Abbreviated Final Study Report for I4V-MC-B004

[Pangaea ID 2018-6958]

A Retrospective Cohort Study to Assess the Long-Term Safety of Baricitinib Compared with Other Therapies Used in the Treatment of Adults with Moderate-to-Severe Rheumatoid Arthritis in the Course of Routine Clinical Care

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PASS Information

Title	Study I4V-MC-B004: A Retrospective Cohort Study to Assess the Long-Term Safety of Baricitinib Compared with Other Therapies Used in the Treatment of Adults with Moderate-to-Severe Rheumatoid Arthritis in the Course of Routine Clinical Care
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Marketing authorisation holder(s)	Eli Lilly Nederland B.V, Papendorpseweg 83, 3528BJ Utrecht, The Netherlands
Joint PASS	No
Research question and objectives	The goal of this study was to monitor the incidence and nature of key serious infections, MACE, VTE, and malignancies amongst patients exposed long term to baricitinib compared to patients treated long-term with bDMARDs or cDMARDs. This goal was to be achieved through the following specific objectives: 1) To assess and compare the risk of the following aggregate outcomes: serious infections and opportunistic infections, MACE, malignancies, and VTE, among patients with long-term exposure to baricitinib compared to similar patients with RA with long-term exposure to other indicated medications 2)To describe the incidence rates of the following individual outcomes: lymphoma; herpes zoster; opportunistic infections; rhabdomyolysis; myelosuppression (agranulocytosis); hyperlipidaemia (hypercholesterolaemia, hypertriglyceridaemia); gastrointestinal perforations; and evidence of drug-induced liver injury A secondary objective was to describe the incidence of the above outcomes in very elderly patients (aged ≥75 years old).
Country(-ies) of study	United States
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Signature of principal investigator	Signature on file

Abbreviations: ATC = Anatomical Therapeutic Chemical; bDMARD = biologic disease-modifying antirheumatic drug; cDMARD = conventional disease-modifying antirheumatic drug; EU PAS = European Union electronic Register of Post-Authorisation Studies; MACE = major adverse cardiovascular event; PASS = postauthorisation safety study; RA = rheumatoid arthritis; VTE = venous thromboembolism.

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1. List of Abbreviations

Term	Definition
AE	adverse event
bDMARD	biologic disease-modifying antirheumatic drug
cDMARD	conventional disease-modifying antirheumatic drug
DMARD	disease-modifying antirheumatic drug
ED	emergency department
EU PAS	European Union electronic Register of Post-Authorisation Studies
HCPCS	Health Care Common Procedure Coding System
HIRD	HealthCore® Integrated Research Database℠
JAK	Janus kinase
JAKi	Janus kinase inhibitor
MACE	major adverse cardiovascular event
MI	myocardial infarction
NDC	National Drug Code
PASS	post-authorisation safety study
PML	progressive multifocal leukoencephalopathy
RA	rheumatoid arthritis
SD	standard deviation
TNF	antitumour necrosis factor
VTE	venous thromboembolism

2. Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	5 years after market availability in the US, estimated Q1 2024	14 Oct 2019	
Registration in the EU PAS register	Prior to extraction of data	04 April 2019	
Study progress report 1	Included annually in baricitinib PBRER/PSUR after start of data collection	Done annually in the EU Regional Appendix 4* of the annual PSUR-PBRER	Updates included in • 2019 with PSUR-PBRER04 • 2020 PSUR-PBRER06 • 2021 PSUR-PBRER08 • 2022 PSUR-PBRER10
Final report of study results	30 June 2030	See Page 1	

Abbreviations: EU PAS = European Union electronic Register of Post-Authorisation Studies; PBRER = periodic benefit-risk evaluation report; PSUR = periodic safety update report; Q1 = Quarter 1.

* The annual progress report submitted with PSUR04 in 2019 was included within a cover letter accompanying the submission. All subsequent progress reports were in EU Regional Appendix 4.

3. Rationale and Background

RA is a chronic autoimmune inflammatory disease characterised by progressive joint destruction, systemic complications, and reduced survival (Smolen and Steiner 2003; Colmegna et al. 2012). It has a profoundly negative impact on the quality of life of those affected, particularly among those with moderate-to-severe disease (Choy and Panayi 2001; Allaire et al. 2009; Wasserman 2011).

Baricitinib is a JAK1/JAK2 selective inhibitor approved in Europe for the treatment of moderate-to-severe RA. In clinical studies of patients with RA, baricitinib produced clinically meaningful improvements across all relevant domains of efficacy, including signs and symptoms, low disease activity and remission rates, physical function, and patient-reported outcomes, as well as inhibiting progressive radiographic joint damage. Data from clinical trials in patients with RA evaluated and demonstrated that baricitinib is effective and generally well tolerated; however, the long-term safety profile among patients with RA in routine clinical practice had not been characterized at the time of approval.

RA is associated with a number of serious comorbidities (CDC 2020). Obesity and smoking are risk factors for RA, consequently, patients with RA have a higher prevalence of these risk factors than age-matched controls (Crowson et al. 2013; Chang et al. 2014). In addition, among patients with RA, there is a high prevalence of comorbidities including MI, stroke, malignancy, VTE, infections, hypertension, and gastrointestinal ulcer (Matta et al. 2009; Chung et al. 2014; Dougados et al. 2014). At the time of study commitment, The EU RMP for baricitinib then (v.6.0) described 1 important identified risk (herpes zoster) and 9 important potential risks (malignancies [including lymphoma and typically virus-induced malignancies such as cervical and many oropharyngeal cancers], serious and opportunistic infections [including tuberculosis, *Candida* infections, PML], myelosuppression [agranulocytosis], myopathy including rhabdomyolysis, potential for drug-induced liver injury, gastrointestinal perforations, MACE, VTE, and foetal malformation following exposure in utero); this study was meant to provide data from administrative claims on the incidence of these conditions among patients exposed to baricitinib and other RA therapies.

The long-term safety of biologics and other new therapies entering the market is of interest to rheumatologists, regulators, and health care professionals (Ramiro et al. 2017). The majority of clinical trials collect information about safety for 6 to 12 months in a comparative manner against placebo or active control, but the long-term safety of new therapies may remain unclear. This is especially true for outcomes with long latency periods or that occur infrequently, such as cancer and cardiovascular disease, but could also include the occurrence of serious infections after prolonged exposure to medications, as may occur when treating a chronic disease such as RA.

The goal of this study was to monitor the incidence and nature of key serious infections, MACE, VTE, and malignancies amongst patients exposed long-term to baricitinib compared to patients treated long-term with bDMARDs or cDMARDs.

As part of an Article 20 referral in Europe for all JAKi (EMA [WWW]), the conduct of Study B004 and Study I4V-MC-B003 were terminated in agreement with the Committee for Medicinal Products for Human Use based on the following rationale:

- Both studies relied on enrolment and identification, respectively, in the US, where low market uptake of baricitinib has markedly impacted the ability to identify baricitinib-exposed patients to include in the studies.
- The sample sizes required to conduct comparative analyses are not feasible to attain.
- Addition of Studies I4V-MC-JAJA (JAJA) and I4V-MC-JAJD (JAJD) as a pharmacovigilance activity in the EU RMP addressed the same objectives of these 2 studies, and also provides the additional rigour of a randomised study design. (Of note, subsequent to the Article 20 referral, final positive opinion has been reached in November 2023 to remove JAJA/JAJD from the EU RMP).
- Long-term safety information will be available from Study I4V-MC-B011, which provides extended longitudinal follow-up, in high-quality Nordic data sources, for assessing long-term outcomes, such as malignancy.

With the termination of Study I4V-MC-B004 (B004), this abbreviated study report is meant to provide a high-level summary of the design of the study as well as information on participants that were available up until the time the study was terminated.

4. Research Question and Objectives

The goal of this study was to monitor the incidence and nature of key serious infections, MACE, VTE, and malignancies amongst patients exposed long term to baricitinib compared to patients treated long-term with bDMARDs or cDMARDs. This goal was to be achieved through the following specific objectives:

1. To assess and compare the risk of the following aggregate outcomes: serious infections (including herpes zoster) and opportunistic infections (including tuberculosis, *Candida* infections, and PML); MACE; malignancies (including lymphoma and typically virus-induced malignancies, such as cervical and many oropharyngeal cancers); and VTE, among patients with long-term exposure to baricitinib compared to similar patients with RA with long-term exposure to other indicated medications.
2. To describe the incidence rates of the following individual outcomes: lymphoma; herpes zoster; opportunistic infections (such as tuberculosis, *Candida*, and PML); rhabdomyolysis; myelosuppression (agranulocytosis); hyperlipidaemia (hypercholesterolaemia, hypertriglyceridaemia); gastrointestinal perforations; and evidence of drug-induced liver injury.

A secondary objective was to describe the incidence of the above outcomes in very elderly patients (aged ≥75 years old).

5. Research Methods

5.1. Study Design

This was a retrospective cohort study using data from an administrative claims database, the HIRD, and selected outcomes were to be confirmed using clinical information. The data source included information on patient demographics, RA diagnosis, records of filled prescriptions or administrations of RA treatment, comorbidities, hospitalisations, and medication use, among others.

5.2. Subjects

This study aimed to include adult patients with RA enrolled in the US health care database during the period of 2018 to 2030 who, during the study period, were exposed to baricitinib or other approved DMARDs used to treat RA. The study aimed to include only new users defined as patients who were not exposed to the same DMARD within a 12-month period. Some additional or alternate exclusions were planned for specific analyses. The study inclusion and exclusion criteria for specific analyses are detailed below.

Inclusion criteria

1. The patient has 2 RA diagnosis codes from physician encounters on at least 2 separate visits (on different dates) and initiated baricitinib or a different DMARD* (date of treatment initiation defined as index date).
2. The patient is aged at least 18 years or older on the index date,
3. The patient has continuous medical and prescription drug coverage for a specified minimum duration prior to the index date. Primary analyses would include only those patients with at least 12 months of enrolment, and medical and prescription drug coverage prior to index date. A sensitivity analysis using 6 months of enrolment was also planned.

   *Initiation of a DMARD was defined as dispensing of one of the following DMARDs without prior dispensing of the DMARD during the baseline period (at least 12 months, but all available data will be used). Eligible conventional DMARDs included methotrexate, hydroxychloroquine, leflunomide, and sulfasalazine. Eligible bDMARDs included abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, sarilumab, and tocilizumab. Eligible targeted synthetic DMARDs included tofacitinib. Azathioprine, cyclosporine, minocycline, and gold were not included due to infrequent use for RA treatment, based on the 2015 American College of Rheumatology Guideline for the treatment of RA (Singh et al. 2016).

Exclusion criteria

1. The patient has ≥1 filled prescription for a JAKi prior to the index date.

Outcome-specific exclusions:

- Serious infection: ED visit or inpatient hospitalization with a discharge diagnosis code for infection within 6 months before or on the index date
- MACE: ED visit or inpatient hospitalization with a discharge diagnosis code for acute MI or stroke within 6 months before or on the index date
- VTE: ED visit or inpatient hospitalization with a discharge diagnosis code for VTE within 6 months before or on the index date
- Malignancy: ED visit, hospitalization, or outpatient visit with a cancer diagnosis code within 6 months before or on the index date

5.3. Variables

Data on patient demographics (age, sex, geographic region); history of prior RA treatment; prior medical history (for example, comorbidities, prior VTE); hospitalizations; concomitant medication use; and health care resource utilisation were to be assessed. All information was obtained via administrative claims data (that is, the HIRD data). Selected outcomes were to be confirmed based on additional clinical information, as feasible. The following sections detail other variables available for this study.

Drug exposure

Exposure to baricitinib or other medications indicated for the treatment of RA were ascertained based on the NDC or Generic Product Identifier for outpatient pharmacy dispensings and based on HCPCS for injections or infusions that occur in a health care setting. Table B004.5.1 displays medications available at the time of study protocol development. Newly available RA medications would have been included as they were approved.

Table B004.5.1 Eligible Medications for Identifying Patients Treated for Rheumatoid Arthritis

Conventional Disease-Modifying Antirheumatic Drugs	Biologic Disease-Modifying Antirheumatic Drugs		Targeted Synthetic Disease-Modifying Antirheumatic Drugs
Methotrexate	Abatacept	Golimumab	Tofacitinib
Sulfasalazine	Adalimumab	Infliximab	
Hydroxychloroquine	Certolizumab pegol	Rituximab	
Leflunomide	Etanercept	Sarilumab	
		Tocilizumab	

Outcomes

The aggregated outcomes were those relevant for the primary objective and included:

- Serious infections
- MACE
- Malignancy, excluding non-melanoma skin cancer, and

- VTE

Individual outcomes were also to be assessed for the secondary objective. See Section 4 for a listing of the planned individual outcomes and the study protocol for details on how each outcome was to be defined.

5.4. Data Sources

The study was conducted using the HIRD, a large health care administrative claims database maintained by HealthCore for use in health outcomes and pharmacoepidemiologic research. The HIRD includes longitudinal medical and pharmacy claims data from health plan members across the US. Member enrolment, medical care (professional and facility claims), outpatient prescription drug use, and health care utilisation may be tracked for health plan members in the database dating back to January 2006, with diagnoses recorded in the International Classification of Diseases -10 since October 2015, with dispensing of self-administered medications recorded in the NDC, and with medications administered at physician offices, hospitals, and outpatient infusion centres, recorded in current procedural terminology code/HCPCS codes. The HealthCore Integrated Research Environment has the ability to link the claims data in the HIRD to complementary data sources, including inpatient and outpatient medical records and national vital statistics records, such as the National Death Index .

5.5. Bias

Because no comparative analysis was performed due to termination of the study (see Sections 5.7 and 8), no adjustment for bias, as detailed in the protocol, was needed and therefore not performed.

5.6. Study Size

Sample size estimates and statistical power calculations were generated using the background incidence rate of MACE from the Corrona Rheumatoid Arthritis Registry (now the CorEvitas® registry). The study size was selected to ensure adequate ability to detect a 1.5-fold increase in the risk of MACE among the baricitinib-treated cohort relative to patients in the biologic medication cohort. Based on the assumptions detailed in the protocol, it was determined that 4000 baricitinib exposed patients and 4000 bDMARD exposed patients would have been needed to achieve 80% power to detect a hazard ratio of 1.5.

5.7. Statistical Methods

Planned statistical analyses can be found in the approved protocol (Version 1.0). This protocol outlines how data obtained from this database was to be used to evaluate the safety of baricitinib in routine clinical practice. Due to termination of the study because of insufficient enrolment, the planned comparative analyses were not executed.

This abbreviated report presents only a summary of the number of patients enrolled, descriptive characteristics for those patients, and occurrence of outcomes up to study termination. Essentially, Study B004 is a single arm descriptive study describing patients treated with

baricitinib. For continuous variables, the mean (SD) and median (interquartile range) were reported. For categorical variables, the number and percentage are presented.

Patient demographics

The distribution of patient demographic characteristics and use of cDMARDs and bDMARDs prior to baricitinib initiation among all identified new users meeting the non–outcome-specific inclusion and exclusion criteria were described.

Patient accrual

Among eligible baricitinib new users, patient accrual by calendar time from June 01, 2018, to October 01, 2021, was plotted graphically.

Duration of treatment

Among new users of baricitinib, treatment episodes were constructed by appending consecutive exposure periods, defined as day's supply of baricitinib plus an allowable gap of 30 days. The duration of the individual patient's initial treatment episodes was summed over the number of patients to determine the total number of person-years of exposure to baricitinib.

Outcomes

Occurrence of serious infection, MACE, VTE, and malignancy were extracted and summarised from HIRD. Based on the agreements between HealthCore and its parent company (Anthem®), legal restrictions on disclosure of individual level data require masking of any cell in a table with a count less than or equal to 10, which is shown as "≤10."

6. Results

6.1. Participants

Assembly of the baricitinib cohort is shown in attrition Table B004.6.1. The study identified 445 patients who initiated baricitinib between 2018 and 2021. Among them, 188 new users satisfied the inclusion criteria before applying the outcome-specific exclusions. The greatest attrition resulted from prior JAKi use any time before the index date (n=161), and the requirement of having continuous enrolment in the 183 days before index date (n=59). Among the outcome-specific exclusions, prior serious infection, prior MACE, and prior malignancy further excluded ≤10 patients, and prior VTE excluded no patients.

Table B004.6.1 Assembly of the Baricitinib New User Cohort from June 01, 2018, to October 01, 2020

	Attrition Steps	Number of Patients Identified	Number of Patients Excluded	% of Patients Excluded from Previous Step
Inclusion criteria				
≥1 prescription of study medication	**1**	445	N/A	N/A
≥18 years of age on index date[a]	**2**	NR	≤10	
Continuous enrolment before index date[a]	**3**			
≥183 days	**3a**	382	59	13.38%
≥365 days	**3b**	363	78	17.69%
≥2 rheumatoid arthritis diagnosis codes on distinct dates that are at least 7 days apart any time before the index date[b]	**4**	349	33	8.64%
Exclusion criteria				
JAK inhibitor use any time before index date (using all available baseline data)[a,c]	**5**	188	161	46.13%
Outcome specific exclusions	**6**			
Serious infection within 6 months before or on index date[a]	**6a**	NR	≤10	
MACE within 6 months before or on index date[a]	**6b**	NR	≤10	
VTE within 6 months before or on index date[a]	**6c**	NR	0	0.00%
Malignancy within 6 months before or on index date[a]	**6d**	NR	≤10	

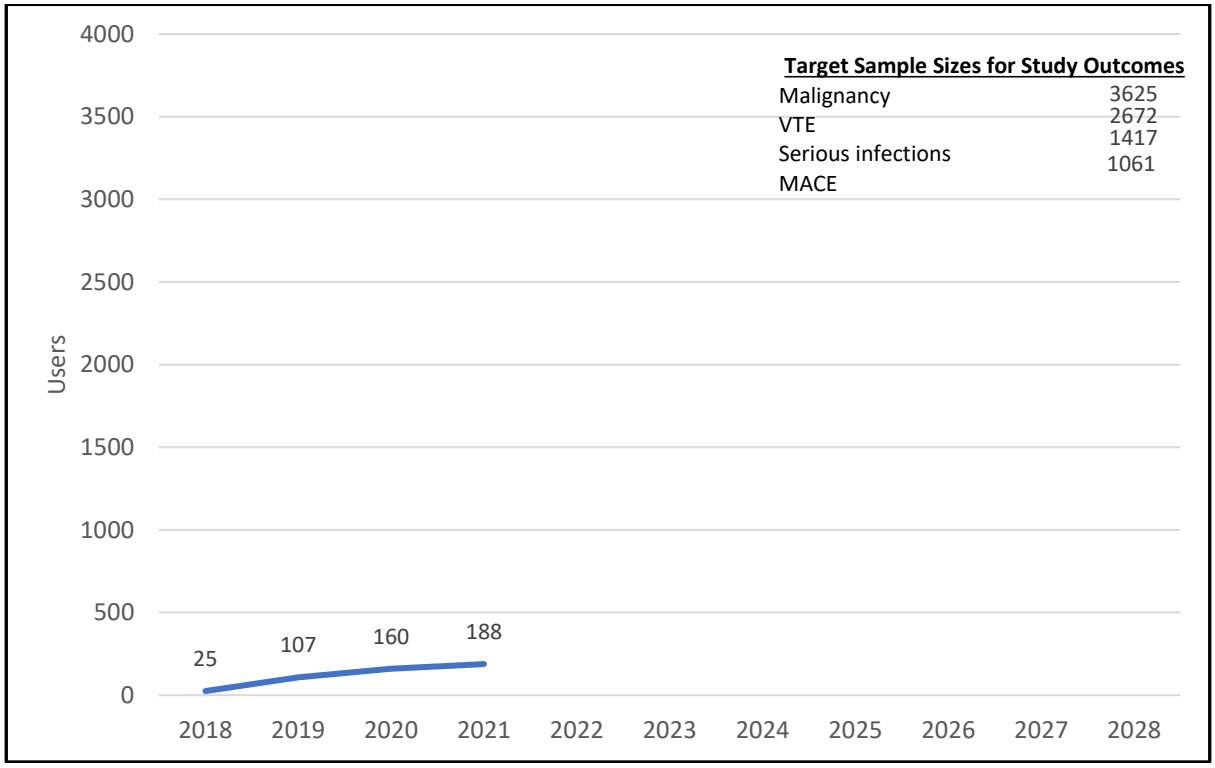
Abbreviations: JAK = Janus kinase; MACE = major adverse cardiac event; N/A = not applicable; NR = not reported; VTE = venous thromboembolism.

[a] Index date is the date of the first filled prescription of baricitinib during the monitoring period.

[b] Following steps based on continuous enrolment ≥183 days (Step 3a) instead of ≥365 days (Step 3b).

[c] N=188 from this step is the population for Table B004.6.2 and Figure B004.6.1.

Accrual of patients and exposed person-time are presented in Figure B004.6.1 and Table B004.6.1. Twenty-five new users satisfied the inclusion criteria between June 01, 2018, and October 01, 2018. A further 82 eligible patients were identified from October 01, 2018, to October 01, 2019; 53 from October 01, 2019, to October 01, 2020; and 28 patients from October 01, 2020, to October 01, 2021. The 188 baricitinib new users contributed 105 person-years of follow-up or about 6 months per patient on average.



Abbreviation: MACE = major adverse cardiac event; VTE = venous thromboembolism.
Note: Please note accrual targets are from the study protocol.

Figure B004.6.1 Accrual of baricitinib new users

6.2. Descriptive Data

The distribution of demographic characteristics and prior DMARD use are presented in Table B004.6.2. The majority of patients were 41 to 64 years of age (n=136, 72%) with the mean age of 55 years (SD=12 years). The majority of patients were female (n=159, 85%). The most frequently used cDMARD in the 183 days prior to the index data was hydroxychloroquine (n=78, 41%), followed by leflunomide (n=61, 32%). One hundred thirty-four patients (71%) used a TNF biologic DMARD in the 183 days prior to the index date, while 96 patients (51%) used a non-TNF biologic DMARD during that period.

Table B004.6.2 Distribution of Demographic Characteristics Among Baricitinib New Users (N=188)

Patient demographics	
Age group (years)	**N (%)**
18-40	20 (10.64%)
41-64	136 (72.34%)
65 or older	32 (17.02%)
Age (years)	
Mean (SD)	55.16 (12.28)
Median (IQR)	56 (48-63)
Min-Max	20-88
Sex	**N (%)**
Female	159 (84.57%)
Male	29 (15.43%)
Census region[a]	**N (%)**
Midwest	53 (29.12%)
Northeast	16 (8.79%)
South	58 (31.87%)
West	55 (30.22%)
Calendar year of treatment initiation	**N (%)**
2018	44 (23.40%)
2019	71 (37.77%)
2020	49 (26.06%)
2021	24 (12.77%)
Duration of first treatment episode (months)[b]	
Mean (SD)	6.71 (6.30)
Median (IQR)	4.27 (1.97-8.67)
Total person-years of first treatment episode[c]	105.09
Prior use of conventional DMARDs	**N (%)**
Methotrexate	13 (6.91%)
Sulfasalazine	32 (17.02%)
Hydroxychloroquine	78 (41.49%)
Leflunomide	61 (32.45%)
Number of conventional DMARDs	
0	74 (39.36%)
1	57 (30.32%)
2 or more	57 (30.32%)
Prior use of biologic DMARD	**N (%)**
Anti-TNF	134 (71.28%)
Non-TNF	96 (51.06%)
Number of biologic DMARDs	**N (%)**
0	27 (14.36%)

1	64 (34.04%)
2 or more	97 (51.60%)

Abbreviations: DMARD = disease-modifying antirheumatic drug; IQR = interquartile range; Max = maximum; Min = minimum; N =number ; SD = standard deviation; TNF = tumour necrosis factor.

[a] The percentages are calculated from available data on census region (N=182).

[b] Months are calculated as days/30.4375.

[c] Years are calculated as days/365.25.

6.3. Outcome Data

The study identified ≤10 incident cases each of serious infection, VTE, and malignancy (Table B004.6.3). There were no incident cases of MACE using the primary position of inpatient diagnosis. When inpatient diagnosis in any position was considered for MACE, the number of incident cases was ≤10.

Table B004.6.3 Number of Incident Outcomes Occurring During the First Baricitinib Treatment Episode between June 01, 2018, and October 01, 2020

	Inpatient Diagnosis, Primary Position*	Inpatient Diagnosis, Any Position**
Serious infection	≤10	
MACE	0	≤10
VTE	≤10	
Malignancy, excluding NMSC	≤10	

Abbreviation: MACE = major adverse cardiac event; NMSC = nonmelanoma skin cancer; VTE = venous thromboembolism.

* The primary position refers to the diagnostic code associated with the most serious and/or resource-intensive activity during the hospitalization or the inpatient encounter.

** A diagnostic code in any position includes secondary diagnosis or “other diagnosis”, which may encompass conditions that coexist at the time of admission, or develop subsequently, and that affect the patient care during the current inpatient episode.

Note: Please note outcomes identified in claims are not validated.

6.4. Adverse Events/Adverse Reactions

Assessment of the protocol defined AEs was not completed per protocol definitions of events. However, a summary of the query of events consistent with the protocol defined AEs was provided in Section 6.3.

7. Discussion

7.1. Key Results

Study B004 was far short of the enrolment trajectory needed to enrol a sufficient number of patients to power comparative analyses (as detailed in Section 5.6). Low market uptake of baricitinib in the US was considered the driving factor for low study numbers.

Among the 445 patients that initiated baricitinib during the study period, 188 new users of baricitinib satisfied the eligibility criteria and contributed a total of 105 person-years of follow-up while exposed to baricitinib. New users of baricitinib were on average 55 years old, most were female (85%), and 71% had used an anti-TNF biologic 183 days prior to index date.

During the follow-up, the numbers of serious infection, MACE, VTE, and malignancy were less than or equal to 10 for each event. No incidents of MACE were identified when restricting to the primary diagnosis.

7.2. Interpretation and Generalisability

Given the limited sample size in Study B004 and study termination, full comparative analyses for the safety events of interest relative to patients with RA treated with other systemic medications were not executed. Thus, no interpretations towards the research objectives can be made.

Furthermore, the B004 study population characteristics are considered representative only of US patients treated with baricitinib for RA and not generalizable to a broader population of patients with RA treated with baricitinib. The US prescribing information for baricitinib in patients with RA only includes a 2-mg dosing option, whereas other major geographies (for example, Europe and Japan) include options for a 4- and 2-mg dosing option with the low 2-mg dose typically reserved for more comorbid, older patients than the 4-mg dose.

8. Conclusions

Study I4V-MC-B004 was terminated in agreement with European regulators as part of the Article 20 referral outcome. Only descriptive information for baricitinib treated patients is available. Because Study B004 was far short of the enrolment trajectory, with insufficient number of patients to power comparative analyses, no comparative analyses were executed, and therefore, no interpretations or conclusions can be drawn from this study.

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