sufficient to warrant separate reporting.

[d] TNFi.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\optum_OPTUM\2. Table 6.7. - Clinical Characteristics Primary VTE Cohorts, Matched [Optum CDM].docx

Table 12B_Optum Baseline Healthcare Resource Utilisation Primary VTE Cohorts, Matched [Optum], Count at Most 1 Visit per Day

Type of Resource Use	Baricitinib (N = 284)	TNFi (N = 284)	Std. Diff.
Physician Office Visits[a]			
n, patients	266 (93.7%)	272 (95.8%)	0.10
n, events	2,127	2,329	
Mean (SD)	7.49 (7.01)	8.20 (7.63)	0.10
Median	6.00 [3.00, 10.00]	7.00 [3.00, 11.00]	
Min, Max	0.0, 45.0	0.0, 66.0	
Rheumatologist Visits[a]			
n, patients	198 (69.7%)	208 (73.2%)	0.08
n, events	565	673	
Mean (SD)	1.99 (1.97)	2.37 (2.34)	0.18
Median	2.00 [0.00, 3.00]	2.00 [0.00, 3.00]	
Min, Max	0.0, 9.0	0.0, 14.0	
Other Outpatient Visits[a]			
n, patients	267 (94.0%)	277 (97.5%)	0.18
n, events	1,903	1,872	
Mean (SD)	6.70 (8.08)	6.59 (8.31)	0.01
Median	5.00 [2.00, 8.00]	5.00 [3.00, 8.00]	
Min, Max	0.0, 80.0	0.0, 106.0	
Inpatient Visits[a]			
n, patients	23 (8.1%)	24 (8.5%)	0.01
n, events	145	128	
Mean (SD)	0.51 (2.78)	0.45 (1.98)	0.03
Median	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	

Min, Max	0.0, 32.0	0.0, 21.0	
ED Visits[a]			
n, patients	53 (18.7%)	70 (24.6%)	0.15
n, events	142	182	
Mean (SD)	0.50 (2.04)	0.64 (1.80)	0.07
Median	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	
Min, Max	0.0, 27.0	0.0, 20.0	

Abbreviations: ED = emergency department; Max = maximum; Min = minimum; N = count of patients in the specified category; PS = propensity score; SD = standard deviation; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism.

[a] In this table, results describe utilisation of healthcare where a maximum of 1 event was allowed per day. In the PS-matching analyses, multiple claims on the same day were allowed to capture additional information on the amount of services received in a given visit. These results are presented in Table 12A in Annex.

Note: Physician office visits do not include rheumatologist visits.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\optum_OPTUM\2. Table 6.12B (count at most 1 visit per day). Baseline Healthcare Resource Utilisation Primary VTE Cohorts, Matched [Optum].docx

10.2.1.7.2. MACE

After propensity score matching, there were 574 patients (287 each in the baricitinib and TNFi cohorts) included in the analysis of MACE (Table 3_Optum). On average, patients analysed were 59.16 years at baseline (range 19 to 89 years) and were almost all (86.6%) female. After propensity score matching, baseline demographics of patients treated with baricitinib were not dissimilar of patients treated with TNFi (standardised differences <0.10).

Clinical characteristics of patients at baseline are described in Table 8_Optum. The most commonly observed conditions were dyslipidaemia (baricitinib 33.8%, TNFi 34.1%), hypertension (baricitinib 46%, TNFi 45.6%), obesity (baricitinib 23.3%, TNFi 24.4%), and chronic lung disease (baricitinib 18.8%, TNFi 13.6%). Smoking was also prevalent in both treatment cohorts (baricitinib 13.9%, TNFi 15.7%). Regarding RA severity, the CIRAS score was not dissimilar among the baricitinib compared to the TNFi cohort (baricitinib 4.16, TNFi 4.11).

RA treatment received prior to the index medication is described in Table 8_Optum. Use of cDMARDs prior to index was common in both patients treated with baricitinib (63.8%) and TNFi (49.8%). Methotrexate was the most frequently recorded cDMARD (baricitinib 31%, TNFi 24.4%). Patients treated with baricitinib were more likely to have >1 cDMARD concomitantly than those treated with TNFi (baricitinib 22.3%, TNFi 14.3%). Prior use of bDMARDs was observed in 34.8% of the baricitinib cohort in contrast to 92.3% of the TNFi cohort. Note that the high prevalence of bDMARD use in the TNFi cohort is due to the eligibility requirement for the TNFi patients in US claims data. Adalimumab (35.2%) was the most frequently recorded prior bDMARD used by the TNFi cohort.

Baseline healthcare resource utilisation is approximately consistent across the baricitinib and TNF cohorts (Table 13B_Optum); however, patients in the TNFi cohort had slightly higher utilisation compared to the baricitinib cohort. Note that Table 13B_Optum reports visit days per patient (ie, at most 1 visit per day, but the propensity scores model controlled for the total

number of visits during the period (ie, more than 1 visit; see Table 13A in Annex 8) could occur per day.

Table 3_Optum Baseline Demographics MACE Cohorts, Matched [Optum]

	Baricitinib			TNFi (N = 287)	Std. Diff. (Any vs TNFi)	Total (N = 574)
	Any (N = 287)	4 mg (N = 0)	2 mg (N = 287)			
Age [yrs]						
n	287	-	287	287		574
Mean (SD)	59.01 (12.16)	-	59.01 (12.16)	59.32 (12.25)	0.02	59.16 (12.20)
Median	60.00 [52.00, 67.00]	-	60.00 [52.00, 67.00]	61.00 [50.00, 69.00]		61.00 [51.00, 68.00]
Min, Max	19.0, 89.0	-	19.0, 89.0	28.0, 88.0		19.0, 89.0
≥65 years	102 (35.5%)	-	102 (35.5%)	109 (38.0%)	0.05	211 (36.8%)
Sex						
Male	39 (13.6%)	-	39 (13.6%)	38 (13.2%)	0.01	77 (13.4%)
Female	248 (86.4%)	-	248 (86.4%)	249 (86.8%)	0.01	497 (86.6%)

Abbreviations: MACE = major adverse cardiovascular event, defined based on primary hospital discharge diagnosis codes for acute myocardial infarction, ischemic or haemorrhagic stroke; Max = maximum; Min = minimum; N = count of patients in the specified category; SD = standard deviation; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor; vs = versus.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\optum_OPTUM\2. Table 6.3. - Baseline Demographics MACE Cohorts, Matched [Optum CDM RA].docx

Table 8_Optum Clinical Characteristics MACE Cohorts, Matched [Optum]

Characteristics	Baricitinib[c] (N = 287)	TNFi (N = 287)	Std. Diff.
Clinical Conditions during baseline			
Cancer	34 (11.8%)	26 (9.1%)	0.09
NMSC	[redacted]	[redacted]	0.20
Chronic lung disease	54 (18.8%)	39 (13.6%)	0.14
Cardiovascular conditions			
Atrial arrhythmia/fibrillation	[redacted]	12 (4.2%)	0.04
Cardiovascular revascularization	0 (0.0%)	0 (0.0%)	-
Congestive heart failure, hospitalized	0 (0.0%)	[redacted]	0.08
Coronary artery disease	24 (8.4%)	30 (10.5%)	0.07
Ischemic heart disease	24 (8.4%)	30 (10.5%)	0.07
Unstable angina	[redacted]	[redacted]	0.05
Ventricular arrhythmia	12 (4.2%)	[redacted]	0.10
Diabetes Mellitus	64 (22.3%)	55 (19.2%)	0.08
Type I	[redacted]	[redacted]	0.04
Type II	63 (22.0%)	55 (19.2%)	0.07
Dyslipidaemia	97 (33.8%)	98 (34.1%)	0.01
Hypertension	132 (46.0%)	131 (45.6%)	0.01
Immune disorders	33 (11.5%)	36 (12.5%)	0.03
AIDS/HIV	0 (0.0%)	[redacted]	0.08
Antiphospholipid syndrome	[redacted]	[redacted]	0.00
SLE	16 (5.6%)	13 (4.5%)	0.05
Primary Sjögren syndrome	17 (5.9%)	25 (8.7%)	0.11
Liver disorder	[redacted]	[redacted]	0.02
Obesity	67 (23.3%)	70 (24.4%)	0.03
Pregnancy	0 (0.0%)	[redacted]	0.12
RA severity (CIRAS Index), mean (SD)	4.16 (1.29)	4.11 (1.20)	0.04
Smoking	40 (13.9%)	45 (15.7%)	0.05
Surgery, trauma & hospitalization, recent	12 (4.2%)	18 (6.3%)	0.09
TIA	[redacted]	[redacted]	0.00
DMARDs			
cDMARDs, during baseline			
n, total	183 (63.8%)	143 (49.8%)	0.28
Mean (SD)	0.95 (0.85)	0.68 (0.74)	0.34
Median	1.00 [0.00, 1.00]	1.00 [0.00, 1.00]	-
Min, Max	0.0, 4.0	0.0, 3.0	-
>1 cDMARD concomitantly	64 (22.3%)	41 (14.3%)	0.21
Hydroxychloroquine	67 (23.3%)	51 (17.8%)	0.14
Leflunomide	59 (20.6%)	31 (10.8%)	0.27
Methotrexate	89 (31.0%)	70 (24.4%)	0.15
Minocycline	[redacted]	[redacted]	0.11
Sulfasalazine	25 (8.7%)	20 (7.0%)	0.07

Characteristics	Baricitinib[c] (N = 287)	TNFi (N = 287)	Std. Diff.
bDMARDs, during baseline[a]			
n, total	100 (34.8%)	265 (92.3%)	1.49
Mean (SD)	0.46 (0.55)	1.47 (0.57)	1.82
Median	0.00 [0.00, 1.00]	1.00 [1.00, 2.00]	-
Min, Max	0.0, 2.0	1.0, 3.0	-
cDMARDs, concomitant	57 (19.9%)	117 (40.8%)	0.47
abatacept	20 (7.0%)	26 (9.1%)	0.08
adalimumab[d]	18 (6.3%)	101 (35.2%)	0.76
anakinra	0 (0.0%)	0 (0.0%)	-
certolizumab pegol[d]	CCI (CCI%)	27 (9.4%)	0.28
etanercept[d]	14 (4.9%)	45 (15.7%)	0.36
golimumab[d]	CCI (CCI%)	45 (15.7%)	0.46
infliximab[d]	CCI (CCI%)	53 (18.5%)	0.60
rituximab	CCI (CCI%)	CCI (CCI%)	0.04
sarilumab	11 (3.8%)	CCI (CCI%)	0.10
tocilizumab	16 (5.6%)	CCI (CCI%)	0.10
Other Prescription Medications			
Antibiotics	130 (45.3%)	135 (47.0%)	0.04
Antidiabetic agents	53 (18.5%)	41 (14.3%)	0.11
Insulins	16 (5.6%)	CCI (CCI%)	0.14
Non-insulins	49 (17.1%)	37 (12.9%)	0.12
Aspirin	0 (0.0%)	0 (0.0%)	-
Cardiovascular			
Anticoagulant	12 (4.2%)	CCI (CCI%)	0.06
Antihypertensives	157 (54.7%)	149 (51.9%)	0.06
Antiplatelet	CCI (CCI%)	CCI (CCI%)	0.04
Nitrates	CCI (CCI%)	CCI (CCI%)	0.00
Hormonal			
HRT	21 (7.3%)	20 (7.0%)	0.01
Oral Contraceptives	CCI (CCI%)	11 (3.8%)	0.08
SERMs	CCI (CCI%)	0 (0.0%)	0.15
Lipid-lowering agents			
Bile acid binding	CCI (CCI%)	CCI (CCI%)	0.08
Cholesterol absorption inhibitor	CCI (CCI%)	CCI (CCI%)	0.11
Fibrates	CCI (CCI%)	CCI (CCI%)	0.03
Niacin	0 (0.0%)	0 (0.0%)	-
Omega-3 fatty acids	CCI (CCI%)	CCI (CCI%)	0.07
Statins	73 (25.4%)	83 (28.9%)	0.08
Rheumatoid arthritis-related			
Cox-2 Inhibitor	29 (10.1%)	20 (7.0%)	0.11
Glucocorticosteroid	174 (60.6%)	170 (59.2%)	0.03
Vaccinations	103 (35.9%)	101 (35.2%)	0.02

Abbreviations: AIDS = acquired immunodeficiency syndrome; bDMARD = biologic disease-modifying antirheumatic drug; cDMARD = conventional disease-modifying antirheumatic drug; CIRAS = Claims-Based Index for RA Severity; DMARD = disease-modifying antirheumatic drug; HIV = human immunodeficiency syndrome; HRT = hormone receptor therapy; MACE = major adverse cardiovascular event, defined based on primary hospital discharge diagnosis codes for acute myocardial infarction, ischemic or haemorrhagic stroke; Max = maximum; Min = minimum; N = count of patients in the specified category; SERM = selective oestrogen receptor modifier; SLE = systemic lupus erythematosus; Std. Diff = standardised difference; TIA = transient ischemic attack; TNFi = tumour necrosis factor inhibitor.

[a] All conditions and characteristics, except for bDMARDs, are measured during the 6 months prior to initiation of study medication including the date at which the qualifying exposure of baricitinib or TNFi occurs (index date). bDMARDs are measured from the 6 months prior to the initiation of study medication until the day prior to baricitinib or the index TNFi exposure, excluding the index date.

[b] Many characteristics of the cohort are included in this table, but propensity score matching is only expected to balance those risk factors listed in Table 4 (see Section 8.3.3, Annex 19) for each outcome (eg, hospitalized congestive heart failure) for VTE. Other factors are included for descriptive purposes only and may not be balanced across treatment groups but do not contribute to confounding bias (eg, Type I diabetes) for VTE.

[c] Both 2- and 4-mg baricitinib doses are included when the 4-mg dose is available. Alternatively, additional columns may be added for each dose where numbers of patients are sufficient to warrant separate reporting.

[d] TNFi.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\optum_OPTUM\2. Table 6.8. - Clinical Characteristics MACE Cohorts, Matched [Optum CDM RA].docx

Table 13B_Optum Baseline Healthcare Resource Utilisation MACE Cohorts, Matched [Optum], Count at Most 1 Visit per Day

Type of Resource Use	Baricitinib (N = 287)	TNFi (N = 287)	Std. Diff.
Physician Office Visits[a]			
n, patients	270 (94.1%)	272 (94.8%)	0.03
n, events	2,121	2,161	
Mean (SD)	7.39 (7.03)	7.53 (6.44)	0.02
Median	5.00 [3.00, 10.00]	6.00 [3.00, 10.00]	
Min, Max	0.0, 45.0	0.0, 41.0	
Rheumatologist Visits[a]			
n, patients	201 (70.0%)	205 (71.4%)	0.03
n, events	565	666	
Mean (SD)	1.97 (1.92)	2.32 (2.67)	0.15
Median	2.00 [0.00, 3.00]	2.00 [0.00, 3.00]	
Min, Max	0.0, 9.0	0.0, 25.0	
Other Outpatient Visits[a]			
n, patients	271 (94.4%)	277 (96.5%)	0.10
n, events	1,868	1,903	
Mean (SD)	6.51 (7.89)	6.63 (8.41)	0.02
Median	4.00 [2.00, 8.00]	5.00 [2.00, 8.00]	
Min, Max	0.0, 80.0	0.0, 106.0	
Inpatient Visits[a]			
n, patients	22 (7.7%)	20 (7.0%)	0.03
n, events	144	141	
Mean (SD)	0.50 (2.75)	0.49 (2.61)	0.00
Median	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	
Min, Max	0.0, 32.0	0.0, 25.0	
ED Visits[a]			
n, patients	50 (17.4%)	62 (21.6%)	0.11
n, events	132	152	
Mean (SD)	0.46 (2.01)	0.53 (1.67)	0.04
Median	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	
Min, Max	0.0, 27.0	0.0, 20.0	

Abbreviations: ED = emergency department; MACE = major adverse cardiovascular event, defined based on primary hospital discharge diagnosis codes for acute myocardial infarction, ischemic or haemorrhagic stroke; Max = maximum; Min = minimum; N = count of patients in the specified category; PS = propensity score; SD = standard deviation; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor.

Note: Physician office visits do not include rheumatologist visits.

[a] In this table, results describe utilisation of healthcare where a maximum of 1 event was allowed per day. In the PS-matching analyses, multiple claims on the same day were allowed to capture additional information on the amount of services received in a given visit. These results are presented in Table 13A.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\optum_OPTUM\2. Table 6.13B (count at most one visit per day). Baseline Healthcare Resource Utilisation MACE Cohorts, Matched [Optum].docx

10.2.1.7.3. Serious infections

After propensity score matching, there were a total of 600 patients (300 each in the baricitinib and TNFi cohorts) included in the analysis of serious infection (Annex 8, Table 4). On average, patients analysed were aged 59.66 years (range 19 to 89 years) and almost all (86.3%) were female. After propensity score matching, patients treated with baricitinib were not dissimilar from patients treated with TNFi in terms of age and gender.

Clinical characteristics of patients at baseline are described in Annex 8, Table 9. The most commonly observed conditions with at least 10% of patients were dyslipidaemia (baricitinib 34.7%, TNFi 37%), hypertension (baricitinib 47.3%, TNFi 46.3%), diabetes (baricitinib 21.0%, TNFi 22%), chronic lung disease (baricitinib 19%, TNFi 16.7%), obesity (baricitinib 23%, TNFi 23.7%), and cancer (baricitinib 11.7%, TNFi 10.3%). Smoking was also prevalent in both treatment cohorts (baricitinib 13.7%, TNFi 13.3%). Regarding RA severity, the CIRAS score was very similar in the baricitinib and TNFi cohorts (baricitinib 4.19, TNFi 4.15).

RA treatment received prior to the index medication is described in Annex 8, Table 9. Approximately half of patients used cDMARDs (baricitinib 64%, TNFi 47.7%) and methotrexate was the most frequently recorded cDMARD (baricitinib 31.3%, TNFi 26.7%). Patients treated with baricitinib were more likely to have >1 cDMARD concomitantly than those treated with TNFi (baricitinib 21.7%, TNFi 13%). Almost all patients in the TNFi cohort received a bDMARD in baseline (93.7%, most frequently adalimumab) whereas 36.7% of baricitinib cohort received a bDMARD in baseline.

10.2.1.8. PharMetrics plus

There were 473 eligible patients treated with baricitinib and 6,576 eligible TNFi patients in the PharMetrics Plus data. Demographic and clinical characteristics for these unmatched cohorts are in Annex 9. From these unmatched cohorts, the number of patients included in analyses of VTE, MACE, or serious infection after 1:1 matching varies. Details of these analysis-specific cohorts follow.

10.2.1.8.1. VTE

After propensity score matching, there were a total of 522 patients (261 each in the baricitinib and TNFi cohorts) included in the analysis of VTE (Table 2_PP). On average, patients analysed were aged 53.9 years at baseline (range 21 to 85 years) and were almost all (84%) female. After propensity score matching, baseline demographics of patients treated with baricitinib were not dissimilar of patients treated with TNFi (standardised differences <0.10).

Clinical characteristics of patients at baseline are described in Table 7_PP. The most commonly observed conditions were dyslipidaemia (baricitinib 28%, TNFi 30%), hypertension (baricitinib 34%, TNFi 35%), diabetes (baricitinib 13%, TNFi 13%), and obesity (baricitinib 20%, TNFi 18%). Smoking was also prevalent (baricitinib 7%, TNFi 8%). Regarding RA severity, the CIRAS score was nearly identical (baricitinib 4.4, TNFi 4.5).

RA treatment received prior to the index medication is described in Table 7_PP. Over half of patients used cDMARDs (baricitinib 62%, TNFi 59%), with methotrexate recorded most

frequently (baricitinib 34%, TNFi 33%). Patients treated with baricitinib and TNFi were equally likely to have >1 cDMARD concomitantly (baricitinib 9%, TNFi 10%). Prior use of bDMARDs was observed in all patients; adalimumab (46%) and etanercept (41%) were the most frequently reported bDMARDs within the TNFi cohort whereas abatacept (20%) and tocilizumab (18%) were the most frequently reported bDMARDs within the baricitinib cohort.

Baseline healthcare resource utilisation was generally similar across the baricitinib and TNFi cohorts (Table 12_PP). Note that the table reports visit days per patient (ie, at most 1 visit per day), but the propensity scores model controlled for the total number of visits during the period (ie, more than 1 visit) could occur per day.

Table 2_PP Baseline Demographics VTE Cohorts, Matched [PP]

	Baricitinib			TNFi	Std. Diff. (Any vs TNFi)	Total
	Any (N = 261)	4 mg (N = 0)	2 mg (N = 261)	(N = 261)		(N = 522)
Age [yrs]						
n	261	0	261	261	-0.1	522
Mean (SD)	53.5 (11)	NA	53.5 (11)	54.3 (10)		53.9 (10)
Median	56.0	NA	56.0	56.0		56.0
Min, Max	21.0, 84.0	NA	21.0, 84.0	22.0, 85.0		21.0, 85.0
≥65 years	28 (11%)	0 (0%)	28 (11%)	23 (9%)		51 (10%)
Sex						
Male	43 (16%)	0 (0%)	43 (16%)	39 (15%)	0.0	82 (16%)
Female	218 (84%)	0 (0%)	218 (84%)	222 (85%)		440 (84%)

Abbreviations: Max = maximum; Min = minimum; N = count of patients in the specified category; NA = not applicable; PP = PharMetrics Plus; SD = standard deviation; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor; vs = versus; VTE = venous thromboembolism.

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Table 7_PP Clinical Characteristics Primary VTE Cohorts, Matched [PP]

Characteristic[a,b]	Baricitinib[c] (N = 261)	TNFi (N = 261)	Std. Diff.
Clinical Conditions during baseline			
Cancer	8 (3%)	4 (2%)	0.1
NMSC	7 (3%)	2 (1%)	0.1
Chronic lung disease	29 (11%)	29 (11%)	0.0
Cardiovascular conditions			
Atrial arrhythmia/fibrillation	1 (0%)	0 (0%)	0.1
Cardiovascular revascularization	0 (0%)	0 (0%)	0.0
Congestive Heart Failure, hospitalized	2 (1%)	0 (0%)	0.1
Coronary artery disease	6 (2%)	9 (3%)	-0.1

Characteristic[a,b]	Baricitinib[c] (N = 261)	TNFi (N = 261)	Std. Diff.
Ischemic heart disease	7 (3%)	11 (4%)	-0.1
Unstable angina	0 (0%)	0 (0%)	0.0
Ventricular arrhythmia	1 (0%)	2 (1%)	-0.1
Diabetes Mellitus	35 (13%)	33 (13%)	0.0
Type I	4 (2%)	3 (1%)	0.0
Type II	34 (13%)	31 (12%)	0.0
Dyslipidaemia	72 (28%)	78 (30%)	-0.1
Hypertension	89 (34%)	92 (35%)	0.0
Immune disorders	30 (11%)	16 (6%)	0.2
AIDS/HIV	0 (0%)	0 (0%)	0.0
Antiphospholipid syndrome	0 (0%)	0 (0%)	0.0
SLE	9 (3%)	2 (1%)	0.2
Primary Sjögren Syndrome	21 (8%)	14 (5%)	0.1
Liver Disorder	1 (0%)	3 (1%)	-0.1
Obesity	52 (20%)	47 (18%)	0.0
Pregnancy	0 (0%)	0 (0%)	0.0
RA Severity (CIRAS Index), mean (SD)	4.4 (1)	4.5 (1)	-0.1
Smoking	19 (7%)	20 (8%)	0.0
Surgery, trauma & hospitalization, recent	3 (1%)	4 (2%)	0.0
TIA	0 (0%)	1 (0%)	-0.1
Genetic Coagulopathies	0 (0%)	1 (0%)	-0.1
DMARDs			
cDMARDs, during baseline			
n, total	163 (62%)	153 (59%)	0.1
Mean (SD)	0.8 (1)	0.8 (1)	0.1
Median	1.0	1.0	
Min, Max	0.0, 3.0	0.0, 3.0	
>1 cDMARD concomitantly	23 (9%)	26 (10%)	0.0
Hydroxychloroquine	55 (21%)	51 (20%)	0.0

Characteristic[a,b]	Baricitinib[c] (N = 261)	TNFi (N = 261)	Std. Diff.
Leflunomide	40 (15%)	38 (15%)	0.0
Methotrexate	88 (34%)	87 (33%)	0.0
Minocycline	0 (0%)	0 (0%)	0.0
Sulfasalazine	19 (7%)	20 (8%)	0.0
bDMARDs, during baseline			
n, total	261 (100%)	261 (100%)	0.0
Mean (SD)	1.1 (0)	1.0 (0)	0.4
Median	1.0	1.0	
Min, Max	1.0, 3.0	1.0, 2.0	
cDMARDs, concomitant	69 (26%)	82 (31%)	-0.1
abatacept	53 (20%)	3 (1%)	0.7
adalimumab[d]	39 (15%)	119 (46%)	-0.7
anakinra	2 (1%)	0 (0%)	0.1
certolizumab pegol[d]	32 (12%)	8 (3%)	0.4
etanercept[d]	36 (14%)	107 (41%)	-0.6
golimumab[d]	16 (6%)	7 (3%)	0.2
infliximab[d]	13 (5%)	20 (8%)	-0.1
rituximab	19 (7%)	0 (0%)	0.4
sarilumab	33 (13%)	1 (0%)	0.5
tocilizumab	48 (18%)	1 (0%)	0.6
Other Prescription Medications			
Antibiotics	15 (6%)	18 (7%)	0.0
Antidiabetic agents	29 (11%)	27 (10%)	0.0
Insulins	7 (3%)	7 (3%)	0.0
Non-insulins	27 (10%)	25 (10%)	0.0
Aspirin	1 (0%)	2 (1%)	-0.1
Cardiovascular			
Anticoagulant	4 (2%)	7 (3%)	-0.1
Antihypertensives	121 (46%)	118 (45%)	0.0
Antiplatelet	2 (1%)	2 (1%)	0.0
Nitrates	2 (1%)	2 (1%)	0.0

Characteristic[a,b]	Baricitinib[c] (N = 261)	TNFi (N = 261)	Std. Diff.
Hormonal			
HRT	24 (9%)	22 (8%)	0.0
Oral Contraceptives	20 (8%)	13 (5%)	0.1
SERMs	2 (1%)	1 (0%)	0.1
Lipid-lowering agents			
Bile acid binding	2 (1%)	3 (1%)	0.0
Cholesterol absorption inhibitor	0 (0%)	3 (1%)	-0.2
Fibrates	2 (1%)	4 (2%)	-0.1
Niacin	0 (0%)	0 (0%)	0.0
Omega-3 fatty acids	0 (0%)	0 (0%)	0.0
Statins	63 (24%)	59 (23%)	0.0
Rheumatoid arthritis-related			
Cox-2 Inhibitor	26 (10%)	17 (7%)	0.1
Glucocorticosteroid	211 (81%)	202 (77%)	0.1
Vaccinations	101 (39%)	81 (31%)	0.2

Abbreviations: AIDS = acquired immunodeficiency syndrome; bDMARDs = biologic disease-modifying antirheumatic drugs; CIRAS = claims-based index for RA severity; cDMARDs = conventional disease-modifying antirheumatic drugs; Chronic lung disease = asthma, chronic obstructive lung disease, interstitial lung disease, pulmonary fibrosis; DMARD = disease-modifying antirheumatic drug; HIV = human immunodeficiency virus; HRT = hormone replacement therapy; Max = maximum; Min = minimum; N = count of patients in the specified category; NMSC = non-melanoma skin cancer; PP = PharMetrics Plus; RA = rheumatoid arthritis; SD = standard deviation; SERMs = selective oestrogen receptor modulators; SLE = systemic lupus erythematosus; Std. Diff. = standardised difference; TIA = transient ischemic attack; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism.

[a] All conditions and characteristics except for the use of bDMARD and concomitant cDMARD are measured during the 6 months prior to initiation of study medication until and including the index date.

[b] Many characteristics of the cohort are included in this table, but propensity score matching is only expected to balance those risk factors listed in Table 4 in protocol Section 8.3.3 (Annex 19) for each outcome (eg, hospitalized congestive heart failure) for VTE. Other factors are included for descriptive purposes only and may not be balanced across treatment groups but do not contribute to confounding bias (eg, Type I diabetes) for VTE.

[c] Both 2- and 4-mg baricitinib doses are included when the 4-mg dose is available. Alternatively, additional columns may be added for each dose where numbers of patients are sufficient to warrant separate reporting.

[d] TNFi.

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Table 12_PP Baseline Healthcare Resource Utilisation Primary VTE Cohorts, Matched [PP]

Type of Resource Use	Baricitinib (N = 261)	TNFi (N = 261)	Std. Diff.
Physician Office Visits			
n, patients	251	253	0.0
n, events	2127	1710	
Mean (SD)	8.1 (11)	6.6 (6)	0.2
Median	5.0	5.0	
Min, Max	0.0, 117.0	0.0, 32.0	
Rheumatologist Visits			
n, patients	184	191	-0.1
n, events	430	442	
Mean (SD)	1.6 (1)	1.7 (1)	0.0
Median	2.0	2.0	
Min, Max	0.0, 8.0	0.0, 7.0	
Other Outpatient Visits			
n, patients	260	260	0.0
n, events	2621	2828	
Mean (SD)	10.0 (7)	10.8 (14)	-0.1
Median	8.0	8.0	
Min, Max	0.0, 36.0	0.0, 210.0	
Inpatient Visits			
n, patients	9	8	0.0
n, events	10	9	
Mean (SD)	0.0 (0)	0.0 (0)	0.0
Median	0.0	0.0	
Min, Max	0.0, 2.0	0.0, 2.0	
ED Visits			
n, patients	33	26	0.1
n, events	59	36	
Mean (SD)	0.2 (1)	0.1 (0)	0.1
Median	0.0	0.0	
Min, Max	0.0, 7.0	0.0, 4.0	

Abbreviations: ED = emergency department; Max = maximum; Min = minimum; N = count of patients in the specified category; PP = PharMetrics Plus; SD = standard deviation;
Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism.

Note: Physician office visits do not include rheumatologist visits. Other outpatient visits do not include physician office visits or rheumatologist visits.

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10.2.1.8.2. MACE

After propensity score matching, there were a total of 524 patients (262 each in the baricitinib and TNFi cohorts) included in the analysis of VTE (Table 3_PP). On average, patients analysed were aged 53.3 years at baseline (range 20 to 84 years) and were almost all (84%) female. After propensity score matching, baseline demographics of patients treated with baricitinib were not dissimilar of patients treated with TNFi (standardised differences <0.10).

Clinical characteristics of patients at baseline are described in Table 8_PP. The most commonly observed conditions were dyslipidaemia (baricitinib 27%, TNFi 25%), hypertension (baricitinib 34%, TNFi 34%), diabetes (baricitinib 13%, TNFi 12%), and obesity (baricitinib 20%, TNFi 18%). Patients treated with baricitinib were more likely to be smokers (baricitinib 7%, TNFi 4%). Regarding RA severity, the CIRAS score was identical (baricitinib 4.4, TNFi 4.4).

RA treatment received prior to the index medication is described in Table 8_PP. Use of cDMARDs prior to index was common in both patients treated with baricitinib (63%) and TNFi (65%). Methotrexate was the most frequently recorded cDMARD (baricitinib 34%, TNFi 43%). Patients treated with baricitinib were slightly more likely to have >1 cDMARD concomitantly than those treated with TNFi (baricitinib 9%, TNFi 7%). Prior use of bDMARDs was observed in all patients; adalimumab (44%) and etanercept (35%) were the most frequently reported bDMARDs within the TNFi cohort whereas abatacept (20%) and tocilizumab (18%) were the most frequently reported bDMARDs within the baricitinib cohort.

Baseline healthcare resource utilisation was generally similar across the baricitinib and TNFi cohorts, however patients treated with baricitinib did have higher mean physician office visits compared to those in the TNFi cohort (baricitinib 8.2, TNFi 6.8) (Table 13_PP). Note that the table reports visit days per patient (ie, at most 1 visit per day), but the propensity scores model controlled for the total number of visits during the period (ie, more than 1 visit) could occur per day.

Table 3_PP Baseline Demographics MACE Cohorts, Matched [PP]

	Baricitinib			TNFi	Std. Diff.	Total
	Any (N = 262)	4 mg (N = 0)	2 mg (N = 262)	(N = 262)	(Any vs TNFi)	(N = 524)
Age [yrs]						
n	262	0	262	262	0.0	524
Mean (SD)	53.4 (11)	NA	53.4 (11)	53.1 (10)		53.3 (11)
Median	55.5	NA	55.5	55.0		55.0
Min, Max	21.0, 84.0	NA	21.0, 84.0	20.0, 79.0		20.0, 84.0
≥65 years	28 (11%)	0 (0%)	28 (11%)	21 (8%)		49 (9%)
Sex						
Male	43 (16%)	0 (0%)	43 (16%)	42 (16%)	0.0	85 (16%)
Female	219 (84%)	0 (0%)	219 (84%)	220 (84%)		439 (84%)

Abbreviations: MACE = major adverse cardiovascular event, defined based on primary hospital discharge diagnosis codes for acute myocardial infarction, ischemic or haemorrhagic stroke; Max = maximum; Min = minimum; N = count of patients in the specified category; NA = not applicable; PP = PharMetrics Plus; SD = standard deviation; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor; vs = versus.

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Table 8_PP Clinical Characteristics MACE Cohorts, Matched [PP]

Characteristic[a,b]	Baricitinib (N = 262)	TNFi (N = 262)	Std. Diff.
Clinical Conditions during baseline			
Cancer	9 (3%)	11 (4%)	0.0
NMSC	7 (3%)	2 (1%)	0.1
Chronic lung disease	29 (11%)	27 (10%)	0.0
Cardiovascular conditions			
Atrial arrhythmia/fibrillation	1 (0%)	3 (1%)	-0.1
Cardiovascular revascularization	0 (0%)	1 (0%)	-0.1
Congestive Heart Failure, hospitalized	2 (1%)	0 (0%)	0.1
Coronary artery disease	6 (2%)	5 (2%)	0.0
Ischemic heart disease	7 (3%)	5 (2%)	0.1
Unstable angina	0 (0%)	0 (0%)	0.0
Ventricular arrhythmia	1 (0%)	7 (3%)	-0.2
Diabetes Mellitus	35 (13%)	32 (12%)	0.0
Type I	4 (2%)	3 (1%)	0.0
Type II	34 (13%)	29 (11%)	0.1
Dyslipidaemia	72 (27%)	66 (25%)	0.1
Hypertension	90 (34%)	89 (34%)	0.0
Immune disorders	31 (12%)	25 (10%)	0.1

Characteristic[a,b]	Baricitinib (N = 262)	TNFi (N = 262)	Std. Diff.
AIDS/HIV	0 (0%)	0 (0%)	0.0
Antiphospholipid syndrome	1 (0%)	0 (0%)	0.1
SLE	10 (4%)	7 (3%)	0.1
Primary Sjögren Syndrome	21 (8%)	18 (7%)	0.0
Liver Disorder	1 (0%)	3 (1%)	-0.1
Obesity	53 (20%)	47 (18%)	0.1
Pregnancy	0 (0%)	0 (0%)	0.0
RA Severity (CIRAS Index), mean (SD)	4.4 (1)	4.4 (1)	0.0
Smoking	19 (7%)	10 (4%)	0.2
Surgery, trauma & hospitalization, recent	3 (1%)	5 (2%)	-0.1
TIA	0 (0%)	1 (0%)	-0.1
Genetic Coagulopathies	0 (0%)	0 (0%)	0.0
DMARDs			
cDMARDs, during baseline			
n, total	164 (63%)	170 (65%)	0.0
Mean (SD)	0.8 (1)	0.8 (1)	0.0
Median	1.0	1.0	
Min, Max	(0.0, 3.0)	(0.0, 3.0)	

Characteristic[a,b]	Baricitinib (N = 262)	TNFi (N = 262)	Std. Diff.
Clinical Conditions during baseline			
>1 cDMARD concomitantly	23 (9%)	18 (7%)	0.1
Hydroxychloroquine	55 (21%)	51 (19%)	0.0
Leflunomide	41 (16%)	26 (10%)	0.2
Methotrexate	88 (34%)	113 (43%)	-0.2
Minocycline	0 (0%)	0 (0%)	0.0
Sulfasalazine	19 (7%)	18 (7%)	0.0
bDMARDs, during baseline			
n, total	262 (100%)	262 (100%)	0.0
Mean (SD)	1.1 (0)	1.0 (0)	0.4
Median	1.0	1.0	
Min, Max	(1.0, 3.0)	(1.0, 2.0)	
cDMARDs, concomitant	69 (26%)	88 (34%)	-0.2
abatacept	53 (20%)	2 (1%)	0.7
adalimumab[c]	39 (15%)	115 (44%)	-0.7
anakinra	2 (1%)	1 (0%)	0.1
certolizumab pegol[c]	32 (12%)	14 (5%)	0.2
etanercept[c]	36 (14%)	92 (35%)	-0.5
golimumab[c]	16 (6%)	15 (6%)	0.0
infliximab[c]	13 (5%)	26 (10%)	-0.2
rituximab	20 (8%)	0 (0%)	0.4
sarilumab	33 (13%)	0 (0%)	0.5
tocilizumab	48 (18%)	2 (1%)	0.6
Other Prescription Medications			
Antibiotics	15 (6%)	14 (5%)	0.0
Antidiabetic agents	29 (11%)	36 (14%)	-0.1
Insulins	7 (3%)	7 (3%)	0.0
Non-insulins	27 (10%)	34 (13%)	-0.1
Aspirin	1 (0%)	0 (0%)	0.1
Cardiovascular			
Anticoagulant	5 (2%)	2 (1%)	0.1
Antihypertensives	122 (47%)	118 (45%)	0.0
Antiplatelet	2 (1%)	5 (2%)	-0.1
Nitrates	2 (1%)	2 (1%)	0.0

Characteristic[a,b]	Baricitinib (N = 262)	TNFi (N = 262)	Std. Diff.
Clinical Conditions during baseline			
Hormonal			
HRT	24 (9%)	23 (9%)	0.0
Oral Contraceptives	20 (8%)	19 (7%)	0.0
SERMs	2 (1%)	3 (1%)	0.0
Lipid-lowering agents			
Bile acid binding	2 (1%)	2 (1%)	0.0
Cholesterol absorption inhibitor	0 (0%)	3 (1%)	-0.2
Fibrates	2 (1%)	5 (2%)	-0.1
Niacin	0 (0%)	0 (0%)	0.0
Omega-3 fatty acids	0 (0%)	0 (0%)	0.0
Statins	63 (24%)	62 (24%)	0.0
Rheumatoid arthritis-related			
Cox-2 Inhibitor	26 (10%)	18 (7%)	0.1
Glucocorticosteroid	212 (81%)	212 (81%)	0.0
Vaccinations	102 (39%)	93 (35%)	0.1

Abbreviations: AIDS = acquired immunodeficiency syndrome; bDMARDs = biologic disease-modifying antirheumatic drugs; CIRAS = claims-based index for RA severity; cDMARDs = conventional disease-modifying antirheumatic drugs; Chronic lung disease = asthma, chronic obstructive lung disease, interstitial lung disease, pulmonary fibrosis; DMARD = disease-modifying antirheumatic drug; HIV = human immunodeficiency virus; HRT = hormone replacement therapy; MACE = major adverse cardiovascular event, defined based on primary hospital discharge diagnosis codes for acute myocardial infarction, ischemic or haemorrhagic stroke; Max = maximum; Min = minimum; N = count of patients in the specified category; NMSC = non-melanoma skin cancer; PP = PharMetrics Plus; RA = rheumatoid arthritis; SD = standard deviation; SERMs = selective oestrogen receptor modulators; SLE = systemic lupus erythematosus; Std. Diff. = standardised differences; TIA = transient ischemic attack; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism.

[a] All conditions and characteristics except for use of bDMARD and concomitant cDMARD are measured during the 6 months prior to initiation of study medication until and including the index date.

[b] Many characteristics of the cohort are included in this table, but propensity score matching is only expected to balance those risk factors listed in Table 4 in protocol Section 8.3.3 (Annex 19) for each outcome (eg, hospitalized congestive heart failure) for VTE. Other factors are included for descriptive purposes only, may not be balanced across treatment groups but do not contribute to confounding bias (eg, Type I diabetes) for VTE.

[c] TNFi.

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Table 13_PP Baseline Healthcare Resource Utilisation MACE Cohorts, Matched [PP]

Type of Resource Use	Baricitinib (N = 262)	TNFi (N = 262)	Std. Diff.
Physician Office Visits			
n, patients	252	253	0.0
n, events	2148	1777	
Mean (SD)	8.2 (11)	6.8 (8)	0.1
Median	5.0	5.0	
Min, Max	0.0, 117.0	0.0, 63.0	
Rheumatologist Visits			
n, patients	185	185	0.0
n, events	432	419	
Mean (SD)	1.6 (1)	1.6 (1)	0.0
Median	2.0	2.0	
Min, Max	0.0, 8.0	0.0, 13.0	
Other Outpatient Visits			
n, patients	261	261	0.0
n, events	2632	2591	
Mean (SD)	10.0 (7)	9.9 (7)	0.0
Median	8.0	8.0	
Min, Max	0.0, 36.0	0.0, 45.0	
Inpatient Visits			
n, patients	9	8	0.0
n, events	10	12	
Mean (SD)	0.0 (0)	0.0 (0)	0.0
Median	0.0	0.0	
Min, Max	0.0, 2.0	0.0, 4.0	
ED Visits			
n, patients	34	24	0.1
n, events	62	36	
Mean (SD)	0.2 (1)	0.1 (0)	0.2
Median	0.0	0.0	
Min, Max	0.0, 7.0	0.0, 3.0	

Abbreviations: ED = emergency department; MACE = major adverse cardiovascular event, defined based on primary hospital discharge diagnosis codes for acute myocardial infarction, ischemic or haemorrhagic stroke; Max = maximum; Min = minimum; N = count of patients in the specified category; n = number of patients within each specific category; PP = PharMetrics Plus; SD = standard deviation; Std. Diff = standardised differences; TNFi = tumour necrosis factor inhibitor.

Note: Physician office visits do not include rheumatologist visits. Other outpatient visits do not include physician office visits or rheumatologist visits.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\pharmetrics plus_PP\Lilly Baricitinib Results_MACE_PharMetrics Plus_v1.0.docx -page 5

10.2.1.8.3. Serious infections

After propensity score matching, there were a total of 530 patients (265 each in the baricitinib and TNFi cohorts) included in the analysis of VTE (Annex 9, Table 4). On average, patients analysed were aged 54.0 years at baseline (range 20 to 85 years) and were almost all (82%) female. After propensity score matching, baseline demographics of patients treated with baricitinib were not dissimilar of patients treated with TNFi (standardised differences <0.10).

Clinical characteristics of patients at baseline are described in Annex 9, Table 9. The most commonly observed conditions were dyslipidaemia (baricitinib 28%, TNFi 20%), hypertension (baricitinib 36%, TNFi 35%), diabetes (baricitinib 13%, TNFi 9%), chronic lung disease (baricitinib 11%, TNFi 8%), and obesity (baricitinib 21%, TNFi 17%). Smoking was also prevalent in both treatment cohorts (baricitinib 8%, TNFi 8%). Regarding RA severity, the CIRAS score was similar across the baricitinib and TNFi cohorts (baricitinib 4.4, TNFi 4.5).

RA treatment received prior to the index medication is described in Annex 9, Table 9. Over half of patients used cDMARDs (baricitinib 63%, TNFi 70%) and methotrexate was the most frequently recorded cDMARD (baricitinib 34%, TNFi 49%). Patients treated with baricitinib were less likely to have >1 cDMARD concomitantly than those treated with TNFi (baricitinib 9%, TNFi 12%). All patients in the baricitinib and TNFi cohorts received a bDMARD in baseline, most frequently abatacept in the baricitinib cohort (20%) and adalimumab in the TNFi cohort (42%).

10.2.1.9. PS20

There were 933 eligible patients treated with baricitinib and 3,953 eligible TNFi patients in the PS20 data. Demographic and clinical characteristics for these unmatched cohorts are in Annex 10. From these unmatched cohorts, the number of patients included in analyses of VTE, MACE, or serious infection after 1:1 matching varies. Details of these analysis-specific cohorts follow.

10.2.1.9.1. VTE

After propensity score matching, there were a total of 1,496 patients (748 each in the baricitinib and TNFi cohorts) included in the analysis of VTE (Table 2_PS20). On average, patients analysed were aged 55.2 years at baseline (range 18 to 93 years) and were almost all (85.4%) female. After propensity score matching, baseline demographics of patients treated with baricitinib were not dissimilar of patients treated with TNFi (standardised differences <0.10).

Clinical characteristics of patients at baseline are described in Table 7_PS20. The most commonly observed conditions prevalent in at least 10% of patients were dyslipidaemia (baricitinib 36%, TNFi 36.8%), hypertension (baricitinib 42.9%, TNFi 45.2%), diabetes (baricitinib 19.4%, TNFi 18.7%), chronic lung disease (baricitinib 19%, TNFi 14.8%) and obesity (baricitinib 28.3%, TNFi 28.1%). Smoking was also prevalent (baricitinib 14.8%, TNFi 14.4%). Regarding RA severity, the CIRAS score was the same across the cohorts (baricitinib 4.18, TNFi 4.11).

RA treatment received prior to the index medication is described in Table 7_PS20. Approximately half of patients used cDMARDs (baricitinib 47.1%, TNFi 57%), with methotrexate recorded most frequently (baricitinib 29.1%, TNFi 28.3%). The proportion of patients with concomitant use of >1 cDMARDs prior to index was the same in both cohorts (15.6%). Prior use of bDMARDs was observed in 36.2% of the baricitinib cohort in contrast to 95.7% in the TNFi cohort. Note that the high prevalence of bDMARD use in the TNFi cohort is due to the eligibility requirement for the TNFi patients in US claims data. This is to better align TNFi use in the comparison group with the USPI for baricitinib. Adalimumab (29.8%) and etanercept (30.1%) were the most frequently recorded prior bDMARDs used by the TNFi cohort.

Baseline healthcare resource utilisation was generally consistent between the patients treated with baricitinib and TNFi (Table 12B_PS20); however, patients treated with baricitinib had slightly fewer rheumatologist visits than patients treated with TNFi. Note that Table 12B_PS20 reports visit days per patient (ie, at most 1 visit per day), but the propensity score model controlled for the total number of visits during the period (ie, more than 1 visit; see Table 12A in Annex 10) could occur per day.

Table 2_PS20 Baseline Demographics VTE Cohorts, Matched [PS20]

	Baricitinib			TNFi (N = 748)	Std. Diff. (Any vs TNFi)	Total (N = 1496)
	Any (N = 748)	4 mg (N = 0)	2 mg (N = 748)			
Age [yrs]						
n	748	-	748	748		1,496
Mean (SD)	54.85 (11.26)	-	54.85 (11.26)	55.56 (12.06)	0.06	55.20 (11.67)
Median	57.00 [48.00, 62.00]	-	57.00 [48.00, 62.00]	57.00 [49.00, 63.00]		57.00 [48.00, 62.00]
Min, Max	21.0, 92.0	-	21.0, 92.0	18.0, 93.0		18.0, 93.0
≥65 years	114 (15.2%)	-	114 (15.2%)	140 (18.7%)	0.09	254 (17.0%)
Sex						
Male	105 (14.0%)	-	105 (14.0%)	113 (15.1%)	0.03	218 (14.6%)
Female	643 (86.0%)	-	643 (86.0%)	635 (84.9%)	0.03	1,278 (85.4%)

Abbreviations: Max = maximum; Min = minimum; N = count of patients in the specified category; PS20 = Private Source 20; SD = standard deviation; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor; vs = versus; VTE = venous thromboembolism; yrs = years.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\healthverity ps20_PS20\6. Table 6.2. – Baseline Demographics VTE Cohorts, Matched [HealthVerity, PS20].docx

Table 7_PS20 Clinical Characteristics Primary VTE Cohorts, Matched [PS20]

Characteristic[a,b]	Baricitinib[c] (N = 748)	TNFi (N = 748)	Std. Diff.
Clinical Conditions during baseline			
Cancer	58 (7.8%)	56 (7.5%)	0.01
NMSC	5 (0.7%)	8 (1.1%)	0.04
Chronic lung disease	142 (19.0%)	111 (14.8%)	0.11
Cardiovascular conditions			
Atrial arrhythmia/fibrillation	23 (3.1%)	20 (2.7%)	0.02
Cardiovascular revascularization	0 (0.0%)	0 (0.0%)	0.01
Congestive heart failure, hospitalized	7 (0.9%)	2 (0.3%)	0.09
Coronary artery disease	42 (5.6%)	33 (4.4%)	0.06
Ischemic heart disease	42 (5.6%)	33 (4.4%)	0.06
Unstable angina	2 (0.3%)	5 (0.7%)	0.06
Ventricular arrhythmia	17 (2.3%)	25 (3.3%)	0.07
Diabetes Mellitus	145 (19.4%)	140 (18.7%)	0.02
Type I	13 (1.7%)	8 (1.1%)	0.06
Type II	140 (18.7%)	135 (18.0%)	0.02
Dyslipidaemia	269 (36.0%)	275 (36.8%)	0.02
Hypertension	321 (42.9%)	338 (45.2%)	0.05
Immune disorders	89 (11.9%)	104 (13.9%)	0.06
AIDS/HIV	1 (0.1%)	5 (0.7%)	0.09
Antiphospholipid syndrome	1 (0.1%)	1 (0.1%)	0.00
SLE	40 (5.3%)	40 (5.3%)	0.00
Primary Sjögren syndrome	55 (7.4%)	66 (8.8%)	0.05
Liver disorder	13 (1.7%)	15 (2.0%)	0.02
Obesity	212 (28.3%)	210 (28.1%)	0.01
Pregnancy	0 (0.0%)	0 (0.0%)	-
RA severity (CIRAS Index), mean (SD)	4.18 (1.23)	4.11 (1.28)	0.06
Smoking	111 (14.8%)	108 (14.4%)	0.01
Surgery, trauma & hospitalization, recent	39 (5.2%)	45 (6.0%)	0.04
TIA	2 (0.3%)	3 (0.4%)	0.02
DMARDs			
cDMARDs, during baseline			
n, total	352 (47.1%)	426 (57.0%)	0.20
Mean (SD)	0.68 (0.84)	0.77 (0.75)	0.11
Median	0.00 [0.00, 1.00]	1.00 [0.00, 1.00]	-
Min, Max	0.0, 5.0	0.0, 3.0	-
>1 cDMARD concomitantly	117 (15.6%)	117 (15.6%)	0.00
Hydroxychloroquine	110 (14.7%)	142 (19.0%)	0.11
Leflunomide	89 (11.9%)	108 (14.4%)	0.08
Methotrexate	218 (29.1%)	212 (28.3%)	0.02
Minocycline	4 (0.5%)	5 (0.7%)	0.02
Sulfasalazine	38 (5.1%)	50 (6.7%)	0.07

Characteristic[a,b]	Baricitinib[c] (N = 748)	TNFi (N = 748)	Std. Diff.
bDMARDs, during baseline[a]			
n, total	271 (36.2%)	716 (95.7%)	1.61
Mean (SD)	0.40 (0.53)	1.39 (0.53)	1.86
Median	0.00 [0.00, 1.00]	1.00 [1.00, 2.00]	-
Min, Max	0.0, 2.0	1.0, 3.0	-
cDMARDs, concomitant	158 (21.1%)	371 (49.6%)	0.62
abatacept	44 (5.9%)	122 (16.3%)	0.34
adalimumab[d]	51 (6.8%)	223 (29.8%)	0.62
anakinra	2 (0.3%)	3 (0.4%)	0.02
certolizumab pegol[d]	17 (2.3%)	62 (8.3%)	0.27
etanercept[d]	42 (5.6%)	225 (30.1%)	0.67
golimumab[d]	25 (3.3%)	109 (14.6%)	0.40
infliximab[d]	10 (1.3%)	119 (15.9%)	0.54
rituximab	17 (2.3%)	11 (1.5%)	0.06
sarilumab	25 (3.3%)	26 (3.5%)	0.01
tocilizumab	49 (6.6%)	52 (7.0%)	0.02
Other Prescription Medications			
Antibiotics	280 (37.4%)	365 (48.8%)	0.23
Antidiabetic agents	90 (12.0%)	111 (14.8%)	0.08
Insulins	29 (3.9%)	34 (4.5%)	0.03
Non-insulins	85 (11.4%)	101 (13.5%)	0.07
Aspirin	16 (2.1%)	20 (2.7%)	0.04
Cardiovascular			
Anticoagulant	20 (2.7%)	18 (2.4%)	0.02
Antihypertensives	265 (35.4%)	378 (50.5%)	0.31
Antiplatelet	15 (2.0%)	14 (1.9%)	0.01
Nitrates	12 (1.6%)	12 (1.6%)	0.00
Hormonal			
HRT	47 (6.3%)	38 (5.1%)	0.05
Oral Contraceptives	21 (2.8%)	20 (2.7%)	0.01
SERMs	2 (0.3%)	4 (0.5%)	0.04
Lipid-lowering agents			
Bile acid binding	5 (0.7%)	12 (1.6%)	0.09
Cholesterol absorption inhibitor	8 (1.1%)	9 (1.2%)	0.01
Fibrates	8 (1.1%)	9 (1.2%)	0.01
Niacin	0 (0.0%)	1 (0.1%)	0.05
Omega-3 fatty acids	7 (0.9%)	2 (0.3%)	0.09
Statins	158 (21.1%)	191 (25.5%)	0.10
Rheumatoid arthritis-related			
Cox-2 Inhibitor	36 (4.8%)	48 (6.4%)	0.07
Glucocorticosteroid	349 (46.7%)	353 (47.2%)	0.01
Vaccinations	201 (26.9%)	227 (30.3%)	0.08

Abbreviations: AIDS = acquired immunodeficiency virus; bDMARD = biologic disease-modifying antirheumatic drug; cDMARD = conventional disease-modifying antirheumatic drug; CIRAS = Claims-Based Index for RA Severity; DMARD = disease-modifying antirheumatic drug; HIV = human immunodeficiency virus; HRT = hormone replacement therapy; Max = maximum; Min = minimum; N = count of patients in the specified category; NMSC = non-melanoma skin cancer; PS20 = Private Source 20; RA = rheumatoid arthritis; SD = standard deviation; SERM = selective oestrogen receptor modifier; SLE = systemic lupus erythematosus; Std. Diff = standardised difference; TIA = transient ischemic attack; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism.

[a] All conditions and characteristics, except for bDMARDs, are measured during the 6 months prior to initiation of study medication including the date at which the qualifying exposure of baricitinib or TNFi occurs (index date). bDMARDs are measured from the 6 months prior to the initiation of study medication until the day prior to baricitinib or the index TNFi exposure, excluding the index date.

[b] Many characteristics of the cohort are included in this table, but propensity score matching is only expected to balance those risk factors listed in Table 4 (see Section 8.3.3, Annex 19) for each outcome (eg, hospitalized congestive heart failure) for VTE. Other factors are included for descriptive purposes only, may not be balanced across treatment groups but do not contribute to confounding bias (eg, Type I diabetes) for VTE.

[c] Both 2- and 4-mg baricitinib doses are included when the 4-mg dose is available. Alternatively, additional columns may be added for each dose when numbers of patients are sufficient to warrant separate reporting.

[d] TNFi.

Source: lillyce\qa\ly3009104\i4v_mc_b023\final\output\shared\tfl\healthverity ps20_PS20\6. Table 6.7. – Clinical Characteristics Primary VTE Cohorts, Matched [HealthVerity, PS20].docx

Table 12B_PS20 Baseline Healthcare Resource Utilisation Primary VTE Cohorts, Matched [PS20], Count at Most 1 Visit per Day

Type of Resource Use	Baricitinib (N = 748)	TNFi (N = 748)	Std. Diff.
Physician Office Visits[a]			
n, patients	252 (33.7%)	276 (36.9%)	0.07
n, events	2,334	2,446	
Mean (SD)	3.12 (6.70)	3.27 (6.03)	0.02
Median	0.00 [0.00, 3.00]	0.00 [0.00, 5.00]	
Min, Max	0.0, 49.0	0.0, 46.0	
Rheumatologist Visits[a]			
n, patients	177 (23.7%)	177 (23.7%)	0.00
n, events	486	621	
Mean (SD)	0.65 (1.41)	0.83 (1.84)	0.11
Median	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	
Min, Max	0.0, 12.0	0.0, 12.0	
Other Outpatient Visits[a]			
n, patients	641 (85.7%)	635 (84.9%)	0.02
n, events	6,134	6,141	
Mean (SD)	8.20 (25.07)	8.21 (23.77)	0.00
Median	3.00 [1.00, 6.00]	3.00 [1.00, 6.00]	
Min, Max	0.0, 180.0	0.0, 180.0	
Inpatient Visits[a]			
n, patients	61 (8.2%)	71 (9.5%)	0.05
n, events	269	352	
Mean (SD)	0.36 (1.71)	0.47 (2.26)	0.06
Median	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	
Min, Max	0.0, 22.0	0.0, 28.0	
ED Visits[a]			
n, patients	152 (20.3%)	163 (21.8%)	0.04
n, events	284	344	
Mean (SD)	0.38 (1.13)	0.46 (2.02)	0.05
Median	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	
Min, Max	0.0, 17.0	0.0, 49.0	

Abbreviations: ED = emergency department; Max = maximum; Min = minimum; N = count of patients in the specified category; PS20 = Private Source 20; SD = standard deviation; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism.

[a] In this table, results describe utilisation of healthcare where a maximum of 1 event was allowed per day. In the PS-matching analyses, multiple claims on the same day were allowed to capture additional information on the amount of services received in a given visit. These results are presented in Table 12A_PS20 in Annex 10.

Note: Physician office visits do not include rheumatologist visits.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\healthverity ps20_PS20\6. Table 6.12B (count at most 1 visit per day). Baseline Healthcare Resource Utilisation Primary VTE Cohorts, Matched [HealthVerity, PS20].docx

10.2.1.9.2. MACE

After propensity score matching, there were 1,486 patients (743 each in the baricitinib and TNFi cohorts) included in the analysis of MACE (Table 3_PS20). On average, patients analysed were 54.95 years at baseline (range 18 to 93 years) and were almost all (86.5%) female. After propensity score matching, baseline demographics of patients treated with baricitinib were not dissimilar of patients treated with TNFi (standardised differences <0.10).

Clinical characteristics of patients at baseline are described in Table 8_PS20. The most commonly observed conditions were dyslipidaemia (baricitinib 35%, TNFi 35.4%), hypertension (baricitinib 42.8%, TNFi 42%), obesity (baricitinib 27.2%, TNFi 28.9%), and chronic lung disease (baricitinib 19%, TNFi 16%). Smoking was also prevalent in both treatment cohorts (baricitinib 14.5%, TNFi 15.1%). Regarding RA severity, the CIRAS score was not dissimilar among the baricitinib compared to the TNFi cohort (baricitinib 4.14, TNFi 4.17).

RA treatment received prior to the index medication is described in Table 8_PS20. Approximately half of patients recorded a cDMARD prior to index (baricitinib 45.9%; TNFi 59%). Methotrexate was the most frequently recorded cDMARD (baricitinib 27.6%, TNFi 37.4%). Patients treated with baricitinib were more likely to have >1 cDMARD concomitantly than those treated with TNFi (baricitinib 14.8%, TNFi 15.1%). Prior use of bDMARDs was observed in 35.8% of the baricitinib cohort in contrast to 96.1% of the TNFi cohort. Note that the high prevalence of bDMARD use in the TNFi cohort is due to the eligibility requirement for the TNFi patients in US claims data. Adalimumab (31.8%) and etanercept (29.7%) were the most frequently recorded prior bDMARDs used by the TNFi cohort.

Baseline healthcare resource utilisation is approximately consistent across the baricitinib and TNF cohorts (Table 13B_PS20); however, patients in the TNFi cohort had slightly higher utilisation of rheumatologist visits compared to the baricitinib cohort. Note that Table 13B_PS20 reports visit days per patient (ie, at most 1 visit per day, but the propensity scores model controlled for the total number of visits during the period (ie, more than 1 visit; see Table 13A in Annex 10) could occur per day.

Table 3_PS20 Baseline Demographics MACE Cohorts, Matched [PS20]

	Baricitinib			TNFi (N = 743)	Std. Diff. (Any vs TNFi)	Total (N = 1486)
	Any (N = 743)	4 mg (N = 0)	2 mg (N = 743)			
Age [yrs]						
n	743	-	743	743		1,486
Mean (SD)	55.11 (11.29)	-	55.11 (11.29)	54.78 (12.50)	0.03	54.95 (11.91)
Median	57.00 [48.00, 62.00]	-	57.00 [48.00, 62.00]	56.00 [48.00, 62.00]		56.00 [48.00, 62.00]
Min, Max	21.0, 92.0	-	21.0, 92.0	18.0, 93.0		18.0, 93.0
≥65 years	118 (15.9%)	-	118 (15.9%)	119 (16.0%)	0.00	237 (15.9%)
Sex						
Male	111 (14.9%)	-	111 (14.9%)	90 (12.1%)	0.08	201 (13.5%)
Female	632 (85.1%)	-	632 (85.1%)	653 (87.9%)	0.08	1,285 (86.5%)

Abbreviations: MACE = major adverse cardiovascular event, defined based on primary hospital discharge diagnosis codes for acute myocardial infarction, ischemic or haemorrhagic stroke; Max = maximum; Min = minimum; N = count of patients in the specified category; PS20 = Private Source 20; SD = standard deviation; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor; vs = versus.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\healthverity ps20_PS20\6. Table 6.3 – Baseline Demographics MACE Cohorts, Matched [HealthVerity, PS20].docx

Table 8_PS20 Clinical Characteristics MACE Cohorts, Matched [PS20]

Characteristic[a,b]	Baricitinib[c] (N = 743)	TNFi (N = 743)	Std. Diff.
Clinical Conditions during baseline			
Cancer	55 (7.4%)	47 (6.3%)	0.04
NMSC	9 (1.2%)	11 (1.5%)	0.02
Chronic lung disease	141 (19.0%)	119 (16.0%)	0.08
Cardiovascular conditions			
Atrial arrhythmia/fibrillation	25 (3.4%)	19 (2.6%)	0.05
Cardiovascular revascularization	0 (0.0%)	0 (0.0%)	-
Congestive heart failure, hospitalized	7 (0.9%)	1 (0.1%)	0.11
Coronary artery disease	42 (5.7%)	39 (5.2%)	0.02
Ischemic heart disease	42 (5.7%)	39 (5.2%)	0.02
Unstable angina	2 (0.3%)	2 (0.3%)	0.00
Ventricular arrhythmia	19 (2.6%)	28 (3.8%)	0.07
Diabetes Mellitus	142 (19.1%)	144 (19.4%)	0.01
Type I	12 (1.6%)	13 (1.7%)	0.01
Type II	137 (18.4%)	138 (18.6%)	0.00
Dyslipidaemia	260 (35.0%)	263 (35.4%)	0.01
Hypertension	318 (42.8%)	312 (42.0%)	0.02
Immune disorders	87 (11.7%)	86 (11.6%)	0.00
AIDS/HIV	1 (0.1%)	0 (0.0%)	0.05
Antiphospholipid syndrome	1 (0.1%)	2 (0.3%)	0.03
SLE	37 (5.0%)	35 (4.7%)	0.01
Primary Sjögren syndrome	56 (7.5%)	54 (7.3%)	0.01
Liver disorder	13 (1.7%)	16 (2.2%)	0.03
Obesity	202 (27.2%)	215 (28.9%)	0.04
Pregnancy	0 (0.0%)	3 (0.4%)	0.09
RA severity (CIRAS Index), mean (SD)	4.14 (1.23)	4.17 (1.31)	0.03
Smoking	108 (14.5%)	112 (15.1%)	0.02
Surgery, trauma & hospitalization, recent	40 (5.4%)	30 (4.0%)	0.06
TIA	3 (0.4%)	1 (0.1%)	0.05
DMARDs			
cDMARDs, during baseline			
n, total	341 (45.9%)	438 (59.0%)	0.26
Mean (SD)	0.66 (0.83)	0.78 (0.75)	0.16
Median	0.00 [0.00, 1.00]	1.00 [0.00, 1.00]	-
Min, Max	0.0, 5.0	0.0, 4.0	-
>1 cDMARD concomitantly	110 (14.8%)	112 (15.1%)	0.01
Hydroxychloroquine	105 (14.1%)	127 (17.1%)	0.08
Leflunomide	87 (11.7%)	88 (11.8%)	0.00
Methotrexate	205 (27.6%)	278 (37.4%)	0.21
Minocycline	3 (0.4%)	6 (0.8%)	0.05
Sulfasalazine	42 (5.7%)	41 (5.5%)	0.01

Characteristic[a,b]	Baricitinib[c] (N = 743)	TNFi (N = 743)	Std. Diff.
bDMARDs, during baseline[a]			
n, total	266 (35.8%)	714 (96.1%)	1.65
Mean (SD)	0.40 (0.54)	1.39 (0.54)	1.85
Median	0.00 [0.00, 1.00]	1.00 [1.00, 2.00]	-
Min, Max	0.0, 2.0	1.0, 3.0	-
cDMARDs, concomitant	154 (20.7%)	374 (50.3%)	0.65
abatacept	37 (5.0%)	130 (17.5%)	0.40
adalimumab[d]	47 (6.3%)	236 (31.8%)	0.69
anakinra	2 (0.3%)	0 (0.0%)	0.07
certolizumab pegol[d]	16 (2.2%)	75 (10.1%)	0.34
etanercept[d]	47 (6.3%)	221 (29.7%)	0.64
golimumab[d]	35 (4.7%)	91 (12.2%)	0.27
infliximab[d]	13 (1.7%)	113 (15.2%)	0.50
rituximab	15 (2.0%)	11 (1.5%)	0.04
sarilumab	24 (3.2%)	27 (3.6%)	0.02
tocilizumab	45 (6.1%)	48 (6.5%)	0.02
Other Prescription Medications			
Antibiotics	273 (36.7%)	329 (44.3%)	0.15
Antidiabetic agents	85 (11.4%)	112 (15.1%)	0.11
Insulins	30 (4.0%)	31 (4.2%)	0.01
Non-insulins	78 (10.5%)	102 (13.7%)	0.10
Aspirin	13 (1.7%)	15 (2.0%)	0.02
Cardiovascular			
Anticoagulant	21 (2.8%)	20 (2.7%)	0.01
Antihypertensives	264 (35.5%)	347 (46.7%)	0.23
Antiplatelet	13 (1.7%)	11 (1.5%)	0.02
Nitrates	13 (1.7%)	15 (2.0%)	0.02
Hormonal			
HRT	42 (5.7%)	38 (5.1%)	0.02
Oral Contraceptives	16 (2.2%)	36 (4.8%)	0.15
SERMs	2 (0.3%)	3 (0.4%)	0.02
Lipid-lowering agents			
Bile acid binding	5 (0.7%)	7 (0.9%)	0.03
Cholesterol absorption inhibitor	9 (1.2%)	7 (0.9%)	0.03
Fibrates	8 (1.1%)	7 (0.9%)	0.01
Niacin	0 (0.0%)	0 (0.0%)	-
Omega-3 fatty acids	8 (1.1%)	4 (0.5%)	0.06
Statins	157 (21.1%)	149 (20.1%)	0.03
Rheumatoid arthritis-related			
Cox-2 Inhibitor	37 (5.0%)	51 (6.9%)	0.08
Glucocorticosteroid	361 (48.6%)	350 (47.1%)	0.03
Vaccinations	200 (26.9%)	209 (28.1%)	0.03

Abbreviations: AIDS = acquired immunodeficiency syndrome; bDMARD = biologic disease-modifying antirheumatic drug; cDMARD = conventional disease-modifying antirheumatic drug; CIRAS = Claims-Based Index for RA Severity; DMARD = disease-modifying antirheumatic drug; HIV = human immunodeficiency syndrome; HRT = hormone replacement therapy; MACE = major adverse cardiovascular event, defined based on primary hospital discharge diagnosis codes for acute myocardial infarction, ischemic or haemorrhagic stroke; N = count of patients in the specified category; NMSC = non-melanoma skin cancer; PS20 = Private Source 20; RA = rheumatoid arthritis; SD = standard deviation; SERM = selective oestrogen receptor modifier; SLE = systemic lupus erythematosus; Std. Diff = standardised difference; TIA = transient ischemic attack; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism.

[a] All conditions and characteristics, except for bDMARDs, are measured during the 6 months prior to initiation of study medication including the date at which the qualifying exposure of baricitinib or TNFi occurs (index date). bDMARDs are measured from the 6 months prior to the initiation of study medication until the day prior to baricitinib or the index TNFi exposure, excluding the index date.

[b] Many characteristics of the cohort are included in this table, but propensity score matching is only expected to balance those risk factors listed in Table 4 (see Section 8.3.3, Annex 19) for each outcome (eg, hospitalized congestive heart failure) for VTE. Other factors are included for descriptive purposes only, may not be balanced across treatment groups but do not contribute to confounding bias (eg, Type I diabetes) for VTE.

[c] Both 2- and 4-mg baricitinib doses are included when the 4-mg dose is available. Alternatively, additional columns may be added for each dose when numbers of patients are sufficient to warrant separate reporting.

[d] TNFi.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\healthverity ps20_PS20\6. Table 6.8. – Clinical Characteristics MACE Cohorts, Matched [HealthVerity, PS20].docx

Table 13B_PS20 Baseline Healthcare Resource Utilisation MACE Cohorts, Matched [PS20], Count at Most 1 Visit per Day

Type of Resource Use	Baricitinib (N = 743)	TNFi (N = 743)	Std. Diff.
Physician Office Visits[a]			
n, patients	246 (33.1%)	280 (37.7%)	0.10
n, events	2,229	2,526	
Mean (SD)	3.00 (6.33)	3.40 (6.11)	0.07
Median	0.00 [0.00, 4.00]	0.00 [0.00, 5.00]	
Min, Max	0.0, 46.0	0.0, 46.0	
Rheumatologist Visits[a]			
n, patients	180 (24.2%)	188 (25.3%)	0.03
n, events	505	669	
Mean (SD)	0.68 (1.45)	0.90 (1.90)	0.13
Median	0.00 [0.00, 0.00]	0.00 [0.00, 1.00]	
Min, Max	0.0, 12.0	0.0, 12.0	
Other Outpatient Visits[a]			
n, patients	631 (84.9%)	626 (84.3%)	0.02
n, events	5,855	6,040	
Mean (SD)	7.88 (24.04)	8.13 (24.41)	0.01
Median	3.00 [1.00, 6.00]	3.00 [1.00, 6.00]	
Min, Max	0.0, 180.0	0.0, 180.0	
Inpatient Visits[a]			
n, patients	63 (8.5%)	58 (7.8%)	0.03
n, events	290	268	
Mean (SD)	0.39 (1.89)	0.36 (2.00)	0.02
Median	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	
Min, Max	0.0, 22.0	0.0, 28.0	
ED Visits[a]			
n, patients	150 (20.2%)	177 (23.8%)	0.09
n, events	275	401	
Mean (SD)	0.37 (1.10)	0.54 (2.18)	0.10
Median	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	
Min, Max	0.0, 17.0	0.0, 49.0	

Abbreviations: ED = emergency department; MACE = major adverse cardiovascular event, defined based on primary hospital discharge diagnosis codes for acute myocardial infarction, ischemic or haemorrhagic stroke; Max = maximum; Min = minimum; N = count of patients in the specified category; PS20 = Private Source 20; SD = standard deviation; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor.

[a] In this table, results describe utilisation of healthcare where a maximum of 1 event was allowed per day. In the PS-matching analyses, multiple claims on the same day were allowed to capture additional information on the amount of services received in a given visit. These results are presented in Table 13A_PS20 in Annex 10.

Note: Physician office visits do not include rheumatologist visits.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\healthverity ps20_PS20\6. Table 6.13B (count at most 1 visit per day). Baseline Healthcare Resource Utilisation MACE Cohorts, Matched [HealthVerity, PS20].docx

10.2.1.9.3. Serious infections

After propensity score matching, there were a total of 1,496 patients (748 each in the baricitinib and TNFi cohorts) included in the analysis of serious infection (Annex 10, Table 4). On average, patients analysed were aged 55.17 years (range 18 to 93 years) and almost all (86.3%) were female. After propensity score matching, patients treated with baricitinib were not dissimilar from patients treated with TNFi in terms of age and gender.

Clinical characteristics of patients at baseline are described in Annex 10, Table 9. The most commonly observed conditions with at least 10% of patients were dyslipidaemia (baricitinib 36.2%, TNFi 34%), hypertension (baricitinib 43.4%, TNFi 42.8%), diabetes (baricitinib 19.5%, TNFi 17.5%), chronic lung disease (baricitinib 18.9%, TNFi 21.1%), and obesity (baricitinib 28.6%, TNFi 28.2%). Smoking was also prevalent in both treatment cohorts (baricitinib 15.5%, TNFi 14.4%). With regard to RA severity, the CIRAS score was the same in the baricitinib cohort compared to the TNFi cohort (baricitinib 4.15, TNFi 4.10).

RA treatment received prior to the index medication is described in Annex 10, Table 9. Approximately half of patients used cDMARDs (baricitinib 48.7%, TNFi 63.5%) and methotrexate was the most frequently recorded cDMARD (baricitinib 28.7%, TNFi 40.5%). A similar proportion of patients in the baricitinib and TNFi cohorts recorded >1 cDMARD concomitantly (baricitinib 16.0%, TNFi 17.0%). Almost all patients in the TNFi cohort (95.5%) received a bDMARD in baseline (most frequently etanercept, 31.6% or adalimumab, 30.7%) whereas 35.7% of baricitinib cohort received a bDMARD in baseline.

10.2.2. Europe and Japan data sources

10.2.2.1. ARTIS

There were 1,737 eligible patients treated with baricitinib (1,381 with 4 mg and 354 with 2 mg) and 6,230 treated with TNFi in the ARTIS data. Demographic and clinical characteristics for these unmatched cohorts are in Annex 11. The final number of patients analysed after 1:1 propensity score matching varies by outcome. Details of these analysis-specific cohorts follow.

10.2.2.1.1. VTE

After propensity score matching, there were a total of 3,370 patients (1,685 each in the baricitinib and TNFi cohorts) included in the analysis of VTE (Table 2_ARTIS). Within the baricitinib cohort, 80% of patients were treated with the 4 mg dose (n = 1353) and the rest with 2 mg (n = 330). On average, patients analysed were aged 59 years at baseline (range 18 to 92 years) and the majority (82%) were female. After propensity score matching, patients treated with baricitinib were similar to patients treated with TNFi in terms of age and gender, and other characteristics.

Clinical characteristics of patients at baseline are described in Table 7_ARTIS. The prevalence of some clinical conditions appears low. This is caused by defining those conditions based on the main diagnosis entered in the National Patient Register at the time of a clinical visit. Prescription medicines provide a useful and often more accurate measure of clinical conditions, even when comorbidities are defined differently. Anti-hypertensive medications were used by 43% of

baricitinib patients and 40% of TNFi patients. In both the baricitinib and TNFi cohort, 11% used anti-platelet agents. Statin and antidiabetic agent use was similar across cohorts, with statins reported in 14% of baricitinib and 15% of TNFi patients and antidiabetics in 8% and 7%, respectively. For clinical conditions, diabetes was the most prevalent condition recorded at baseline (baricitinib 8%, TNFi 7%), consistent with medication use. Smoking (current or former) was common among patients in ARTIS (baricitinib 48%, TNFi 44%). After matching, the distribution of clinical conditions was balanced between the two cohorts, as shown by the standardised differences <0.1. Patients in the baricitinib cohort had slightly higher disease severity, with 37% of baricitinib patients having high disease activity (ie, DAS28 ≥5.2) compared to 32% of TNFi.

RA treatment received prior to the index medication is described in Table 7_ARTIS. The majority of patients received cDMARDs (baricitinib 55%, TNFi 61%), with methotrexate recorded most frequently (43% in each cohort). The proportion of patients with prior use of bDMARDs was similar in both the baricitinib and TNFi cohorts (baricitinib 54%, TNFi 62%), with etanercept recorded most frequently (baricitinib 19%, TNFi 35%).

Baseline healthcare resource utilisation was similar across the baricitinib and TNFi cohorts in the ARTIS data (Table 12_ARTIS).

Table 2_ARTIS Baseline Demographics VTE Cohorts, Matched [ARTIS]

	Baricitinib			TNFi (N = 1685)	Std. Diff. (Any vs TNFi)
	Any (N = 1685)	4 mg (n = 1353)	2 mg (n = 330)		
Age [yrs]					
n	1685	1353	330	1685	-0.006
Mean (SD)	59 (13.6)	56 (12.9)	70 (10.5)	59 (13.9)	
Median	60	57	73	60	
Min, Max	18, 92	18, 89	30, 92	18, 88	
≥ 65 years	651 (39%)	403 (30%)	246 (75%)	666 (40%)	
Sex					
Male	303 (18%)	248 (18%)	55 (17%)	292 (17%)	0.016
Female	1382 (82%)	1105 (82%)	275 (83%)	1393 (83%)	

Abbreviations: Max = maximum; Min = minimum; N = count of patients in the specified category; SD = standard deviation; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor; vs = versus; VTE = venous thromboembolism.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\ARTIS\Table1_demographics_08MAR22.xlsx

Table 7_ARTIS Clinical Characteristics Primary VTE Cohorts, Matched [ARTIS]

Characteristic[a,b]	Baricitinib[c] (N = 1685)	TNFi (N = 1685)	Std. Diff.
Clinical Conditions during baseline			
Cancer	<5	<5	-0.015
NMSC	<5	<5	0.031
Chronic lung disease	11 (1%)	17 (1%)	-0.045
Cardiovascular conditions			
Atrial arrhythmia	<5	7 (0%)	-0.037
Cardiovascular revascularization	<5	6 (0%)	-0.060
Congestive heart failure	<5	<5	0.000
Coronary artery disease	<5	<5	-0.028
Ischemic heart disease	7 (0%)	5 (0%)	0.022
Unstable angina	<5	<5	0.031
Ventricular arrhythmia	9 (1%)	<5	0.050
Diabetes Mellitus	141 (8%)	114 (7%)	0.058
Type I	NA	NA	
Type II	NA	NA	
Dyslipidaemia	<5	<5	.
Hypertension	12 (1%)	5 (0%)	0.060
Immune disorders			
AIDS/HIV	NA	NA	
Antiphospholipid syndrome	NA	NA	
SLE	NA	NA	
Primary Sjögren syndrome	<5	6 (0%)	-0.022
Liver disorder	5 (0%)	5 (0%)	0.000
Obesity	NA	NA	
Pregnancy	5 (0%)	<5	0.021
RA severity (DAS28)	**924**	**447**	
Mean (SD)	4.6 (1.27)	4.4 (1.44)	
DAS28 <2.6 (remission)	57 (6 %)	97 (12%)	-0.114
Mean	2.02	1.96	
DAS28 <3.2 (low)	73 (8 %)	66 (8%)	0.021
Mean	2.97	2.91	
DAS28 <5.2 (moderate)	454 (49 %)	376 (48%)	0.106
Mean	4.26	4.23	
DAS28 5.2+ (high)	340 (37 %)	248 (32%)	0.143
Mean	5.94	5.98	
Smoking, current or former	803 (48%)	738 (44%)	0.078
Surgery	1345 (80%)	1340 (80%)	0.007
TIA	<5	<5	0.028
DMARDs			
cDMARDs, during baseline			
n, total	935 (55%)	1024 (61%)	-0.114
Mean (SD)	1 (0.6)	1 (0.7)	
Median	1	1	
Min, Max	0, 3	0, 4	

Characteristic[a,b]	Baricitinib[c] (N = 1685)	TNFi (N = 1685)	Std. Diff.
Hydroxychloroquine	92 (5%)	123 (7%)	-0.074
Leflunomide	74 (4%)	103 (6%)	-0.086
Methotrexate	724 (43%)	727 (43%)	-0.004
Minocycline[d]	NA	NA	NA
Sulfasalazine	154 (9%)	241 (14%)	-0.161
bDMARDs, during baseline			
n, total	908 (54%)	1039 (62%)	-0.157
Mean (SD)	1 (0.6)	1 (0.6)	
Median	1	1	
Min, Max	0, 3	0, 4	
abatacept	165 (10%)	63 (4%)	0.263
adalimumab[d]	190 (11%)	266 (16%)	-0.146
anakinra	<5	<5	0.049
certolizumab pegol[e]	46 (3%)	68 (4%)	-0.085
etanercept[e]	318 (19%)	598 (35%)	-0.410
golimumab[e]	30 (2%)	51 (3%)	-0.091
infliximab[e]	57 (3%)	120 (7%)	-0.188
rituximab	72 (4%)	12 (1%)	0.240
sarilumab	27 (2%)	<5	0.149
tocilizumab	129 (8%)	44 (3%)	0.250
Other Prescription Medications			
Antibiotics	416 (25%)	360 (21%)	0.081
Antidiabetic agents	141 (8%)	112 (7%)	0.063
Insulins	76 (5%)	62 (4%)	0.041
Non-insulins	97 (6%)	74 (4%)	0.059
Aspirin	157 (9%)	169 (10%)	-0.025
Cardiovascular			
Anticoagulant	66 (4%)	51 (3%)	0.049
Antihypertensives	718 (43%)	678 (40%)	0.049
Antiplatelet	181 (11%)	188 (11%)	-0.014
Nitrates	50 (3%)	35 (2%)	0.059
Hormonal			
HRT	132 (8%)	138 (8%)	-0.013
Oral Contraceptives	61 (4%)	53 (3%)	0.024
SERMs	<5	<5	0.000
Lipid-lowering agents			
Bile acid binding	<5	<5	0.012
Cholesterol absorption inhibitor	29 (2%)	13 (1%)	0.085
Fibrates	<5	<5	0.021
Niacin	NA	NA	
Omega-3 fatty acids	NA	NA	
Statins	228 (14%)	246 (15%)	-0.031
Rheumatoid arthritis-related			
Cox-2 Inhibitor	121 (7%)	108 (6%)	0.030
Glucocorticosteroid	1073 (64%)	1052 (62%)	0.026
Vaccinations	NA	NA	

Abbreviations: AIDS = acquired immunodeficiency syndrome; bDMARDs = biologic disease-modifying antirheumatic drugs; cDMARDs = conventional disease-modifying antirheumatic drugs; CIRAS = claims-based index for RA severity; DAS28 = Disease Activity Score 28; DMARD = disease-modifying antirheumatic drug; HIV = human immunodeficiency virus; HRT = hormone replacement therapy; Max = maximum; Min = minimum; N = count of patients in the specified category; NMSC = non-melanoma skin cancer; RA = rheumatoid arthritis; SD = standard deviation; SERMs = selective oestrogen receptor modulators; SLE = systemic lupus erythematosus; Std. Diff. = standardised difference; TIA = transient ischemic attack; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism.

[a] All conditions and characteristics are measured during the 6 months prior to initiation of study medication until and including the day prior to baricitinib or the index TNFi exposure that qualifies the patient for the cohort. Clinical conditions are defined based on the "main diagnosis" in the National Patient Register.

[b] Many characteristics of the cohort are included in this table, but propensity score matching is only expected to balance those risk factors listed in Table 4 in protocol Section 8.3.3 (Annex 19) for each outcome (eg, hospitalized congestive heart failure) for VTE. Other factors are included for descriptive purposes only and may not be balanced across treatment groups but do not contribute to confounding bias (eg, Type I diabetes) for VTE.

[c] Both 2- and 4-mg baricitinib doses are included when the 4-mg dose is available. Alternatively, additional columns may be added for each dose when numbers of patients are sufficient to warrant separate reporting.

[d] Minocycline is not used to treat RA in Sweden.

[e] TNFi.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\ARTIS\Table2_clinical_16May22_update.xlsx

Table 12_ARTIS Baseline Healthcare Resource Utilisation Primary VTE Cohorts, Matched [ARTIS]

Type of Resource Use	Baricitinib (N = 1685)	TNFi (N = 1685)	Std. Diff.
Physician Office Visits	NA	NA	
n, patients			
n, events			
Mean (SD)			
Median			
Min, Max			
Rheumatologist Visits			
n, patients	1357	1343	
n, events	3429	3327	0.032
Mean (SD)	2 (2.0)	2 (1.8)	
Median	2	2	
Min, Max	0, 12	0, 17	
Other Outpatient Visits			
n, patients	1536	1517	
n, events	5726	5621	0.021
Mean (SD)	3 (3.1)	3 (3.0)	
Median	3	3	
Min, Max	0, 27	0, 30	
Inpatient Visits			
n, patients	227	211	
n, events	338	318	0.020
Mean (SD)	0 (0.6)	0 (0.6)	
Median	0	0	
Min, Max	0, 9	0, 11	
ED Visits	NA	NA	
n, patients			
n, events			
Mean (SD)			
Median			
Min, Max			

Abbreviations: ED = emergency department; Max = maximum; Min = minimum; N = number of patients in the specified category; n = number of patients within each specific category; NA = not applicable; SD = standard deviation; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism.

Note: Physician office visits do not include rheumatologist visits. Other outpatient visits do not include physician office visits or rheumatologist visits.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\ARTIS\ Table3_HCRU_08MAR22.xlsx

10.2.2.1.2. MACE

After propensity score matching, there were a total of 3,362 patients (1,681 each in the any baricitinib and TNFi cohorts) included in the analysis of VTE (Table 3_ARTIS). Within the matched baricitinib cohort, 80% of patients were treated with the 4 mg dose (n = 1350) and the rest with 2 mg (n = 329). On average, patients analysed were aged 59 years at baseline

(range 18 to 92 years) and the majority (82%) were female. After propensity score matching, patients treated with baricitinib were similar to patients treated with TNFi in terms of age and gender, as well as other characteristics.

Clinical characteristics of patients at baseline are described in Table 8_ARTIS. Prevalence of clinical conditions at baseline was low in ARTIS. In this situation, non-RA prescription medicines used in baseline inform clinical conditions. Medications used in baseline that inform overall clinical conditions commonly reported in other data sources include: antihypertensives (baricitinib 42%, TNFi 40%); antiplatelets (baricitinib 10%, TNFi 9%), antidiabetic agents (baricitinib 8%, TNFi 6%) and statins (baricitinib 13%, TNFi 13%). Diabetes was the most prevalent of recorded conditions at baseline (baricitinib 8%, TNFi 6%). Smoking (current or former) was common among patients in ARTIS (baricitinib 48%, TNFi 44%). After matching, the distribution of clinical conditions was balanced between the two cohorts, as determined by standardised differences <0.1. Patients in the baricitinib cohort had slightly higher disease severity with 37% of baricitinib patients having high disease activity (ie, DAS28 ≥5.2) compared to 28% of TNFi.

RA treatment received prior to the index medication is described in Table 8_ARTIS. The majority of patients used cDMARDs (any baricitinib 56%, TNFi 73%), with methotrexate recorded most frequently (baricitinib 43%. TNFi 62%). Proportion of patients with prior use of bDMARDs was similar in the baricitinib and TNFi cohorts (any baricitinib 54%, TNFi 62%). Etanercept was the most frequently recorded prior bDMARD (any baricitinib 19%, TNFi 34%).

Baseline healthcare resource utilisation was similar across the baricitinib and TNFi cohorts in the ARTIS (Table 13_ARTIS).

Table 3_ARTIS Baseline Demographics MACE Cohorts, Matched [ARTIS]

	Baricitinib				
	Any (N = 1681)	4 mg (n = 1350)	2 mg (n = 329)	TNFi (N = 1681)	Std. Diff. (Any vs TNFi)
Age [yrs]					
n	1681	1350	329	1681	0.022
Mean (SD)	59 (13.6)	56 (12.9)	70 (10.5)	59 (13.9)	
Median	60	57	73	60	
Min, Max	18, 92	18, 89	30, 92	18, 89	
≥ 65 years	649 (39%)	400 (30%)	247 (75%)	638 (38%)	
Sex					
Male	300 (18%)	246 (18%)	54 (16%)	286 (17%)	-0.021
Female	1381 (82%)	1104 (82%)	275 (84%)	1395 (83%)	

Abbreviations: MACE = major adverse cardiovascular event; Max = maximum; Min = minimum; N = count of patients in the specified category; SD = standard deviation; Std. Diff. = standardised difference; TNFi = tumour necrosis factor inhibitor; vs = versus.

Source: lillyce\prd\ly3009104\i4v_mc_b023\final\output\shared\tfl\ARTIS\Table1_demographics_08MAR22.xlsx

Table 8_ARTIS Clinical Characteristics MACE Cohorts, Matched [ARTIS]

Characteristic[a,b]	Baricitinib[c] (N = 1681)	TNFi (N = 1681)	Std. Diff.
Clinical Conditions during baseline			
Cancer	<5	7 (0%)	-0.059
NMSC	<5	<5	0.031
Chronic lung disease	11 (1%)	13 (1%)	-0.015
Cardiovascular conditions			
Atrial arrhythmia	<5	10 (1%)	-0.074
Cardiovascular revascularization	<5	<5	-0.066
Congestive heart failure	<5	<5	0.000
Coronary artery disease	<5	<5	0.031
Ischemic heart disease	<5	<5	0.022
Unstable angina	<5	<5	0.000
Ventricular arrhythmia	9 (1%)	<5	0.052
Diabetes Mellitus	141 (8%)	106 (6%)	0.076
Type I	NA	NA	
Type II	NA	NA	
Dyslipidaemia	<5	<5	
Hypertension	12 (1%)	5 (0%)	0.060
Immune disorders			
AIDS/HIV	NA	NA	
Antiphospholipid syndrome	NA	NA	
SLE	NA	NA	
Primary Sjögren syndrome	<5	6 (0%)	-0.022
Liver disorder	5 (0%)	<5	0.012
Obesity	NA	NA	
Pregnancy	5 (0%)	13 (1%)	-0.056
RA severity (DAS28)	**923**	**783**	
Mean (SD)	4.6 (1.27)	4.3 (1.40)	
DAS28 <2.6 (remission)	57 (6%)	101 (13%)	-0.125
Mean	2.02	1.88	
DAS28 <3.2 (low)	73 (8%)	60 (8%)	0.039
Mean	2.97	2.95	
DAS28 <5.2 (moderate)	453 (49%)	399 (51%)	0.073
Mean	4.26	4.23	
DAS28 5.2+ (high)	340 (37%)	223 (28%)	0.183
Mean	5.94	5.93	
Smoking, current or previous	800 (48%)	743 (44%)	0.068
Surgery	1341 (80%)	1280 (76%)	0.085
TIA	<5	<5	0.000
DMARDs			
cDMARDs, during baseline			
n, total	1054	1452	-0.363
Mean (SD)	1 (0.6)	1 (0.7)	
Median	1	1	
Min, Max	0, 3	0, 4	

Characteristic[a,b]	Baricitinib[c] (N = 1681)	TNFi (N = 1681)	Std. Diff.
Hydroxychloroquine	91 (5%)	121 (7%)	-0.072
Leflunomide	73 (4%)	75 (4%)	-0.006
Methotrexate	723 (43%)	1039 (62%)	-0.386
Minocycline[d]	NA	NA	NA
Sulfasalazine	153 (9%)	222 (13%)	-0.128
bDMARDs, during baseline			
n, total	1033	1020	0.014
Mean (SD)	1 (0.6)	1 (0.6)	
Median	1	1	
Min, Max	0, 3	0, 4	
abatacept	165 (10%)	65 (4%)	0.258
adalimumab[e]	190 (11%)	271 (16%)	-0.156
anakinra	<5	<5	0.049
certolizumab pegol[e]	46 (3%)	69 (4%)	-0.089
etanercept[e]	317 (19%)	573 (34%)	-0.376
golimumab[e]	29 (2%)	55 (3%)	-0.113
infliximab[e]	57 (3%)	117 (7%)	-0.180
rituximab	72 (4%)	15 (1%)	0.228
sarilumab	27 (2%)	<5	0.156
tocilizumab	129 (8%)	45 (3%)	0.247
Other Prescription Medications			
Antibiotics	415 (25%)	346 (21%)	0.101
Antidiabetic agents	141 (8%)	104 (6%)	0.080
Insulins	76 (5%)	57 (3%)	0.056
Non-insulins	97 (6%)	72 (4%)	0.064
Aspirin	151 (9%)	142 (8%)	0.019
Cardiovascular			
Anticoagulant	67 (4%)	71 (4%)	-0.013
Antihypertensives	714 (42%)	670 (40%)	0.054
Antiplatelet	175 (10%)	158 (9%)	0.034
Nitrates	45 (3%)	26 (2%)	0.078
Hormonal			
HRT	132 (8%)	158 (9%)	-0.058
Oral Contraceptives	61 (4%)	52 (3%)	0.027
SERMs	<5	<5	0.031
Lipid-lowering agents	<5	8 (0%)	-0.047
Bile acid binding	30 (2%)	8 (0%)	0.116
Cholesterol absorption inhibitor	<5	<5	0.000
Fibrates	NA	NA	
Niacin	NA	NA	
Omega-3 fatty acids	223 (13%)	217 (13%)	0.010
Statins			
Rheumatoid arthritis-related	121 (7%)	111 (7%)	0.023
Cox-2 Inhibitor	1071 (64%)	1068 (64%)	0.004
Glucocorticosteroid	NA	NA	

Vaccinations

Abbreviations: AIDS = acquired immunodeficiency syndrome; bDMARDs = biologic disease-modifying antirheumatic drugs; cDMARDs = conventional disease-modifying antirheumatic drugs; DAS28 = Disease Activity Score 28; DMARD = disease-modifying antirheumatic drug; HIV = human immunodeficiency virus; HRT = hormone replacement therapy; MACE = major adverse cardiovascular event; Max = maximum; Min = minimum; N = count of patients in the specified category; NA = not applicable; NMSC = non-melanoma skin cancer; RA = rheumatoid arthritis; SD = standard deviation; SERMs = selective oestrogen receptor modulators; SLE = systemic lupus erythematosus; Std. Diff. = standardised difference; TIA = transient ischemic attack; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism.

[a] All conditions and characteristics are measured during the 6 months prior to initiation of study medication until and including the day prior to baricitinib or the index TNFi exposure that qualifies the patient for the cohort. Clinical conditions are defined based on the "main diagnosis" in the National Patient Register.

[b] Many characteristics of the cohort are included in this table, but propensity score matching is only expected to balance those risk factors listed in Table 4 in protocol Section 8.3.3 (Annex 19) for each outcome (eg, hospitalized congestive heart failure) for VTE. Other factors are included for descriptive purposes only and may not be balanced across treatment groups but do not contribute to confounding bias (eg, Type I diabetes) for VTE.

[c] Both 2- and 4-mg baricitinib doses are included when the 4-mg dose is available. Alternatively, additional columns may be added for each dose when numbers of patients are sufficient to warrant separate reporting.

[d] Minocycline is not used to treat RA in Sweden.

[e] TNFi.

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Table 13_ARTIS Baseline Healthcare Resource Utilisation MACE Cohorts, Matched [ARTIS]

Type of Resource Use	Baricitinib (N = 1681)	TNFi (N = 1681)	Std. Diff.
Physician Office Visits	NA	NA	
n, patients			
n, events			
Mean (SD)			
Median			
Min, Max			
Rheumatologist Visits			
n, patients	1353	1352	
n, events	3414	3342	0.023
Mean (SD)	2 (1.9)	2 (1.9)	
Median	2	2	
Min, Max	0, 12	0, 20	
Other Outpatient Visits			
n, patients	1532	1514	
n, events	5702	5579	0.025
Mean (SD)	3 (3.1)	3 (3.0)	
Median	3	3	
Min, Max	0, 27	0, 30	
Inpatient Visits			
n, patients	222	229	
n, events	330	327	0.003
Mean (SD)	0 (0.6)	0 (0.6)	
Median	0	0	
Min, Max	0, 9	0, 11	
ED Visits	NA	NA	
n, patients			
n, events			
Mean (SD)			
Median			
Min, Max			

Abbreviations: ED = emergency department; MACE = major adverse cardiovascular event; Max = maximum; Min = minimum; N = count of patients in the specified category; NA = not applicable; SD = standard deviation; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor.

Note: Physician office visits do not include rheumatologist visits. Other outpatient visits do not include physician office visits or rheumatologist visits.

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10.2.2.1.3. Serious infections

After propensity score matching, there were a total of 3,366 patients (1,683 each in the any baricitinib and TNFi cohorts) included in the analysis of serious infections (Annex 11, Table 4). Within the baricitinib cohort, 80% of patients were treated with the 4 mg dose (n = 1343) and the rest with the 2 mg (n = 339). On average, patients analysed were aged 59 years at baseline (range 18 to 92 years) and the majority (82%) were female. After propensity score matching,

patients treated with baricitinib were not dissimilar from patients treated with TNFi in terms of age and gender, as well as other characteristics.

Clinical characteristics of patients at baseline are described in Annex 11, Table 9. Medications used in baseline that inform overall clinical conditions commonly reported in other data sources include: antihypertensives (baricitinib 43%, TNFi 41%); antiplatelets (baricitinib 10%, TNFi 11%), antidiabetic agents (baricitinib 8%, TNFi 7%) and statins (baricitinib 14%, TNFi 16%). Diabetes was the most prevalent condition at baseline (baricitinib 8%, TNFi 7%). Smoking (current or former) was common among patients in ARTIS (baricitinib 47%, TNFi 44%). After matching, the distribution of clinical conditions was balanced between the two cohorts, as determined by standardised differences <0.1. Not included in the propensity score and therefore not expected to balance, the proportion of patients in the baricitinib cohort with high disease activity (ie, DAS28 ≥5.2) was slightly higher than in the TNFi cohort (ie, 20% and 14%), respectively.

RA treatment received prior to the index medication is described in Annex 11, Table 9. The majority of patients used cDMARDs (baricitinib 56%, TNFi 73%), with methotrexate recorded most frequently (baricitinib 43%. TNFi 60%). Proportion of patients with prior use of bDMARDs was lower in the baricitinib compared to TNFi cohort (any baricitinib 53%, TNFi 61%). Etanercept was the most frequently recorded prior bDMARD (any baricitinib 19%, TNFi 34%).

10.2.2.2. BKK

There were 851 eligible patients treated with baricitinib (699 with 4 mg and 152 with 2 mg) and 3,332 eligible TNFi patients in the BKK data. Demographic and clinical characteristics for these unmatched cohorts are in Annex 12. From these unmatched cohorts, the number of patients included in analyses of VTE, MACE, or serious infection after 1:1 matching varies. Details of these analysis-specific cohorts follow.

10.2.2.2.1. VTE

After propensity score matching, there were a total of 1,530 patients (765 each in the any baricitinib and TNFi cohorts) included in the analysis of VTE (Table 2_BKK). Within the baricitinib cohort, 82% of patients (n = 628) were treated with 4 mg and the rest with 2 mg (n = 137). On average, patients analysed were aged 56.3 years at baseline (range 18 to 94 years) and the majority (75%) were female.

Clinical characteristics of patients at baseline are described in Table 7_BKK. The most commonly observed conditions prevalent in at least 10% of patients were dyslipidaemia (any baricitinib 27%, TNFi 26%), hypertension (any baricitinib 46%, TNFi 47%), diabetes (any baricitinib 16%, TNFi 16%), chronic lung disease (any baricitinib 16%, TNFi 17%) and obesity (any baricitinib 16%, TNFi 16%). Smoking was also prevalent (baricitinib 12%, TNFi 10%). With regard to RA severity, the CIRAS score was slightly higher in patients treated with baricitinib compared with TNFi (7.1 vs. 7.0, respectively).

RA treatment received prior to the index medication is described in Table 7_BKK. Approximately half of patients used cDMARDs (any baricitinib 58%, TNFi 50%), with methotrexate recorded most frequently (any baricitinib 40%, TNFi 39%). Patients treated with baricitinib were slightly more likely to have >1 cDMARD concomitantly than those treated TNFi (any baricitinib 6%, TNFi 4%). Prior use of bDMARDs was observed equally among the any baricitinib treated cohort (40%) and patients treated with TNFi (40%). Etanercept was the most frequently recorded prior bDMARDs used by the any baricitinib cohort and the TNFi cohort (any baricitinib 12%, TNFi 10%).

Baseline healthcare resource utilisation was similar across the baricitinib and TNFi cohorts (Table 12_BKK).

Table 2_BKK Baseline Demographics VTE Cohorts, Matched [BKK]

	Baricitinib			TNFi	Std. Diff.	Total
	Any (N = 765)	4 mg (N = 628)	2 mg (N = 137)	(N = 765)	(Any vs TNFi)	(N = 1530)
Age [yrs]						
n	765	628	137	765	2.9	1530
Mean (SD)	56.5 (13)	54.2 (12)	66.8 (13)	56.1 (14)		56.3 (13)
Median	56.0	55.0	70.0	57.0		57.0
Min, Max	18.0, 92.0	18.0, 84.0	24.0, 92.0	18.0, 94.0		18.0, 94.0
≥65 years	193 (25%)	114 (18%)	79 (58%)	201 (26%)		394 (26%)
Sex						
Male	193 (25%)	163 (26%)	30 (22%)	192 (25%)	0.3	385 (25%)
Female	572 (75%)	465 (74%)	107 (78%)	573 (75%)		1145 (75%)

Abbreviations: BKK = Betriebskrankenkasse; Max = maximum; Min = minimum; N = number of patients in the specific category; n = number of patients within each specific category; SD = standard deviation; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor; SD = standard deviation; vs = versus; VTE = venous thromboembolism.

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Table 7_BKK Clinical Characteristics Primary VTE Cohorts, Matched [BKK]

Characteristic[a,b]	Baricitinib[c] (N = 765)	4 mg (N = 628)	2 mg (N = 137)	TNFi (N = 765)	Std. Diff.
Clinical Conditions during baseline					
Cancer	89 (12%)	66 (11%)	23 (17%)	71 (9%)	7.8
NMSC	11 (1%)	6 (1%)	5 (4%)	19 (2%)	-8.5
Chronic lung disease	126 (16%)	101 (16%)	25 (18%)	127 (17%)	-0.4
Cardiovascular conditions					
Atrial arrhythmia/fibrillation	13 (2%)	9 (1%)	4 (3%)	11 (1%)	2.2
Cardiovascular revascularization	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NA
Congestive heart failure, hospitalized	8 (1%)	6 (1%)	2 (1%)	3 (0%)	7.7
Coronary artery disease	46 (6%)	31 (5%)	15 (11%)	45 (6%)	0.6
Ischemic heart disease	50 (7%)	34 (5%)	16 (12%)	48 (6%)	1.1
Unstable angina	1 (0%)	0 (0%)	1 (1%)	1 (0%)	0
Ventricular arrhythmia	37 (5%)	24 (4%)	13 (9%)	36 (5%)	0.6
Diabetes mellitus	124 (16%)	90 (14%)	34 (25%)	123 (16%)	0.4
Type I	20 (3%)	16 (3%)	4 (3%)	10 (1%)	8.8
Type II	111 (15%)	80 (13%)	31 (23%)	121 (16%)	-3.9
Dyslipidaemia	203 (27%)	156 (25%)	47 (34%)	199 (26%)	1.2
Hypertension	349 (46%)	265 (42%)	84 (61%)	359 (47%)	-2.6
Immune disorders	39 (5%)	31 (5%)	8 (6%)	33 (4%)	3.8
AIDS/HIV	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NA
Antiphospholipid syndrome	1 (0%)	1 (0%)	0 (0%)	1 (0%)	0
SLE	3 (0%)	3 (0%)	0 (0%)	7 (1%)	-7.1
Primary Sjögren Syndrome	38 (5%)	30 (5%)	8 (6%)	26 (3%)	8.1
Liver disorder	19 (2%)	12 (2%)	7 (5%)	13 (2%)	5.8
Obesity	125 (16%)	104 (17%)	21 (15%)	121 (16%)	1.4
Pregnancy	2 (0%)	2 (0%)	0 (0%)	4 (1%)	-3.2
RA Severity (CIRAS index), mean (SD)	7.1 (2)	7.2 (2)	6.4 (2)	7.0 (2)	1.2
Smoking	93 (12%)	70 (11%)	23 (17%)	76 (10%)	7.1
Surgery, trauma & hospitalization, recent	108 (14%)	86 (14%)	22 (16%)	107 (14%)	0.4
TIA	1 (0%)	0 (0%)	1 (1%)	2 (0%)	-2
Genetic coagulopathies	3 (0%)	1 (0%)	2 (1%)	2 (0%)	2.1
DMARDs					
cDMARDs, during baseline					
n, total	441 (58%)	365 (58%)	76 (55%)	386 (50%)	14.5
Mean (SD)	0.7 (1)	0.7 (1)	0.7 (1)	0.6 (1)	16
Median	1.0	1.0	1.0	1.0	
Min, Max	0.0, 3.0	0.0, 3.0	0.0, 3.0	0.0, 3.0	

Characteristic[a,b]	Baricitinib[c] (N = 765)	4 mg (N = 628)	2 mg (N = 137)	TNFi (N = 765)	Std. Diff.
>1 cDMARD concomitantly	46 (6%)	40 (6%)	6 (4%)	32 (4%)	7.7
Hydroxychloroquine	33 (4%)	24 (4%)	9 (7%)	21 (3%)	8.2
Leflunomide	140 (18%)	114 (18%)	26 (19%)	84 (11%)	20.1
Methotrexate	303 (40%)	256 (41%)	47 (34%)	299 (39%)	1.1
Minocycline	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NA
Sulfasalazine	52 (7%)	37 (6%)	15 (11%)	37 (5%)	7.7
bDMARDs, during baseline					
n, total	308 (40%)	265 (42%)	43 (31%)	307 (40%)	0.3
Mean (SD)	0.4 (1)	0.4 (1)	0.3 (1)	0.4 (1)	0.5
Median	0.0	0.0	0.0	0.0	
Min, Max	0.0, 2.0	0.0, 2.0	0.0, 2.0	0.0, 2.0	
cDMARDs, concomitant	100 (13%)	90 (14%)	10 (7%)	98 (13%)	0.9
abatacept	35 (5%)	28 (4%)	7 (5%)	25 (3%)	7.2
adalimumab[d]	52 (7%)	45 (7%)	7 (5%)	70 (9%)	-10.3
anakinra	1 (0%)	1 (0%)	0 (0%)	4 (1%)	-8.9
certolizumab pegol[d]	31 (4%)	28 (4%)	3 (2%)	42 (5%)	-7.9
etanercept[d]	91 (12%)	75 (12%)	16 (12%)	76 (10%)	7.2
golimumab[d]	21 (3%)	18 (3%)	3 (2%)	30 (4%)	-7.9
infliximab[d]	3 (0%)	2 (0%)	1 (1%)	21 (3%)	-29.1
rituximab	15 (2%)	14 (2%)	1 (1%)	3 (0%)	14.6
sarilumab	11 (1%)	10 (2%)	1 (1%)	8 (1%)	3.9
tocilizumab	60 (8%)	54 (9%)	6 (4%)	39 (5%)	12.3
Other Prescription Medications					
Antibiotics	222 (29%)	175 (28%)	47 (34%)	240 (31%)	-5.2
Antidiabetic agents	74 (10%)	55 (9%)	19 (14%)	69 (9%)	2.3
Insulins	40 (5%)	31 (5%)	9 (7%)	25 (3%)	9.5
Non-insulins	56 (7%)	40 (6%)	16 (12%)	59 (8%)	-1.6
Aspirin	3 (0%)	3 (0%)	0 (0%)	4 (1%)	-2.1

Characteristic[a,b]	Baricitinib[c] (N = 765)	4 mg (N = 628)	2 mg (N = 137)	TNFi (N = 765)	Std. Diff.
Cardiovascular					
Anticoagulant	21 (3%)	18 (3%)	3 (2%)	21 (3%)	0
Antihypertensives	326 (43%)	244 (39%)	82 (60%)	336 (44%)	-2.7
Antiplatelet	4 (1%)	3 (0%)	1 (1%)	8 (1%)	-7.1
Nitrates	1 (0%)	0 (0%)	1 (1%)	1 (0%)	0
Hormonal					
HRT	41 (5%)	31 (5%)	10 (7%)	62 (8%)	-12.2
Oral Contraceptives	3 (0%)	3 (0%)	0 (0%)	2 (0%)	1.8
SERMs	0 (0%)	0 (0%)	0 (0%)	1 (0%)	-10.7
Lipid-lowering agents					
Bile acid binding	10 (1%)	9 (1%)	1 (1%)	3 (0%)	9
Cholesterol absorption inhibitor	6 (1%)	4 (1%)	2 (1%)	4 (1%)	3.2
Fibrates	3 (0%)	2 (0%)	1 (1%)	1 (0%)	4.7
Niacin	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NA
Omega-3 fatty acids	1 (0%)	1 (0%)	0 (0%)	0 (0%)	5.4
Statins	75 (10%)	53 (8%)	22 (16%)	77 (10%)	-0.9
Rheumatoid arthritis-related					
Cox-2 Inhibitor	123 (16%)	104 (17%)	19 (14%)	116 (15%)	2.5
Glucocorticosteroid	549 (72%)	449 (71%)	100 (73%)	531 (69%)	5
Vaccinations	11 (1%)	10 (2%)	1 (1%)	15 (2%)	-4.3

Abbreviations: AIDS = acquired immunodeficiency syndrome; bDMARDs = biologic disease-modifying antirheumatic drugs; BKK = Betriebskrankenkasse; cDMARDs = conventional disease-modifying antirheumatic drugs; Concom. cDMARDs = concomitant cDMARDs; CIRAS = claims-based index for RA severity; HIV = human immunodeficiency virus; HRT = hormone replacement therapy; Max = maximum; Min = minimum; N = count of patients in the specified category; NA = not applicable; NMSC = non-melanoma skin cancer; RA = rheumatoid arthritis; SD = standard deviation; SERMs = selective oestrogen receptor modulators; SLE = systemic lupus erythematosus; Std. Diff. = standardised difference; TIA = transient ischemic attack; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism.

[a] All conditions and characteristics except for the use of bDMARD and concomitant cDMARD are measured during the 6 months prior to initiation of study medication until, and including, the index date.

[b] Many characteristics of the cohort are included in this table, but propensity score matching is only expected to balance those risk factors listed in Table 4 in protocol Section 8.3.3 (Annex 19) for each outcome (e.g., hospitalized congestive heart failure for VTE. Other factors are included for descriptive purposes only and may not be balanced across treatment groups but do not contribute to confounding bias (e.g., Type I diabetes for VTE.

[c] Both 2- and 4-mg baricitinib doses are included when the 4-mg dose is available. Alternatively, additional columns may be added for each dose when numbers of patients are sufficient to warrant separate reporting.

[d] TNF inhibitors.

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Table 12_BKK Baseline Healthcare Resource Utilisation Primary VTE Cohorts, Matched [BKK]

	Baricitinib				
Type of Resource Use	Any (N = 765)	4 mg (N = 628)	2 mg (N = 137)	TNFi (N = 765)	Std. Diff.
Physician Office Visits					
n, patients	763	626	137	765	-4.8
n, events	13159	10338	2821	13420	-3.2
Mean (SD)	17.2 (10)	16.5 (9)	20.6 (13)	17.5 (11)	
Median	15.0	15.0	18.0	15.0	
Min, Max	0.0, 74.0	0.0, 61.0	1.0, 74.0	1.0, 88.0	
Rheumatologist Visits					
n, patients	582	489	93	594	-3.6
n, events	2867	2408	459	2726	5.4
Mean (SD)	3.7 (4)	3.8 (4)	3.4 (4)	3.6 (3)	
Median	3.0	3.0	3.0	3.0	
Min, Max	0.0, 22.0	0.0, 19.0	0.0, 22.0	0.0, 23.0	
Other Outpatient Visits					
n, patients	140	114	26	129	3.7
n, events	248	196	52	221	4.6
Mean (SD)	0.3 (1)	0.3 (1)	0.4 (1)	0.3 (1)	
Median	0.0	0.0	0.0	0.0	
Min, Max	0.0, 5.0	0.0, 5.0	0.0, 4.0	0.0, 7.0	
Inpatient Visits and ED Visits					
n, patients	179	143	36	173	1.9
n, events	239	189	50	226	2.6
Mean (SD)	0.3 (1)	0.3 (1)	0.4 (1)	0.3 (1)	
Median	0.0	0.0	0.0	0.0	
Min, Max	0.0, 7.0	0.0, 7.0	0.0, 4.0	0.0, 6.0	
ED Visits					
n, patients	NA	NA	NA	NA	
n, events	NA	NA	NA	NA	
Mean (SD)	NA	NA	NA	NA	
Median	NA	NA	NA	NA	
Min, Max	NA	NA	NA	NA	

Abbreviations: BKK = Betriebskrankenkasse; ED = emergency department; Max = maximum; Min = minimum; N = count of patients in the ; NA = not applicable SD = standard deviation; Std. Diff = standardised differences; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism.

Note: Physician office visits do not include rheumatologist visits. Other outpatient visits do not include physician office visits or rheumatologist visits.

[a] ED visits cannot be separated from inpatient visits in the BKK data source.

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10.2.2.2.2. MACE

After propensity score matching, there were a total of 1,514 patients (757 each in the any baricitinib and TNFi cohorts) included in the analysis of MACE (Table 3_BKK). Within the matched baricitinib cohort, 83% of patients were treated with the 4 mg dose (n = 625) and the rest with the 2 mg (n = 132) on 2 mg. On average, patients analysed were aged 56.4 years at baseline (range 18 to 94 years) and were majority (75%) female. After propensity score matching, patients treated with baricitinib were not dissimilar from patients treated with TNFi in terms of age and gender.

Clinical characteristics of patients at baseline are described in Table 8_BKK. The most commonly observed conditions were dyslipidaemia (any baricitinib 26%, TNFi 25%), hypertension (any baricitinib 47%, TNFi 43%), diabetes (any baricitinib 16%, TNFi 14%), obesity (any baricitinib 17%, TNFi 15%), and chronic lung disease (any baricitinib 16%, TNFi 15%). Smoking was also prevalent in both treatment cohorts (any baricitinib 11%, TNFi 9%). With regard to RA severity, the CIRAS score was not dissimilar among the any baricitinib cohort compared to the TNFi cohort (any baricitinib 7.1, TNFi 7.0).

RA treatment received prior to the index medication is described in Table 8_BKK. Approximately half of patients used cDMARDs (any baricitinib 59%, TNFi 50%), with methotrexate recorded most frequently (any baricitinib 41%, TNFi 36%). Patients treated with any baricitinib or TNFi were equally likely to have >1 cDMARD concomitantly (any baricitinib 6%, TNFi 6%). Prior use of bDMARDs was observed slightly more frequently in the any baricitinib treated cohort (39%) as compared to patients treated with TNFi (38%). Etanercept was the most frequently recorded prior bDMARDs used by the any baricitinib cohort and the TNFi cohort (any baricitinib 11%, TNFi 10%).

Baseline healthcare resource utilisation was similar across the baricitinib and TNFi cohorts (Table 13_BKK).

Table 3_BKK Baseline Demographics MACE Cohorts, Matched [BKK]

	Baricitinib					
	Any (N = 757)	4 mg (N = 625)	2 mg (N = 132)	(N = 757) TNFi	Std. Diff. (Any vs TNFi)	Total (N = 1514)
Age [yrs]						
n	757	625	132	757	1.7	1514
Mean (SD)	56.5 (13)	54.3 (12)	67.1 (13)	56.3 (13)		56.4 (13)
Median	57.0	55.0	70.0	57.0		57.0
Min, Max	18.0, 92.0	18.0, 84.0	24.0, 92.0	18.0, 94.0		18.0, 94.0
≥ 65 years	195 (26%)	116 (19%)	79 (60%)	198 (26%)		393 (26%)
Sex						
Male	188 (25%)	158 (25%)	30 (23%)	195 (26%)	-2.0	383 (25%)
Female	569 (75%)	467 (75%)	102 (77%)	562 (74%)		1131 (75%)

Abbreviations: BKK = Betriebskrankenkasse; MACE = major adverse cardiovascular event, defined based on primary hospital discharge diagnosis codes for acute myocardial infarction, ischemic or haemorrhagic stroke; Max = maximum; Min = minimum;
N = count of patients in the specified category; SD = standard deviation; Std. Diff. = standardised difference; TNFi = tumour necrosis factor inhibitor;
vs = versus; yrs = years.

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Table 8_BKK Clinical Characteristics MACE Cohorts, Matched [BKK]

Characteristic a, b	Baricitinib (N = 757)	4 mg (N = 625)	2 mg (N = 132)	TNFi (N = 757)	Std. Diff.
Clinical Conditions during baseline					
Cancer	89 (12%)	66 (11%)	23 (17%)	77 (10%)	5.3
NMSC	10 (1%)	5 (1%)	5 (4%)	16 (2%)	-6.3
Chronic lung disease	123 (16%)	100 (16%)	23 (17%)	117 (15%)	2.2
Cardiovascular conditions					
Atrial arrhythmia/fibrillation	15 (2%)	10 (2%)	5 (4%)	9 (1%)	6.5
Cardiovascular revascularization	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.0
Congestive heart failure, hospitalized	9 (1%)	6 (1%)	3 (2%)	4 (1%)	7.8
Coronary artery disease	45 (6%)	31 (5%)	14 (11%)	35 (5%)	5.7
Ischemic heart disease	48 (6%)	34 (5%)	14 (11%)	36 (5%)	6.6
Unstable angina	1 (0%)	0 (0%)	1 (1%)	1 (0%)	0.0
Ventricular arrhythmia	33 (4%)	20 (3%)	13 (10%)	39 (5%)	-3.7
Diabetes mellitus	122 (16%)	90 (14%)	32 (24%)	108 (14%)	5.2
Type I	22 (3%)	16 (3%)	6 (5%)	8 (1%)	12.4
Type II	109 (14%)	81 (13%)	28 (21%)	103 (14%)	2.4
Dyslipidaemia	197 (26%)	153 (24%)	44 (33%)	188 (25%)	2.8
Hypertension	354 (47%)	270 (43%)	84 (64%)	329 (43%)	6.7
Immune disorders	39 (5%)	31 (5%)	8 (6%)	35 (5%)	2.5
AIDS/HIV	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.0
Antiphospholipid syndrome	1 (0%)	1 (0%)	0 (0%)	2 (0%)	-3.0
SLE	4 (1%)	4 (1%)	0 (0%)	7 (1%)	-5.4
Primary Sjögren Syndrome	37 (5%)	29 (5%)	8 (6%)	27 (4%)	6.8
Liver disorder	18 (2%)	12 (2%)	6 (5%)	9 (1%)	8.9
Obesity	127 (17%)	108 (17%)	19 (14%)	111 (15%)	5.7
Pregnancy	2 (0%)	2 (0%)	0 (0%)	5 (1%)	-4.9
RA severity (CIRAS index), mean (SD)	7.1 (2)	7.2 (2)	6.3 (2)	7.0 (2)	2.8
Smoking	84 (11%)	64 (10%)	20 (15%)	70 (9%)	6.0
Surgery, trauma & hospitalization, recent	112 (15%)	88 (14%)	24 (18%)	118 (16%)	-2.3
TIA	2 (0%)	1 (0%)	1 (1%)	5 (1%)	-6.2
Genetic coagulopathies	3 (0%)	1 (0%)	2 (2%)	3 (0%)	0.0

Characteristic a, b	Baricitinib (N = 757)	4 mg (N = 625)	2 mg (N = 132)	TNFi (N = 757)	Std. Diff.
DMARDs					
cDMARDs, during baseline					
n, total	446 (59%)	369 (59%)	77 (58%)	376 (50%)	18.6
Mean (SD)	0.7 (1)	0.7 (1)	0.8 (1)	0.6 (1)	13.7
Median	1.0	1.0	1.0	0.0	
Min, Max	0.0, 3.0	0.0, 3.0	0.0, 3.0	0.0, 3.0	
>1 cDMARD concomitantly	46 (6%)	40 (6%)	6 (5%)	49 (6%)	-1.7
Hydroxychloroquine	33 (4%)	24 (4%)	9 (7%)	27 (4%)	4.1
Leflunomide	137 (18%)	111 (18%)	26 (20%)	111 (15%)	9.4
Methotrexate	308 (41%)	259 (41%)	49 (37%)	269 (36%)	10.7
Minocycline	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.0
Sulfasalazine	55 (7%)	40 (6%)	15 (11%)	44 (6%)	5.7
bDMARDs, during baseline					
n, total	298 (39%)	262 (42%)	36 (27%)	287 (38%)	3.5
Mean (SD)	0.4 (1)	0.4 (1)	0.3 (0)	0.4 (1)	3.6
Median	0.0	0.0	0.0	0.0	
Min, Max	0.0, 2.0	0.0, 2.0	0.0, 2.0	0.0, 2.0	
cDMARDs, concomitant	105 (14%)	92 (15%)	13 (10%)	86 (11%)	8.7
abatacept	33 (4%)	28 (4%)	5 (4%)	23 (3%)	7.3
adalimumab[c]	48 (6%)	44 (7%)	4 (3%)	68 (9%)	-11.6
anakinra	1 (0%)	1 (0%)	0 (0%)	4 (1%)	-9.0
certolizumab pegol[c]	33 (4%)	29 (5%)	4 (3%)	35 (5%)	-1.5
etanercept[c]	87 (11%)	74 (12%)	13 (10%)	73 (10%)	6.8
golimumab[c]	19 (3%)	16 (3%)	3 (2%)	24 (3%)	-4.4
infliximab[c]	2 (0%)	2 (0%)	0 (0%)	22 (3%)	-32.8
rituximab	14 (2%)	13 (2%)	1 (1%)	3 (0%)	13.6
sarilumab	13 (2%)	12 (2%)	1 (1%)	8 (1%)	6.7
tocilizumab	62 (8%)	56 (9%)	6 (5%)	39 (5%)	13.6
Other Prescription Medications					
Antibiotics	223 (29%)	178 (28%)	45 (34%)	235 (31%)	-3.5
Antidiabetic agents	72 (10%)	55 (9%)	17 (13%)	55 (7%)	8.0
Insulins	42 (6%)	32 (5%)	10 (8%)	23 (3%)	12.1
Non-insulins	54 (7%)	40 (6%)	14 (11%)	46 (6%)	4.2
Aspirin	3 (0%)	3 (0%)	0 (0%)	8 (1%)	-10.7

Characteristic a, b	Baricitinib (N = 757)	4 mg (N = 625)	2 mg (N = 132)	TNFi (N = 757)	Std. Diff.
Cardiovascular					
Anticoagulant	21 (3%)	17 (3%)	4 (3%)	22 (3%)	-0.8
Antihypertensives	329 (43%)	249 (40%)	80 (61%)	304 (40%)	6.8
Antiplatelet	4 (1%)	3 (0%)	1 (1%)	6 (1%)	-3.6
Nitrates	1 (0%)	0 (0%)	1 (1%)	2 (0%)	-2.8
Hormonal					
HRT	42 (6%)	31 (5%)	11 (8%)	49 (6%)	-4.1
Oral Contraceptives	3 (0%)	3 (0%)	0 (0%)	2 (0%)	1.9
SERMs	0 (0%)	0 (0%)	0 (0%)	1 (0%)	-10.8
Lipid-lowering agents					
Bile acid binding	10 (1%)	9 (1%)	1 (1%)	4 (1%)	7.8
Cholesterol absorption inhibitor	7 (1%)	5 (1%)	2 (2%)	2 (0%)	8.0
Fibrates	3 (0%)	2 (0%)	1 (1%)	2 (0%)	2.4
Niacin	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.0
Omega-3 fatty acids	1 (0%)	1 (0%)	0 (0%)	0 (0%)	5.5
Statins	72 (10%)	52 (8%)	20 (15%)	67 (9%)	2.3
Rheumatoid arthritis-related					
Cox-2 Inhibitor	123 (16%)	103 (16%)	20 (15%)	110 (15%)	4.7
Glucocorticosteroid	543 (72%)	447 (72%)	96 (73%)	559 (74%)	-4.5
Vaccinations	10 (1%)	9 (1%)	1 (1%)	13 (2%)	-3.3

Abbreviations: AIDS = acquired immunodeficiency syndrome; bDMARDs = biologic disease-modifying antirheumatic drugs; BKK = Betriebskrankenkasse; cDMARDs = conventional disease-modifying antirheumatic drugs; CIRAS = claims-based index for RA severity; HIV = human immunodeficiency virus; HRT = hormone replacement therapy;
MACE = major adverse cardiovascular event; Max = maximum; Min = minimum; N = count of patients in ;
NMSC = non-melanoma skin cancer; RA = rheumatoid arthritis; SD = standard deviation; SERMs = selective oestrogen receptor modulators; SLE = systemic lupus erythematosus; Std. Diff. = standardised difference; TIA = transient ischemic attack; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism.

a All conditions and characteristics except for use of bDMARD and concomitant cDMARD are measured during the 6 months prior to initiation of study medication until, and including, the index date.

b Many characteristics of the cohort are included in this table, but propensity score matching is only expected to balance those risk factors listed in Table 4 (see Section 8.3.3, Annex 19) for each outcome (e.g., hospitalized congestive heart failure for VTE. Other factors that are included for descriptive purposes only, may not be balanced across treatment groups but do not contribute to confounding bias (e.g., Type I diabetes for VTE.

c TNF inhibitors.

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Table 13_BKK Baseline Healthcare Resource Utilisation MACE Cohorts, Matched [BKK]

Type of Resource Use	Baricitinib 4 mg (N = 757)	2 mg (N = 625)	TNFi (N = 132)	(N = 757)	Std. Diff.
Physician Office Visits					
n, patients	755	623	132	756	-2.4
n, events	13079	10368	2711	13103	-0.3
Mean (SD)	17.3 (10)	16.6 (9)	20.5 (12)	17.3 (11)	
Median	15.0	15.0	18.0	15.0	
Min, Max	0.0, 74.0	0.0, 61.0	2.0, 74.0	0.0, 78.0	
Rheumatologist Visits					
n, patients	575	487	88	604	-8.8
n, events	2734	2335	399	2795	-2.4
Mean (SD)	3.6 (3)	3.7 (3)	3.0 (3)	3.7 (3)	
Median	3.0	3.0	3.0	3.0	
Min, Max	0.0, 19.0	0.0, 19.0	0.0, 12.0	0.0, 24.0	
Other Outpatient Visits					
n, patients	131	106	25	130	0.3
n, events	233	182	51	231	0.3
Mean (SD)	0.3 (1)	0.3 (1)	0.4 (1)	0.3 (1)	
Median	0.0	0.0	0.0	0.0	
Min, Max	0.0, 5.0	0.0, 5.0	0.0, 4.0	0.0, 5.0	
Inpatient and ED Visits					
n, patients	181	142	39	179	0.6
n, events	245	190	55	226	3.9
Mean (SD)	0.3 (1)	0.3 (1)	0.4 (1)	0.3 (1)	
Median	0.0	0.0	0.0	0.0	
Min, Max	0.0, 7.0	0.0, 7.0	0.0, 4.0	0.0, 4.0	
ED Visits					
n, patients	NA	NA	NA	NA	
n, events	NA	NA	NA	NA	
Mean (SD)	NA	NA	NA	NA	
Median	NA	NA	NA	NA	
Min, Max	NA	NA	NA	NA	

Abbreviations: BKK = Betriebskrankenkasse; ED = emergency department; MACE = major adverse cardiovascular event, defined based on primary hospital discharge diagnosis codes for acute myocardial infarction, ischemic or haemorrhagic stroke; Max = maximum; Min = minimum; N = counts of patients in the ; NA = not applicable; SD = standard deviation; Std. Diff = standardised difference; TNFi = tumour necrosis factor inhibitor.

Note: Physician office visits do not include rheumatologist visits. Other outpatient visits do not include physician office visits or rheumatologist visits.

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10.2.2.2.3. Serious infections

After propensity score matching, there were a total of 1,718 patients (859 each in the baricitinib and TNFi cohorts) included in the analysis of serious infections (Annex 12, Table 4). Within the baricitinib cohort, 80% of patients were treated with 4 mg (n = 691) and the rest with 2 mg (n = 168). On average, patients analysed were aged 58 years at baseline (range 18 to 92 years) and the majority (73%) were female.

Clinical characteristics of patients at baseline are described in Annex 12, Table 9. The most commonly observed conditions were dyslipidaemia (any baricitinib 30%, TNFi 28%), hypertension (any baricitinib 50%, TNFi 53%), diabetes (any baricitinib 18%, TNFi 19%), chronic lung disease (any baricitinib 18%, TNFi 17%), and obesity (any baricitinib 18%, TNFi 17%). RA severity using the CIRAS index was the same between the two cohorts (6.9).

10.2.2.3. Cegedim

There were 213 eligible patients treated with baricitinib and 814 eligible TNFi patients in the French Cegedim THIN data (Annex 13). All patients within the Cegedim data are included in the national SNDS data, which includes all French residents. Because of this overlap, Cegedim data was not included in the meta-analysis. Analyses executed with the Cegedim data are presented in Annex 13 for transparency.

10.2.2.4. CorEvitas Japan

There were 210 eligible patients treated with baricitinib (184 with 4 mg and 21 with 2 mg) and 354 eligible TNFi patients in the CorEvitas Japan data. Demographic and clinical characteristics for these unmatched cohorts are in Annex 14. From these unmatched cohorts, the number of patients included in analyses of VTE, MACE, or serious infection after 1:1 matching varies. Details of these analysis-specific cohorts follow.

10.2.2.4.1. VTE

After propensity score matching, there were a total of 342 patients (171 each in the baricitinib and TNFi cohorts) included in the analysis of VTE (Table 2_Cor_JP). The small size of the analysis cohort limits the ability to evaluate the characteristics of the treatment groups at baseline. Within the baricitinib cohort, 90% of patients were treated with the 4 mg dose (n = 155) with only a few treated with the 2 mg (n = 15). On average, patients analysed were aged 61.0 years at baseline (range 22 to 86 years) and were majority (83%) female. Patients in the baricitinib cohort reported alcohol use less often than patients in TNFi cohort (baricitinib 39.8%; 43.3%). Based on standardised differences >0.10 after propensity score matching, patients in the any baricitinib and TNFi cohorts were not dissimilar.

Clinical characteristics of patients at baseline are described in Table 7_Cor_JP. The most commonly observed conditions prevalent in at least 10% of patients were hyperlipidaemia (any baricitinib 12.9%, TNFi 14.0%), hypertension (any baricitinib 28.1%, TNFi 29.8%) and diabetes (any baricitinib 11.1%, TNFi 13.5%). Current smoking was also prevalent in both treatment cohorts (any baricitinib 10.5%, TNFi 11.7%). With regard to RA severity, the CDAI score was

slightly higher in the baricitinib cohort compared to the TNFi cohort (baricitinib 23.4, TNFi 22.7).

RA treatment received prior to the index medication is described in Table 7_Cor_JP. The majority of patients reported use of at least 1 cDMARDs at any point (any baricitinib 91.8%, TNFi 90.6%), with methotrexate recorded most frequently (any baricitinib 85.4%, TNFi 85.4%). Concomitant use of cDMARDs at baseline was slightly higher in the TNFi treated cohort (baricitinib 61.4%, TNFi 64.3%). Prior use of bDMARDs was observed more frequently among the any baricitinib treated cohort (60.2%) as compared to patients treated with TNFi (45%).

Table 2_Cor_JP Baseline Demographics VTE Cohorts, Matched [Cor_JP]

	Baricitinib					
	Any (N = 171)	2 mg (N = 15)	4 mg (N = 155)	TNFi (N = 171)	Std. Diff (Any vs TNFi)	Total (N = 342)
Age [yrs]						
n	171	15	155	171	0.009	342
Mean±SD	60.9 ±13.6	71.6 ± 8.1	59.8 ±13.7	61.1 ±15.2		61.0 ±14.4
Median	63.0	73.0	62.0	63.0		63.0
Min, Max	25.0, 85.0	56.0, 84.0	25.0, 85.0	22.0, 86.0		22.0, 86.0
≥ 65 years	80 (46.8%)	12 (80.0%)	67 (43.2%)	75 (43.9%)	0.059	155 (45.3%)
Gender						
Male	26 (15.2%)	0 (0.0%)	26 (16.8%)	32 (18.7%)	0.094	58 (17.0%)
Female	145 (84.8%)	15 (100.0%)	129 (83.2%)	139 (81.3%)		284 (83.0%)
BMI						
n	171	15	155	171	0.016	342
Mean±SD	22.8 ± 4.5	21.6 ± 4.4	22.9 ± 4.5	22.9 ± 4.1		22.8 ± 4.3
Median	21.8	22.0	21.8	22.2		22.0
Min, Max	16.1, 45.2	16.2, 33.7	16.1, 45.2	14.3, 47.1		14.3, 47.1
Smoking (current)	18 (10.5%)	2 (13.3%)	16 (10.3%)	20 (11.7%)	0.037	38 (11.1%)
Alcohol use	68 (39.8%)	7 (46.7%)	61 (39.4%)	74 (43.3%)	0.071	142 (41.5%)
Education						
Primary	15 (8.8%)	2 (13.3%)	13 (8.4%)	17 (9.9%)	0.040	32 (9.4%)
High School	99 (57.9%)	9 (60.0%)	89 (57.4%)	100 (58.5%)	0.012	199 (58.2%)
College/University	48 (28.1%)	3 (20.0%)	45 (29.0%)	45 (26.3%)	0.039	93 (27.2%)

Abbreviations: BMI = body mass index; Cor_JP = CorEvitas Japan; Max = maximum; Min = minimum; N = count of patients in the specified category; SD = standard deviation; Std Diff = absolute value of the standardized difference; TNFi = tumour necrosis factor inhibitor; vs = versus.

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Table 7_Cor_JP Clinical Characteristics Primary VTE Cohorts, Matched [Cor_JP]

	Baricitinib (N = 171)	TNFi (N = 171)	Std. Diff.	Total (N = 342)
History of MD-reported comorbidities (ever experienced)				
Cancer, non-NMSC	9 (5.3%)	11 (6.4%)	0.050	20 (5.8%)
Cancer, NMSC only	0 (0.0%)	1 (0.6%)	0.108	1 (0.3%)
Chronic Lung Disease (COPD, pulmonary fibrosis, asthma, interstitial lung disease)	16 (9.4%)	17 (9.9%)	0.020	33 (9.6%)
CVD-VTE risk (congestive heart failure, ventricular arrhythmia)	1 (0.6%)	1 (0.6%)	0.000	2 (0.6%)
CVD-MACE risk (unstable angina, congestive heart failure, ventricular arrhythmia, cardiovascular revascularization, coronary artery disease, TIA)	3 (1.8%)	3 (1.8%)	0.000	6 (1.8%)
Cardiovascular revascularization	2 (1.2%)	0 (0.0%)	0.154	2 (0.6%)
Congestive heart failure (hospitalized)	1 (0.6%)	0 (0.0%)	0.108	1 (0.3%)
Coronary artery disease	0 (0.0%)	1 (0.6%)	0.108	1 (0.3%)
Ischemic heart disease (myocardial infarction, unstable angina, revascularization, coronary artery disease, acute coronary syndrome)	4 (2.3%)	3 (1.8%)	0.041	7 (2.0%)
TIA	0 (0.0%)	0 (0.0%)		0 (0.0%)
Unstable angina	0 (0.0%)	1 (0.6%)	0.108	1 (0.3%)
Ventricular arrhythmia	0 (0.0%)	1 (0.6%)	0.108	1 (0.3%)
Diabetes mellitus	19 (11.1%)	23 (13.5%)	0.071	42 (12.3%)
Hyperlipidaemia	22 (12.9%)	24 (14.0%)	0.034	46 (13.5%)
Hypertension (hospitalized & non-hospitalized)	48 (28.1%)	51 (29.8%)	0.039	99 (28.9%)
Immune disorders	14 (8.2%)	12 (7.0%)	0.044	26 (7.6%)
Secondary Sjogren Syndrome	14 (8.2%)	12 (7.0%)	0.044	26 (7.6%)
Liver Disorder (hepatic event hospitalized & hepatic event non-hospitalized)	1 (0.6%)	1 (0.6%)	0.000	2 (0.6%)
Obesity, current	14 (8.2%)	9 (5.3%)	0.117	23 (6.7%)
Pregnancy, recent (current or since last visit)	0 (0.0%)	0 (0.0%)		0 (0.0%)
Smoking (current)	18 (10.5%)	20 (11.7%)	0.037	38 (11.1%)
RA severity (CDAI)				
n	171	171	0.058	342
Mean±SD	23.4 ±13.0	22.7 ±13.6		23.0 ±13.3
Median	21.0	20.0		20.1
Min, Max	1.0, 64.2	0.5, 67.2		0.5, 67.2
Prevalent outcomes				
VTE (at any time in the past)	0 (0.0%)	0 (0.0%)		0 (0.0%)
MACE (at any time in the past)	4 (2.3%)	3 (1.8%)	0.041	7 (2.0%)
Myocardial infarction	2 (1.2%)	2 (1.2%)	0.000	4 (1.2%)
Stroke	2 (1.2%)	1 (0.6%)	0.063	3 (0.9%)
Serious infection (at any time in the past)	17 (9.9%)	13 (7.6%)	0.083	30 (8.8%)
TB, hospitalized (at any time in the past)	0 (0.0%)	0 (0.0%)		0 (0.0%)

	Baricitinib (N = 171)	TNFi (N = 171)	Std. Diff.	Total (N = 342)
DMARD history				
Number of cDMARDs used (ever)				
0	14 (8.2%)	16 (9.4%)	0.041	30 (8.8%)
1	119 (69.6%)	118 (69.0%)	0.013	237 (69.3%)
2+	38 (22.2%)	37 (21.6%)	0.014	75 (21.9%)
Methotrexate (prior use)	146 (85.4%)	146 (85.4%)	0.000	292 (85.4%)
Number of bDMARDs used (ever)				
0	68 (39.8%)	94 (55.0%)	0.308	162 (47.4%)
1	51 (29.8%)	48 (28.1%)	0.039	99 (28.9%)
2+	52 (30.4%)	29 (17.0%)	0.320	81 (23.7%)
Prior bDMARD use[a]	103 (60.2%)	77 (45.0%)	0.308	180 (52.6%)
Prior TNFi bDMARD use	79 (46.2%)	45 (26.3%)	0.423	124 (36.3%)
Prior non-TNFi bDMARD use	64 (37.4%)	53 (31.0%)	0.136	117 (34.2%)
DMARD, current (baseline)				
cDMARD, concomitant use at baseline	105 (61.4%)	110 (64.3%)	0.061	215 (62.9%)
Methotrexate (current use)	94 (55.0%)	103 (60.2%)	0.107	197 (57.6%)
Prescription medication use, current (baseline)				
Cardiovascular medications				
Anticoagulant (coumadin/warfarin; patient-reported)	0 (0.0%)	0 (0.0%)		0 (0.0%)
Antihypertensives (blood pressure-lowering medication(s); patient-reported)	40 (23.4%)	42 (24.6%)	0.027	82 (24.0%)
Antiplatelet (Plavix; patient-reported)	1 (0.6%)	2 (1.2%)	0.063	3 (0.9%)
Nitrates (angina/nitrate medications; patient-reported)	2 (1.2%)	0 (0.0%)	0.154	2 (0.6%)
Lipid-lowering agents (cholesterol medication; patient-reported)	29 (17.0%)	26 (15.2%)	0.048	55 (16.1%)
RA-related				
Aspirin (includes non-prescription)	2 (1.2%)	5 (2.9%)	0.124	7 (2.0%)
Prednisone	40 (23.4%)	46 (26.9%)	0.081	86 (25.1%)
Vaccinations				
Shingles (ever)	1 (0.6%)	0 (0.0%)	0.108	1 (0.3%)

Abbreviations: bDMARDs = biologic disease-modifying antirheumatic drugs; CDAI = clinical disease activity index; cDMARDs = conventional disease-modifying antirheumatic drugs; COPD = chronic obstructive pulmonary disease; Cor_JP = CorEvitas Japan; CVD = cardiovascular disease; DMARD = disease-modifying antirheumatic drug; MACE = major adverse cardiovascular event; Max = maximum; Min = minimum; N = count of patients in the specified category; NMSC = non-melanoma skin cancer; RA = rheumatoid arthritis; SD = standard deviation; Std Diff = absolute value of the standardised difference; TB = tuberculosis; TIA = transient ischemic attack; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism.

Note: Many characteristics of the cohort are included in this table but propensity score matching is only expected to balance those risk factors listed in Table 66 for each outcome (eg, congestive heart failure) for VTE. Other factors are included for descriptive purposes only and may not be balanced across treatment groups but do not contribute to confounding bias (eg, diabetes) for VTE.

[a] Per CorEvitas' contractual obligations, reports on individual drugs are subject to review by individual market authorization holders who are also subscribers to the Corrona registry and have therefore not been included in this table.

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10.2.2.4.2. MACE

After propensity score matching, there were a total of 336 patients (168 each in the any baricitinib and TNFi cohorts) included in the analysis of VTE (Table 3_Cor_JP). The small size of the analysis cohort limits the ability to evaluate the characteristics of the treatment groups at baseline. Within the baricitinib cohort, almost all patients recorded 4 mg (n = 152) with n = 15 on 2 mg. On average, patients analysed were aged 61.1 years at baseline (range 22 to 86 years) and were majority (83.9%) female. Based on standardised differences >0.10 after propensity score matching, patients in the any baricitinib and TNFi cohorts were not dissimilar.

Clinical characteristics of patients at baseline are described in Table 8_Cor_JP. The most commonly observed conditions prevalent in at least 10% of patients were hyperlipidaemia (any baricitinib 13.1%, TNFi 13.1%), hypertension (any baricitinib 28%, TNFi 32.1%) and diabetes (any baricitinib 10.1%, TNFi 12.5%). Current smoking was less prevalent in the baricitinib compared to the TNFi cohort (any baricitinib 8.9%, TNFi 14.3%). With regard to RA severity, the CDAI score was not dissimilar between the baricitinib cohort and the TNFi cohort (baricitinib 23.4, TNFi 23.5).

RA treatment received prior to the index medication is described in Table 8_Cor_JP. The majority of patients reported use of at least 1 cDMARDs at any time (baricitinib 91.7%, TNFi 90.5%), with prior use of methotrexate recorded most frequently (baricitinib 85.1%, TNFi 85.7%). Concomitant use of cDMARDs at baseline was higher in the TNFi treated cohort (baricitinib 60.7%, TNFi 70.2%). Prior use of bDMARDs was observed more frequently among the any baricitinib treated cohort (59.5%) as compared to patients treated with TNFi (47.0%).

Table 3_Cor_JP Baseline Demographics, MACE Cohorts, Matched [Cor_JP]

	Any (N = 168)	Baricitinib 2 mg (N = 15)	Baricitinib 4 mg (N = 152)	TNFi (N = 168)	Std. Diff (Any vs TNFi)	Total (N = 336)
Age [yrs]						
n	168	15	152	168	0.035	336
Mean±SD	60.8 ±13.7	71.6 ± 8.1	59.7 ±13.7	61.3 ±15.8		61.1 ±14.8
Median	63.0	73.0	62.0	63.0		63.0
Min, Max	25.0, 85.0	56.0, 84.0	25.0, 85.0	22.0, 86.0		22.0, 86.0
≥ 65 years	78 (46.4%)	12 (80.0%)	65 (42.8%)	82 (48.8%)	0.048	160 (47.6%)
Gender						
Male	24 (14.3%)	0 (0.0%)	24 (15.8%)	30 (17.9%)	0.097	54 (16.1%)
Female	144 (85.7%)	15 (100.0%)	128 (84.2%)	138 (82.1%)		282 (83.9%)
BMI						
n	168	15	152	168	0.022	336
Mean±SD	22.7 ± 4.4	21.6 ± 4.4	22.8 ± 4.4	22.8 ± 4.1		22.7 ± 4.3
Median	21.8	22.0	21.8	22.2		22.0
Min, Max	16.1, 45.2	16.2, 33.7	16.1, 45.2	14.3, 47.1		14.3, 47.1
Smoking (current)	15 (8.9%)	2 (13.3%)	13 (8.6%)	24 (14.3%)	0.168	39 (11.6%)
Alcohol use	67 (39.9%)	7 (46.7%)	60 (39.5%)	72 (42.9%)	0.060	139 (41.4%)
Education						
Primary	14 (8.3%)	2 (13.3%)	12 (7.9%)	21 (12.5%)	0.137	35 (10.4%)
High School	99 (58.9%)	9 (60.0%)	89 (58.6%)	94 (56.0%)	0.060	193 (57.4%)
College/University	46 (27.4%)	3 (20.0%)	43 (28.3%)	44 (26.2%)	0.027	90 (26.8%)

Abbreviations: BMI = body mass index; Cor_JP = CorEvitas Japan; Max = maximum; Min = minimum; N = number of patients in the specified category; SD = standard deviation; Std Diff = absolute value of the standardized difference; TNFi = tumour necrosis factor inhibitor; vs = versus.

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Table 8_Cor_JP Clinical Characteristics, MACE Cohorts, Matched [Cor_JP]

	Baricitinib (N = 168)	TNFi (N = 168)	Std. Diff.	Total (N = 336)
History of MD-reported comorbidities (ever experienced)				
Cancer, non-NMSC	8 (4.8%)	17 (10.1%)	0.205	25 (7.4%)
Cancer, NMSC only	0 (0.0%)	1 (0.6%)	0.109	1 (0.3%)
Chronic Lung Disease (COPD, pulmonary fibrosis, asthma, interstitial lung disease)	16 (9.5%)	17 (10.1%)	0.020	33 (9.8%)
CVD-VTE risk (congestive heart failure, ventricular arrhythmia)	1 (0.6%)	0 (0.0%)	0.109	1 (0.3%)
CVD-MACE risk (unstable angina, congestive heart failure, ventricular arrhythmia, cardiovascular revascularization, coronary artery disease, TIA)	3 (1.8%)	2 (1.2%)	0.049	5 (1.5%)
Cardiovascular revascularization	2 (1.2%)	0 (0.0%)	0.155	2 (0.6%)
Congestive heart failure (hospitalized)	1 (0.6%)	0 (0.0%)	0.109	1 (0.3%)
Coronary artery disease	0 (0.0%)	1 (0.6%)	0.109	1 (0.3%)
Ischemic heart disease (myocardial infarction, unstable angina, revascularization, coronary artery disease, acute coronary syndrome)	4 (2.4%)	3 (1.8%)	0.042	7 (2.1%)
TIA	0 (0.0%)	0 (0.0%)		0 (0.0%)
Unstable angina	0 (0.0%)	1 (0.6%)	0.109	1 (0.3%)
Ventricular arrhythmia	0 (0.0%)	0 (0.0%)		0 (0.0%)
Diabetes mellitus	17 (10.1%)	21 (12.5%)	0.075	38 (11.3%)
Hyperlipidaemia	22 (13.1%)	22 (13.1%)	0.000	44 (13.1%)
Hypertension (hospitalized & non-hospitalized)	47 (28.0%)	54 (32.1%)	0.091	101 (30.1%)
Immune disorders	13 (7.7%)	15 (8.9%)	0.043	28 (8.3%)
Secondary Sjogren Syndrome	13 (7.7%)	15 (8.9%)	0.043	28 (8.3%)
Liver Disorder (hepatic event hospitalized & hepatic event non-hospitalized)	1 (0.6%)	1 (0.6%)	0.000	2 (0.6%)
Obesity, current	13 (7.7%)	8 (4.8%)	0.123	21 (6.3%)
Pregnancy, recent (current or since last visit)	0 (0.0%)	2 (1.2%)	0.155	2 (0.6%)
Smoking (current)	15 (8.9%)	24 (14.3%)	0.168	39 (11.6%)
RA severity (CDAI)				
n	168	168	0.003	336
Mean ± SD	23.4 ±13.1	23.5 ±14.1		23.4 ±13.6
Median	20.3	20.3		20.3
Min, Max	1.0, 64.2	0.5, 67.2		0.5, 67.2
Prevalent outcomes				
VTE (at any time in the past)	0 (0.0%)	3 (1.8%)	0.191	3 (0.9%)
MACE (at any time in the past)	4 (2.4%)	3 (1.8%)	0.042	7 (2.1%)
Myocardial infarction	2 (1.2%)	1 (0.6%)	0.063	3 (0.9%)
Stroke	2 (1.2%)	2 (1.2%)	0.000	4 (1.2%)
Serious infection (at any time in the past)	16 (9.5%)	14 (8.3%)	0.042	30 (8.9%)
TB, hospitalized (at any time in the past)	0 (0.0%)	0 (0.0%)		0 (0.0%)

	Baricitinib (N = 168)	TNFi (N = 168)	Std. Diff.	Total (N = 336)
DMARD history				
Number of cDMARDs used (ever)				
0	14 (8.3%)	16 (9.5%)	0.042	30 (8.9%)
1	117 (69.6%)	109 (64.9%)	0.102	226 (67.3%)
2+	37 (22.0%)	43 (25.6%)	0.084	80 (23.8%)
Methotrexate (prior use)	143 (85.1%)	144 (85.7%)	0.017	287 (85.4%)
Number of bDMARDs used (ever)				
0	68 (40.5%)	89 (53.0%)	0.253	157 (46.7%)
1	49 (29.2%)	51 (30.4%)	0.026	100 (29.8%)
2+	51 (30.4%)	28 (16.7%)	0.327	79 (23.5%)
Prior bDMARD use[a]	100 (59.5%)	79 (47.0%)	0.253	179 (53.3%)
Prior TNFi bDMARD use	76 (45.2%)	48 (28.6%)	0.351	124 (36.9%)
Prior non-TNFi bDMARD use	62 (36.9%)	51 (30.4%)	0.139	113 (33.6%)
DMARD, current (baseline)				
cDMARD, concomitant use at baseline	102 (60.7%)	118 (70.2%)	0.201	220 (65.5%)
Methotrexate (current use)	92 (54.8%)	111 (66.1%)	0.233	203 (60.4%)
Prescription medication use, current (baseline)				
Cardiovascular medications				
Anticoagulant (coumadin/warfarin; patient-reported)	0 (0.0%)	0 (0.0%)		0 (0.0%)
Antihypertensives (blood pressure lowering medication(s); patient-reported)	40 (23.8%)	46 (27.4%)	0.082	86 (25.6%)
Antiplatelet (Plavix; patient-reported)	1 (0.6%)	2 (1.2%)	0.063	3 (0.9%)
Nitrates (angina/nitrate medications; patient-reported)	2 (1.2%)	0 (0.0%)	0.155	2 (0.6%)
Lipid-lowering agents (cholesterol medication; patient-reported)	28 (16.7%)	29 (17.3%)	0.016	57 (17.0%)
RA-related				
Aspirin (includes non-prescription)	2 (1.2%)	4 (2.4%)	0.090	6 (1.8%)
Prednisone	39 (23.2%)	42 (25.0%)	0.042	81 (24.1%)
Vaccinations				
Shingles (ever)	1 (0.6%)	0 (0.0%)	0.109	1 (0.3%)

Abbreviations: bDMARDs = biologic disease-modifying antirheumatic drugs; CDAI = clinical disease activity index; cDMARDs = conventional disease-modifying antirheumatic drugs; COPD = chronic obstructive pulmonary disease; Cor_JP = CorEvitas Japan; CVD = cardiovascular disease; DMARD = disease-modifying antirheumatic drug; MACE = major adverse cardiovascular event; Max = maximum; Min = minimum; N = count of patients in the specified category; NMSC = non-melanoma skin cancer; RA = rheumatoid arthritis; SD = standard deviation; Std Diff = absolute value of the standardised difference; TB = tuberculosis; TIA = transient ischemic attack; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism.

Note: Many characteristics of the cohort are included in this table but propensity score matching is only expected to balance those risk factors listed in Table 66 for each outcome (eg, congestive heart failure) for VTE. Other factors are included for descriptive purposes only and may not be balanced across treatment groups but do not contribute to confounding bias (eg, diabetes) for VTE.

[a] Per CorEvitas' contractual obligations, reports on individual drugs are subject to review by individual market authorization holders who are also subscribers to the Corrona registry and have therefore not been included in this table.

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10.2.2.4.3. Serious infections

After propensity score matching, there were a total of 340 patients (170 each in the any baricitinib and TNFi cohorts) included in the analysis of VTE (Annex 14, Table 4). The small size of the analysis cohort limits the ability to evaluate the characteristics of the treatment groups at baseline. Within the baricitinib cohort, almost all patients recorded 4 mg (n = 154) with n = 15 on 2 mg. On average, patients analysed were aged 60.9 years at baseline (range 22 to 85 years) and were majority (83.2%) female. Based on standardised differences >0.10 after propensity score matching, patients in the any baricitinib and TNFi cohorts were not dissimilar.

Clinical characteristics of patients at baseline are described in Annex 14, Table 9. The most commonly observed conditions prevalent in at least 10% of patients were hyperlipidaemia (any baricitinib 12.9%, TNFi 14.1%), hypertension (any baricitinib 28.2%, TNFi 33.5%) and diabetes (any baricitinib 10.6%, TNFi 12.4%). Current smoking was also prevalent in both treatment cohorts (any baricitinib 9.4%, TNFi 12.4%). With regard to RA severity, the CDAI score was slightly higher in the baricitinib cohort compared to the TNFi cohort (baricitinib 23.5, TNFi 23.9).

RA treatment received prior to the index medication is described in Annex 14, Table 9. The majority of patients reported ever use of at least 1 cDMARDs (any baricitinib 91.8%, TNFi 91.8%), with methotrexate recorded most frequently (any baricitinib 85.3%, TNFi 87.1%). Concomitant use of cDMARDs at baseline was slightly higher in the TNFi treated cohort (baricitinib 60.0%, TNFi 70.0%). Prior use of bDMARDs was observed more frequently among the any baricitinib treated cohort (60.0%) as compared to patients treated with TNFi (48.2%).

10.2.2.5. JMDC

There were 243 eligible patients treated with baricitinib (143 with 4 mg and 100 with 2 mg) and 1,721 eligible TNFi patients in the JMDC data. Demographic and clinical characteristics for these unmatched cohorts are in Annex 15. From these unmatched cohorts, the number of patients

included in analyses of VTE, MACE, or serious infection after 1:1 matching varies. Details of these analysis-specific cohorts follow.

10.2.2.5.1. VTE

After propensity score matching, there were a total of 426 patients (213 each in the any baricitinib and TNFi cohorts) included in the analysis of VTE (Table 2_JMDC). Within the baricitinib cohort, 121 patients recorded 4 mg and 92 recorded 2 mg. On average, patients analysed were aged 51.61 years at baseline (range 19 to 74 years) and were majority (77.7%) female. Based on standardised differences >0.10 after propensity score matching, patients treated with any baricitinib were slightly less often aged ≥65 years than the TNFi cohort (baricitinib 7.0%; TNFi 9.9%). The small size of the baricitinib cohort limits the ability to evaluate the characteristics of patients on 4 vs. 2 mg; however, the patients on 4 mg tended to be slightly younger.

Clinical characteristics of patients at baseline are described in Table 7_JMDC. Patients within the JMDC had much fewer comorbidity burden compared to other data sources (US and European). Noting the lower overall prevalence, the most commonly observed conditions with at least 10 total cases were chronic lung disease (any baricitinib 15.5%, TNFi 9.4%), dyslipidaemia (any baricitinib 7.5%, TNFi 6.6%), diabetes (any baricitinib 2.8%, TNFi 1.9%), and cancer (any baricitinib 4.2%, TNFi 3.8%). No smokers were identified with the definition used in insurance claims databases (see Section 9.4.3). In the clinical characteristics table below, smoking is defined based on information recorded in the variable “Annual health checkup – Smoking habit”. With regard to RA severity, the CIRAS score was nearly identical (baricitinib 6.59, TNFi 6.57).

RA treatment received prior to the index medication is described in Table 7_JMDC. The vast majority of patients used cDMARDs (any baricitinib 84.5%, TNFi 85%), with methotrexate recorded most frequently (any baricitinib 75.1%, TNFi 74.2%). Patients treated with baricitinib and TNFi recorded similar proportions of >1 concomitant cDMARD (any baricitinib 16.4%, TNFi 17.4%). Proportion of patients with prior use of bDMARDs was similar in the baricitinib and TNFi cohorts (any baricitinib 49.8%, TNFi 50.7%). Tocilizumab was the most frequently recorded prior bDMARD (any baricitinib 19.2%, TNFi 18.3%). 10 days

Baseline healthcare resource utilisation was similar across the baricitinib and TNFi cohorts in the JMDC (Table 12B_JMDC). Note that the table reports visit days per patient (ie, at most 1 visit per day), but the propensity scores model controlled for the total number of visits during the period (ie, more than one visit; see Table 12A_JMDC in Annex 15) could occur per day.