Abbreviated Final Study Report for I4V-MC-B003

(Pangea ID 2017-5915)

A Prospective Observational Study to Assess the Long-Term Safety of Baricitinib Compared With Other Therapies Used in the Treatment of Adults in the United States With Moderate-to-Severe Rheumatoid Arthritis in the Course of Routine Clinical Care

Document ID: VV-PVG-107844

PASS Information

Title	Study I4V-MC-B003: A Prospective Observational Study to Assess the Long-Term Safety of Baricitinib Compared With Other Therapies Used in the Treatment of Adults in the United States With Moderate-to-Severe Rheumatoid Arthritis in the Course of Routine Clinical Care
Version identifier of the final study report	Number 1.0
Date of last version of the final study report	Not applicable
EU PAS register number	EUPAS25139
Active substance	Baricitinib; ATC code L04AA37
Medicinal product(s)	Olumiant® 2 mg and 4 mg film-coated tablets
Product reference	EU/1/16/1170
Procedure number	EMEA/H/C/004085
Marketing authorization holder(s)	Eli Lilly Nederland BV, Papendorpseweg 83, 3528BJ Utrecht, The Netherlands
Joint PASS	No
Research question and objectives	The primary objectives of this study were to 1. compare the incidence rates of key aggregate outcomes, including serious and opportunistic infections, MACE, malignancies, and VTE among patients with long-term exposure to baricitinib compared with patients treated long-term with bDMARDS or cDMARDS. 2. describe incidence rates of the following individual outcomes: lymphoma, herpes zoster, TB, *Candida* infections, PML, rhabdomyolysis, myelosuppression, hyperlipidemia, gastrointestinal perforations, and evidence of drug-induced liver injury. A secondary objective was to describe incidence of above outcomes in very elderly patients (aged ≥75 years).
Country of study	United States
Author	Lilly Global Patient Safety Pharmacoepidemiologist Eli Lilly and Company Lilly Corporate Center Indianapolis, Indiana 46285 United States
Signature of principal investigator	Signature on file

Abbreviations: bDMARDS = biologic disease modifying anti-rheumatic drug; cDMARDS = conventional disease modifying anti-rheumatic drug; MACE = major adverse cardiovascular event; PAS = post-authorization studies; PASS = post-authorization safety study; PML = progressive multifocal leukoencephalopathy; TB = tuberculosis; VTE = venous thromboembolism.

Marketing Authorization Holder

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1. List of Abbreviations

Term	Definition
AE	adverse event
B003	Study I4V-MC-B003
bDMARD	biologic disease modifying anti-rheumatic drug
cDMARD	conventional disease modifying anti-rheumatic drug
CHMP	Committee for Medicinal Products for Human Use
CorEvitas	Consortium of Rheumatology Researchers of North America (previously CORRONA, LLC)
CORRONA	Consortium of Rheumatology Researchers of North America (currently CorEvitas, LLC)
JAJA	Study I4V-MC-JAJA
JAJD	Study I4V-MC-JAJD
JAK	Janus kinase
JAKi	Janus kinase inhibitor
Lilly	Eli Lilly and Company
MACE	major adverse cardiovascular event
PASS	post-authorization safety study
PML	progressive multifocal leukoencephalopathy
RA	rheumatoid arthritis
RMP	risk management plan
TAE	targeted adverse event
TB	tuberculosis
tsDMARD	targeted synthetic disease modifying anti-rheumatic drug
VTE	venous thromboembolism

2. Milestones

Milestone	Planned Date	Actual Date	Comments
Start of data collection	31 March 2019	31 July 2018	
Registration in the EU PAS register	Prior to start of data collection	03 April 2019	
Study progress reports	Included annually in baricitinib PSUR-PBRER after start of data collection	Submitted annually in the EU Regional Appendix 4* of the annual PSUR-PBRER	2019 with PSUR-PBRER04 2020 PSUR-PBRER06 2021 PSUR-PBRER08 2022 PSUR-PBRER10
Final report of study results	31 December 2031	See date on Page 1	

Abbreviations: PAS = Post Authorization Safety; PBRER = Periodic Benefit-Risk Evaluation Report; PSUR = Periodic Safety Update Report.

* 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 characterized 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 February 2017. 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 have been evaluated and demonstrate 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 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:

- myocardial infarction
- stroke
- malignancy
- VTE
- infections
- hypertension, and
- gastrointestinal ulcer (Matta et al. 2009; Chung et al. 2014; Dougados et al. 2014).

At the time of approval in the EU, the EU RMP for baricitinib described 2 important identified risks:

- herpes zoster and
- hyperlipidaemia

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 TB, *Candida* infections, and PML)
- myelosuppression (agranulocytosis)
- myopathy including rhabdomyolysis
- potential for drug-induced liver injury
- gastrointestinal perforations
- MACE
- VTE, and
- foetal malformation after exposure in utero.

The purpose of this study was to provide systematically collected observational post-marketing data on the incidence of these conditions among patients exposed to baricitinib and other RA therapies.

As part of an Article 20 referral in Europe for all JAKi (EMA 2023), the conduct of this study and Study I4V-MC-B004 were terminated in agreement with the CHMP on the basis of the following rationale (CHMP opinion for the referral was reached on 23 January 2023):

- 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 and I4V-MC-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 randomized study design. (Of note, subsequent to the Article 20 referral in August of 2023, positive opinion has been reached to remove Studies JAJA and 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-B003 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 aggregate serious and opportunistic infections, MACE, malignancies, and VTE among patients with long-term exposure to baricitinib compared with patients treated long-term with bDMARDs or cDMARDs and to describe the incidence of key individual outcomes. This goal was to be achieved through the following specific objectives:

The primary objectives were:

1. to compare the incidence rates and profiles of the following aggregate outcomes:
    a. serious infections (including herpes zoster) and opportunistic infections (including TB, *Candida* infections, and PML)
    b. MACE
    c. malignancies (including lymphoma and typically virus-induced malignancies such as cervical and many oropharyngeal cancers), and
    d. VTE

    among patients with long-term exposure to baricitinib versus patients with long-term exposure to other medications indicated for moderate-to-severe RA.

2. to describe the incidence rates of the following individual outcomes:
    a. lymphoma
    b. herpes zoster
    c. opportunistic infections (including TB, *Candida* infections, and PML)
    d. rhabdomyolysis
    e. myelosuppression (agranulocytosis)
    f. hyperlipidaemia (hypercholesterolaemia, hypertriglyceridaemia)
    g. gastrointestinal perforations, and
    h. 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. Amendments and Updates

Not applicable.

6. Research Methods

6.1. Study Design

This was a cohort study, using primary data collected from the CorEvitas Rheumatoid Arthritis Registry (previously 'CORRONA'), an existing multi-center, prospective, observational RA registry. All sites providing data for this study were selected and managed by CorEvitas.

6.2. Subjects

The study population included all patients in the registry, and eligibility was as follows:

- patient was diagnosed with RA by a rheumatologist and
- patient was at least aged 18 years or older.

The patient was excluded from the study if any of the following applied:

- patient was unwilling to provide consent or
- patient had a history of JAKi use prior to initiation of drug.

There were 2 additional considerations to the exclusion criteria for certain statistical analyses that are described in the protocol (Section 9.2.2.2) that are not detailed here given the termination of the study and absence of conducting statistical analyses. One included consideration of previous tsDMARD use for class-level analysis.

6.3. Variables

CorEvitas included adult RA patients enrolled prospectively in the registry and observed over the study period. Longitudinal follow-up data were obtained via CorEvitas questionnaires completed by patients with RA and their treating rheumatologists (also known as 'providers').

During the course of routinely scheduled clinic visits, data on patient demographics, smoking history, RA duration, RA severity, disease activity, history of prior RA treatment, comorbidities, hospitalizations, targeted adverse events (TAEs), concomitant medication use, patient-reported outcomes, and laboratory results were collected directly from patients and through providers by means of study forms. The following sections detail the variables available for this study. All information is obtained via physician and patient enrollment, follow-up questionnaires, and TAE report forms.

Drug Exposure

Baricitinib was the exposure of interest. Assignment to exposure groups for other RA medications was based on medications presented in Table B003.6.1. A patient could have enrolled in the registry prior to treatment or after having initiated a treatment, and was allowed to subsequently switch or add another medication.

Table B003.6.1. Medications Included in Exposure Cohorts

cDMARDs	bDMARDs		tsDMARDs
Hydroxychloroquine	Abatacept	Anakinra	Tofacitinib
Leflunomide	Adalimumab	Etanercept	
Methotrexate	Golimumab	Infliximab	
Sulfasalazine	Rituximab	Certolizumab	
	Tocilizumab		

Abbreviations: bDMARD = biologic disease modifying anti-rheumatic drug; cDMARD = conventional disease modifying anti-rheumatic drug; tsDMARD = targeted synthetic disease modifying anti-rheumatic drug.

Outcomes

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

- serious infections
- MACE
- malignancy, excluding nonmelanoma 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.

6.4. Study Size

Sample size and statistical power calculations were performed at the time of protocol development to evaluate the statistical power available to detect a 1.5-fold increase in risk of the aggregate outcomes specified in the first primary objectives among baricitinib-exposed patients compared with bDMARD- or cDMARD-exposed patients, if such a risk truly existed. Based on the assumptions detailed in the protocol, it was determined that 4000 baricitinib-exposed patients and 4000 bDMARD-exposed patients would be needed to achieve approximately 71% power to detect a true difference in a risk as small as 1.5-fold for VTE. Other aggregate outcomes would have more than 90% power.

6.5. Statistical Methods

Planned statistical analyses can be found in the approved protocol (version 1.0). Because of the termination of the study, the planned analyses were not executed. What is presented in this abbreviated report includes only a summary of the number of patients enrolled and descriptive characteristics for those patients, presented by number, percent, and means, as appropriate.

7. Results

7.1. Participants

The first patient treated with baricitinib was enrolled in Study B003 on 31 July 2018, only weeks after market launch in the US. After approximately 4.5 years of registry enrollment for baricitinib, there were 419 patients treated with baricitinib in the registry, 359 of which initiated treatment with baricitinib at or after enrollment.

The last summary report Lilly received from CorEvitas for Study B003 was the "Q1 2023 CorEvitas RA Registry Quarterly Report" and contained data through 31 March 2023. The descriptive data included in this abbreviated final report are drawn from the Q1 2023 quarterly report from CorEvitas.

7.2. Descriptive Data

There were 37,094 prevalent users of b/tsDMARDs in the CorEvitas RA registry. This includes patients who iniatated their b/tsDMARD either prior to, at, or after enrollment in the registry. Of these, 419 patients were prevalent users of baricitinib. Total time of exposure to baricitinib was not estimated because of early termination of the study, absence of execution of statistical analyses, and exposure time for baricitinib patients was not a standard metric provided in the quarterly reports.

When restricting to only new users of a b/tsDMARD (that is, those who initated the b/tsDMARD either at the time of, or after, registry enrollment), there were 22,288 RA patients with new use of b/tsDMARDs. Of these, 359 were new users of baricitinib. The majority (83.8%) of new users of baricitinib had used previous b- or ts-DMARDs. Baseline characteristics for the new users of baricitinib are presented in Table B003.7.1, stratified by whether the individual was b/tsDMARD naïve or experienced.

The product share for baricitinib, across all b/tsDMARDs, remained stable from 2018 through 2022.

Table B003.7.1. Baseline Characteristics of Baricitinib Initiations, by Whether Individual Was b/tsDMARD Naïve or Experienced

	Incident Baricitinib Patients (n=359)		All b/tsDMARD Experienced Patients[a] (n=27,143)
Demographics	**Naïve to b/tsDMARDs (n=58)**	**Experienced b/tsDMARD Patients (n=301)**	
Age, mean	61.4	60.2	58.5
Female (%)	74.1%	81.1%	81.0%
BMI (kg/m^2), mean	31.2	30.6	30.3
Insurance type			
Private	65.5%	61.8%	69.2%

	Incident Baricitinib Patients (n=359)		All b/tsDMARD Experienced Patients[a] (n=27,143)
Demographics	**Naïve to b/tsDMARDs (n=58)**	**Experienced b/tsDMARD Patients (n=301)**	
Medicare	34.5%	44.5%	38.5%
Medicaid	5.2%	9.3%	7.0%
None	0%	1.0%	1.1%
Disease characteristics			
RA duration, years	6.6	15.3	12.5
Prior number of biologics	n/a	4.0	2.1
Prior number of nbDMARDs	1.3	2.3	2.0
RF positive (%)	54.1%	60.1%	65.9%
CCP positive (%)	51.4%	64.4%	61.3%
Xray erosions (%)	42.1%	52.1%	50.8%
CDAI	18.2	20.3	20.5
Disease activity by CDAI (%)			
Remission	5.8%	8.9%	6.9%
Low	15.4%	17.1%	19.7%
Moderate	50.0%	38.4%	34.6%
High	28.8%	35.7%	38.8%
Other disease activity measures			
Tender joint	5.8	7.8	7.2
Swollen joint	4.4	4.2	5.1
Physician global assessment	36.6	35.0	34.6
Pt global	42.8	49.3	48.0
Pt pain	47.5	52.0	50.8
mHAQ	0.4	0.6	0.6

Abbreviations: BMI = body mass index; b/tsDMARD = biologic or targeted synthetic DMARD; CCP = cyclic citrullinated peptide; CDAI = clinical disease activity index; DMARD = disease modifying anti-rheumatic drug; mHAQ = modified health assessment questionnaire; n = number of patients; n/a = not applicable; nbDMARD = non-biologic DMARD; Pt = patient; RA = rheumatoid arthritis; RF = rheumatoid factor.

[a] Patients included in the "All b/tsDMARDs" column include the 301 b/ts experienced baricitinib initiators.

7.3. Outcome Data

No outcome analyses were conducted given the termination of the study.

7.4. Adverse Events/Adverse Reactions

Table B003.7.2 is a summary of the AEs (non-serious and serious) that were reported as part of Study B003 that are consistent with the protocol-defined AEs (as outlined in Section 4). These are counts of reported events only. No estimation of incidence rates are provided, nor consideration of whether the AE met the protocol-defined definitions for analysis of the events. As mentioned in Section 7.2, reasons for this are based in the early termination of the study, which precluded estimates of exposure time and assessment of outcomes per protocol definitions.

Table B003.7.2. Summary of Reported Adverse Events for Study I4V-MC-B003

Adverse Event (AE)	Non-serious AE (n)	Serious AE (n)
Aggregate endpoints		
Serious infections (including herpes zoster)	n/a	29 (6 pneumonia, 3 each of COVID-19 and sepsis, all other infections with counts of 2 or 1)
MACE (fatal or non-fatal MI, fatal or non-fatal ischemic stroke, cardiovascular death)	0	4 (all MI)
Malignancies	0	3 (1 each of hepatobiliary, breast, lung)
VTE (PE or DVT)	0	3 (2 PE, 1 DVT)
Individual outcomes		
Lymphoma	0	0
Herpes zoster	0	1
TB	0	0
Candida infections	1	0
PML	0	0
Rhabdomyolysis	1	0
Myelosuppression	0	0
Hyperlipidemia	3	0
Gastrointestinal perforations	0	0
Drug-induced liver injury	0	0

Abbreviation: AE = adverse event; COVID-19 = coronavirus disease 2019; DVT = deep vein thrombosis; MACE = major adverse cardiovascular event; MI = myocardial infarction; n = number of events reported (not patient); n/a = not applicable; PE = pulmonary embolism; PML = progressive multifocal leukoencephalopathy; TB = tuberculosis; VTE = venous thromboembolism.

8. Discussion

8.1. Key Results

After approximately 4.5 years of enrollment, Study B003 was far short of the enrollment trajectory needed to enroll a sufficient number of patients to power comparative analyses (as detailed in Section 6.4). Low market uptake of baricitinib in the US was considered the driving factor for low enrollment numbers.

Among the 359 new users of baricitinib that enrolled in Study B003, 301 were experienced b/tsDMARD users and 58 were naïve to previous b/tsDMARDs. Biologic experienced, new users of baricitinib were on average 60.2 years old, had mean duration of RA of 15.3 years, and had on average used 4 previous bDMARD medications.

8.2. Interpretation and Generalisability

Given the limited sample size in Study B003 and study termination, full comparative analyses for the safety events of interest relative to patients with RA treated with other systemtic medications was not executed. Thus no interpretations towards the research objectives can be made.

Furthermore, the B003 study population characteristics are considered representative only of US patients treated with baricitinib for RA. They are 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 mg and 2 mg dosing option with the low 2 mg dose typically reserved for more comorbid, older patients than the 4 mg dose.

9. Conclusions

Study B003 was terminated in agreement with European regulators as part of the Article 20 referral outcome. Only descriptive information for baricitinib treated patients is available. No comparative analyses were executed, and no interpretations or conclusions can be drawn from Study B003.

10. References

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