Eli Lilly and Company

Non-interventional Post-Authorization Safety Study

A Retrospective Cohort Study to Assess the Safety of Baricitinib Compared with Other Therapies Used in the Treatment of Rheumatoid Arthritis in Nordic Countries

Objective 4: Assessment of Effectiveness of Additional Risk Minimisation Activities

I4V-MC-B011

Olumiant® (baricitinib)

EU PAS Register Number: EUPAS25151

PRINCIPAL INVESTIGATOR:

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PASS Information

Title	A Retrospective Cohort Study to Assess the Safety of Baricitinib Compared with Other Therapies Used in the Treatment of Rheumatoid Arthritis in Nordic Countries
Version identifier of the final study report	Version 1
Date of last version of the final study report	NA
EU PAS register number	EUPAS25151
Active substance	ATC: L04AA37 Baricitinib
Medicinal product(s)	Olumiant® (baricitinib) 2-mg and 4-mg film-coated tablets
Product reference	EU/1/16/1170
Procedure number	EMEA/H/C/004085
Marketing authorisation holder(s)	Eli Lilly Nederland BV, Papendorpseweg 83, 3528BJ Utrecht, The Netherlands
Joint PASS	No
Research question and objectives	This study aims to evaluate the safety of baricitinib among rheumatoid arthritis (RA) patients treated in routine clinical care. The focus in the current report is for Objective 4, as it pertains to risk minimisation effectiveness: (4) to assess the effectiveness of risk minimisation activities by describing the pattern of use of baricitinib and the occurrence of pregnancy, active tuberculosis or active viral hepatitis, and monitoring and treatment of lipid levels in relation to such use in routine clinical care.
Country(-ies) of study	Denmark, Sweden, Norway and Finland
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Signature of principal investigator	Signature on file/see approval date first page

Abbreviations: ATC = Anatomical Therapeutic Chemical Classification; NA =not applicable.

Marketing Authorisation Holder

Marketing authorisation holder (MAH)	Eli Lilly Nederland BV. Papendorpseweg 83, 3528BJ Utrecht, The Netherlands
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1. Abstract

Title

A Retrospective Cohort Study to Assess the Safety of Baricitinib Compared with Other Therapies Used in the Treatment of Rheumatoid Arthritis in Nordic Countries – Objective 4: Assess Risk Minimisation Activities

Keywords

Baricitinib, risk minimisation activities, real world evidence, observational cohort study

Rationale and background

Baricitinib was granted marketing authorisation by the European Commission for the treatment of moderate to severe rheumatoid arthritis (RA) in 2017. Additional risk minimisation measures (aRMM) committed to with the approval included Healthcare Professional (HCP) educational materials and a Patient Alert Card (PAC). These materials were to inform prescribers and patients

- of the need to avoid using baricitinib during pregnancy
- of common signs and symptoms of infections and the need to inform the doctor if these occur, and
- of the need to monitor blood lipids during treatment.

To assess the effectiveness of these additional risk minimisation activities, Lilly committed to

1. a cross-sectional survey of HCPs to assess understanding of, and adherence to, the key risk messages of the PAC and HCP education materials (as reported in Study I4V-MC-B010, insert procedure) and
2. describe patterns of use within a cohort of patients with RA treated with baricitinib as they pertain to the safety messages in the additional risk minimisation materials (as assessed with “objective 4” of Study I4V-MC-B011 [B011]).

This current report is to address Objective 4 of Study B011 by summarizing patterns of use as they pertain to the key risk messages in the risk minimisation activities.

Research question and objectives

The objective of this analysis is to assess the effectiveness of risk minimisation activities by describing the pattern of use of baricitinib and the occurrence of pregnancy, active tuberculosis (TB) or active viral hepatitis, and changes in lipid levels in relation to baricitinib use in routine clinical care.

Specifically, the following areas are investigated:

- Infection: Examined the occurrence of first prescriptions for baricitinib among patients diagnosed with active TB or active viral hepatitis

- Pregnancy: It was investigated how many women have an overlap between baricitinib and pregnancy, and among these how many started a new treatment period ('refill') of baricitinib during pregnancy
- Changes in lipid parameters: Evaluated the changes in lipid-lowering therapy in relation to use of baricitinib, and described the temporal pattern of diagnostic codes for hyperlipidaemia relative to a first prescription for baricitinib

Study design

Descriptive observational cohort study utilizing routinely collected data.

Setting

This cohort study was based on routinely collected data from Danish, Swedish, Norwegian, and Finnish national registers.

Subjects and study size, including dropouts

The included population was defined via the Danish, Swedish, Norwegian, and Finnish national hospital registers as patients with a diagnosis of RA (International Classification of Disease [ICD]-10 codes DM05* through DM06*) since 2012 in all countries and treatment with baricitinib between 2017 and 2021 for Denmark, 2017 and 2019 for Sweden and Finland, and 2017 through 2020 for Norway. In addition, the following inclusion criteria were applied: 1) age at least 18 years when initiating baricitinib treatment; 2) RA diagnosis before treatment initiation; 3) no migration 5 years prior to index.

Variables and data sources

Baricitinib incident users, all starting treatment after 2017, were identified. The exposure period started at treatment initiation and continued until initiation of a biologic disease modifying antirheumatic drug (bDMARD), another Janus kinase (JAK) inhibitor, discontinuation of baricitinib, end of study period, death, or migration. Baricitinib exposure was gathered from patient registers, prescription registers, and drug reimbursement registers. Baricitinib treatments with less than 180 days distance were coupled as a coherent treatment course.

Information about infections and hyperlipidaemia diagnosis was gathered from national patient registers.

Information about pregnancies (including abortion, malformation, and stillbirth, and end of pregnancy) was gathered from medical birth registers and patient registers. Start of pregnancy was not available for abortions in Sweden, Norway, and Finland, and therefore pregnancy duration for abortions was estimated based on data from Denmark.

Information about statin use was gathered from prescription- and drug-reimbursement registers.

Results

In total, 3908 persons (3373 person-years [PY] of exposure) with incident baricitinib treatment were identified; 428 people (433 PY of exposure) in Denmark, 1993 (1675 PY of exposure) in Sweden, 913 (732 PY exposure) in Norway, and 574 (533 PY exposure) in Finland.

During treatment with baricitinib, there was limited prevalence of infections (0.2%) and hyperlipidaemia (0.5%) while 9.3% had a change in statin prescription, as a marker for lipid level assessment (4.5% initiated statin, 4.5% decreased statin dose, 0.3% either escalated or had a change in statin Anatomical Therapeutic Chemical Classification [ATC]). An estimated total of 8 pregnancies (1% of women aged 18 to 50 years) had a potential overlap with baricitinib treatment, based on the mean duration of overlap in the Danish dataset.

Discussion

This study identified low occurrence of selected infections or pregnancies and the implementation of lipid abnormality monitoring, as reflected by changes in statin prescriptions, suggesting that prescribers adhered to recommendations within the aRMM. There are some limitations to be considered: (1) only registered events could be evaluated. Consequently, the number of events may be underestimated. (2) Only abortions registered in patient registers were included. In data from Sweden, information about stillbirths and congenital malformations was not available. Pregnancy duration is not fully accurate, because pregnancy start date across countries was estimated based on Danish data. Thus, overlap of pregnancy episode with baricitinib may be misassigned. (3) The use of statin prescriptions is a proxy of lipid level assessment, and overlooks patients whose lipid profile was assessed, but who required no change in statin prescription, or had no statin prescription at all.

Conclusion

Utilising national Nordic data, this study was able to describe the occurrence of events relevant to the baricitinib aRMM within a cohort of incident baricitinib users. This study identified low occurrence of selected infections or pregnancies, and evidence of 9.3% of patients had their lipids monitored, based on the proxy measure of changes in their statin medication, suggesting that prescribers adhered to recommendations within the aRMM. The current results from Study B011 suggest effective communication of select risks with baricitinib.

Marketing authorisation holder(s)

Eli Lilly Nederland BV. Papendorpseweg 83, 3528BJ Utrecht, The Netherlands

Names and affiliations of principal investigators

Principal investigator: Chief Physician, Department of Clinical Pharmacology, Bispebjerg and Frederiksberg Hospital

2. List of abbreviations

Term	Definition
aRMM	additional risk minimization measures
ATC	Anatomical Therapeutic Chemical Classification
bDMARD	biologic disease modifying antirheumatic drug
DMARD	disease modifying anti-rheumatic drug
EMA	European Medicines Agency
HCP	healthcare professional
ICD	International Classification of Disease
JAK	Janus kinase
PAC	Patient Alert Card
PY	person-years
RA	rheumatoid arthritis
SAP	statistical analysis plan
TB	tuberculosis

3. Investigators

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Eli Lilly and Company investigators

Director, Pharmacoepidemiology
Global Patient Safety, Eli Lilly and Company

4. Other responsible parties

Project Manager: MedEngine DK ApS

5. Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection[a]	31 December 2018	2 December 2019	
End of data collection	Not applicable	15 August 2022	
Registration in the EU PAS register	Before start of data collection	15 April 2019	
Final report of Objective 4	To be determined based on at least 24 months of data in at least 50% of discrete healthcare databases	See Page 1	

[a] For secondary data sources, the start of data collection corresponds to the date when data extraction is initiated.

6. 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 (grouped as a targeted synthetic DMARD, but in the present study, the class consists of JAK inhibitors only) approved by the European Commission in 2017 for the treatment of moderate-to-severe RA, administered orally. 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 studies 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 has not been characterised.

Additional risk minimisation activities committed to with the marketing authorisation included HCP educational materials and a PAC. These materials were to inform prescribers and patients

- of the need to avoid using baricitinib during pregnancy
- of common signs and symptoms of infections and the need to inform the doctor if these occur, and
- of the need to monitor blood lipids during treatment.

To assess the effectiveness of these additional risk minimisation activities, Lilly committed to

1. a cross-sectional survey of HCPs to assess understanding of, and adherence to, the key risk messages of the PAC and HCP education materials (as reported in Study I4V-MC-B010, Procedure EMEA/H/C/004085/II/0017 with Committee for Medicinal Produce for Human Use positive opinion 29 October 2020) and
2. describe patterns of use within a cohort of patients with RA treated with baricitinib as they pertain to the safety messages in the additional risk minimisation materials (as assessed with “objective 4” of Study I4V-MC-B011 [B011]).

With a total population of 26.6 million and comprehensive national healthcare systems, Nordic countries provide a unique setting for the study of the safety of new medications. RA has a prevalence of 0.5% to 1.0% among adults in these countries, with an incidence of 25 to 45 per 100,000 PY (Puolakka et al. 2010; Neovius et al. 2011; Eriksson et al. 2013; Kuuliala [WWW]; NRF [WWW]). Detailed information on these patients is available from several data sources, including the Nordic patient registers and the national prescription registers.

By combining the patient, prescription, and clinical registers, information about diagnoses, hospital treatments, and redeemed prescriptions were gathered. From this, patients with RA treated with baricitinib were identified. Combined with the lengthy follow-up available for

patients in Nordic healthcare systems, this creates an ideal setting for the study of the safety of new medications.

This current report is to answer Objective 4 of Study I4V-MC-B011 by summarizing patterns of use as they pertain to the key risk messages in the additional risk minimisation activities. The broader Study B011 is ongoing as the other 3 objectives are to assess long-term safety.

7. Research question and objectives

The B011 protocol describes the specific risk minimization effectiveness objective (referred to as "objective 4") as follows:

To assess the effectiveness of risk minimisation activities by describing the pattern of use of baricitinib and the occurrence of pregnancy, active tuberculosis or active viral hepatitis, and changes in lipid levels in relation to baricitinib use in routine clinical care. (This objective complements the aims of Study I4V-MC-B010, which aims to assess the effectiveness of risk minimization activities).

8. Amendments and updates

Not applicable.

9. Research methods

The objective of this analysis is to assess the effectiveness of risk minimization by describing the pattern of use of baricitinib relative to the occurrence of pregnancy, select infections, and changes in lipid levels (as can be assessed based on variables available in national register data). As such, this study is descriptive in nature and provides the number of events happening in proximity to treatment with baricitinib.

9.1. Study design

Descriptive observational cohort study utilising routinely collected data.

9.2. Setting

This cohort study was based on routinely collected data from Danish, Swedish, Norwegian, and Finnish national registers.

9.3. Subjects

The included population was defined via the Danish, Swedish, Norwegian, and Finnish national hospital registers as patients with a diagnosis of RA (ICD-10 codes DM05* through DM06*) and treatment with baricitinib between 2017 and 2021 for Denmark, 2017 and 2019 for Sweden and Finland, and 2017-2020 for Norway. In addition, the following inclusion criteria were applied: 1) age at least 18 years when initiating baricitinib treatment; 2) RA diagnosis before treatment initiation; 3) no migration 5 years prior to index.

9.4. Variables

Below is described how baricitinib exposure and events related to risk minimisation activities are defined and identified.

9.4.1. Exposure

Baricitinib incident users, all starting treatment after 2017, were identified. The exposure period started at treatment initiation and continued until initiation of a bDMARD, another JAK inhibitor, discontinuation of baricitinib, end of study period, death, or migration.

This section includes detail for how exposure was defined for all exposure cohorts in the broader B011 study. Note that only baricitinib exposure is relevant for the currently described results related to Objective 4.

9.4.1.1. Exposure data sources

In Denmark, exposure to DMARDs (including baricitinib) was identified through the national prescription register, for DMARDs available via community pharmacies, and through the national hospital register, which holds information on procedure codes. Administration of DMARDs at hospitals is registered as *procedure codes*. Either the DMARD has a specific procedure code or the DMARD treatment is documented as a *supplementary code* with the ATC code of the DMARD in combination with a procedure code. Procedure codes used in

combination with the supplementary code indicate a drug administration. For example, baricitinib does not have a specific procedure code, and therefore treatment with baricitinib can be documented as procedure code "AAF22 Outpatient visits" in combination with L04AA37 (ATC code for baricitinib) as the supplementary code. To identify procedure codes that indicate an administration of a treatment, all procedure codes, used in combination with DMARDs registered as supplementary codes, were assessed.

In Sweden, Norway, and Finland, data on drug exposure is based on a simpler approach. In Norway, the prescription register and patient register were used to identify treatment based on registrations at pharmacies and hospitals, respectively. Both registers included a variable with ATC codes. In Sweden, the prescription register and, in Finland, the drug reimbursement register were used to identify treatment using ATC codes registered at pharmacies. Neither register covers intravenous treatment, like infliximab, though.

9.4.1.2. Defining treatment periods

When redeeming prescriptions from community pharmacies, the intended treatment period covered is seldom registered. Similarly, registration of DMARD administrations in the national hospital register has some missing values, mainly due to missing registrations by hospital clinicians. To account for registration practice and to combine treatments administrations that make up a treatment period, the durations between redeemed prescriptions, hospital administrations, and hospital dispensations were assessed for the individual DMARD, within each country. For the current report, the only relevant medication assessed is baricitinib. Histograms showing duration between redemptions and/or administrations were assessed, and the maximum allowed duration between redemptions and/or administrations was estimated. For baricitinib, this was estimated to 180 days. The duration was added to the date of redemption, administration, or dispensation to estimate the length of each individual continuous treatment. If the same DMARD was administered before the end of the previous treatment, the treatments were combined as 1 continuous treatment period. The duration for each DMARD treatment was estimated to be similar across countries. This estimated length of continuous treatment is referred to in the results as the "exposure duration".

9.4.2. Outcomes

Table 1 holds an overview of the outcomes, including codes and data source used.

Table 1. Overview of Outcomes

Outcome group	Specific outcome	CODE	Source
Infections	Active tuberculosis	ICD-10: A15-A19	Patient register
	Active viral hepatitis	ICD-10: B15-B19	Patient register
Pregnancy	Pregnancy	ICD-10: 080, O81 O82, O83, O84	Denmark: Medical birth register + patient register and ICD-10 codes Sweden, Norway, and Finland: Medical birth register

Outcome group	Specific outcome	CODE	Source
	Spontaneous abortion	ICD-10: O021, O03	Patient register
	Elective abortion	ICD-10: O04, O05, O06	Patient register
	Malformation	ICD-10: Q	Denmark: patient register and ICD-10 codes Sweden: Not available Norway and Finland: Medical birth register
	Stillbirth	ICD-10: P95	Denmark: Medical birth register + patient register and ICD-10 codes Sweden: Not available Norway and Finland: Medical birth register
Changes in lipid parameters	Hyperlipidaemia	ICD-10: E780, E781	Patient register
	Statin use	ATC: Atorvastatin: C10AA05 Rosuvastatin: C10AA07 Lovastatin: C10AA02 Simvastatin: C10AA01 Pravastatin: C10AA03 Fluvastatin: C10AA04 Pitavastatin: C10AA08	Prescription register

Abbreviations: ATC = Anatomical Therapeutic Chemical Classification; ICD = International Classification of Disease.

More information about how the events were identified is described below.

9.4.2.1. Infection

According to the HCP Educational Material, prescribers are to "*Screen patients to rule out active tuberculosis and active viral hepatitis before starting Olumiant*".

Active TB or active viral hepatitis diagnosis (see ICD codes in Table 1) was identified up to 5 years prior as well as during exposure duration.

9.4.2.2. Pregnancy

Overlap between pregnancy duration and baricitinib exposure duration was estimated. For pregnancies ending in abortion, the start of pregnancy was not available in data from Sweden, Norway, and Finland. To estimate the pregnancy start in data from these countries, the minimum, mean, and maximum duration of pregnancies leading to spontaneous and elective abortions, respectively, were found in data from Denmark, and abortions across countries were assessed with the estimated minimum, mean, and maximum pregnancy duration (see Table 5 in Section 10.4.2 for summary of Denmark pregnancy duration estimates for pregnancies ending in

an abortion). For Sweden, the exact date of pregnancy end was not provided, only month and year. The 15th was imputed as day. Stillbirths were included from Denmark, Norway, and Finland, but was not available from Sweden. Among livebirths, births with congenital malformation were identified in Denmark, Norway, and Finland, but were not available from Sweden. Malformation was identified up to 365 days after birth.

9.4.2.3. Changes in lipid parameters

Hyperlipidaemia diagnosis and change in statin prescriptions were used as proxy for the patients that had their lipid parameters assessed.

Hyperlipidaemia diagnosis was identified up to 1 and 5 years prior as well as during exposure duration.

Redeemed statin prescriptions were identified in a period up to 6 months prior to baricitinib treatment initiation, and between 2 and 8 months after baricitinib treatment initiation. The prescription closest to baricitinib treatment initiation, in the 2 periods, was used. The strength of the tablet was extracted from the registers. It was assumed that the patient used 1 pill per day. From this, the following groups were created:

- **Initiation**: patients with no statin treatment before baricitinib treatment initiation and statin treatment after baricitinib treatment initiation
- **Escalation**: patients with an increase in dose from before to after baricitinib treatment initiation
- **Reduction**: patients with a decrease in dose from before to after baricitinib treatment initiation
- **Change of statin**: patients with no change in dose, but change in statin ATC code

All of these were considered as indications of the lipid parameters being assessed and were summed as a single variable: lipid assessment (yes/no). Patients with a reduction in statin dose include both patients who have a statin prescription before and after baricitinib initiation, and patients with a statin prescription before baricitinib initiation and no statin prescription after baricitinib treatment initiation.

To be able to compare dose across statins, a conversion factor was used so that strength was equivalent to simvastatin strength. Table 2 shows the simvastatin conversion factor used.

Table 2. Simvastatin Conversion Factor

Statin	Simvastatin conversion factor
Lovastatin	0.5
Pravastatin	0.5
Simvastatin	1
Atorvastatin	2
Fluvastatin	0.25
Rosuvastatin	4

Note: Equivalent simvastatin dose obtained from http://www.vhpharmsci.com/vhformulary/Tools/HMGCOAequivalence.htm.

9.5. Data sources

Data from Denmark, Sweden, Norway, and Finland were used. The data sources and the calendar years available are listed in Table 3. Baricitinib was approved by the EMA February 2017. Five years historic data was utilized.

Table 3. The Central Health Registers Used

Register	Data Collection Calendar Years				Used For
	Denmark	Sweden	Norway	Finland	
National hospital registers	2012-2021	2012-2019	2012-2020	2012-2019	Identification of • patients • diagnoses • prior hospitalizations • therapies administered by hospital departments (Denmark)
Civil registration registers	2012-2021	2012-2019	2012-2020	2012-2019	Vital status, demography (for example, migration)
Prescription registers	2012-2021	2012-2019	2012-2020	2012-2019	Information on drug treatment by redeemed drug prescriptions at community pharmacies

For further details about the registers see latest version of the protocol (PASS Protocol I4V-MC-B011).

9.6. Bias

Not applicable.

9.7. Study size

All identified incident baricitinib users will be included. Due to the descriptive, noncomparative nature of this report, a power calculation is not applicable.

9.8. Data transformation

Not applicable.

9.9. Statistical methods

Each outcome event was only counted 1 time within each treatment period. If, for example, a person was admitted to hospital for active TB 2 times during the same treatment period, this was counted as 1 event.

For the result tables, the number of outcome events are summed across patients and calculated as percentage by dividing by the number of persons.

Cells with less than 3 (being either 0, 1 or 2) are masked due to regulations in Denmark regarding health data and privacy.

9.9.1. Infections

According to the HCP Education Material, prescribers are to "*Screen patients to rule out active tuberculosis and active viral hepatitis before starting Olumiant*". To assess the effectiveness of this message, the occurrence of these selected infections was summarized before and after a first initiation of baricitinib treatment.

9.9.2. Pregnancy

According to the HCP Educational Material and PAC, "*Olumiant must not be used during pregnancy*". To assess effectiveness of this message, the proportion of women with a potential overlap between pregnancy duration and baricitinib treatment duration is summarized.

For pregnancies, the same woman can experience more than 1 pregnancy during the baricitinib exposure. Therefore, number of pregnancies was calculated both as 1) number of total pregnancies identified and 2) number of persons who experience at least 1 pregnancy. However, when assessing data, no women had multiple pregnancies during baricitinib exposure, and therefore number of pregnancies is presented as a single number and calculated as a percentage by dividing in number of women aged 18 to 50 years.

9.9.3. Lipid monitoring

According to the HCP Educational Material, prescribers are to "*Assess lipid parameters approximately 12 weeks following initiation of Olumiant therapy*". As data are not available for identifying lipid laboratory tests, proxy measures for lipid monitoring were summarized including diagnosis codes of hyperlipidaemia and changes in lipid lowering therapy in relation to initiation of treatment with baricitinib.

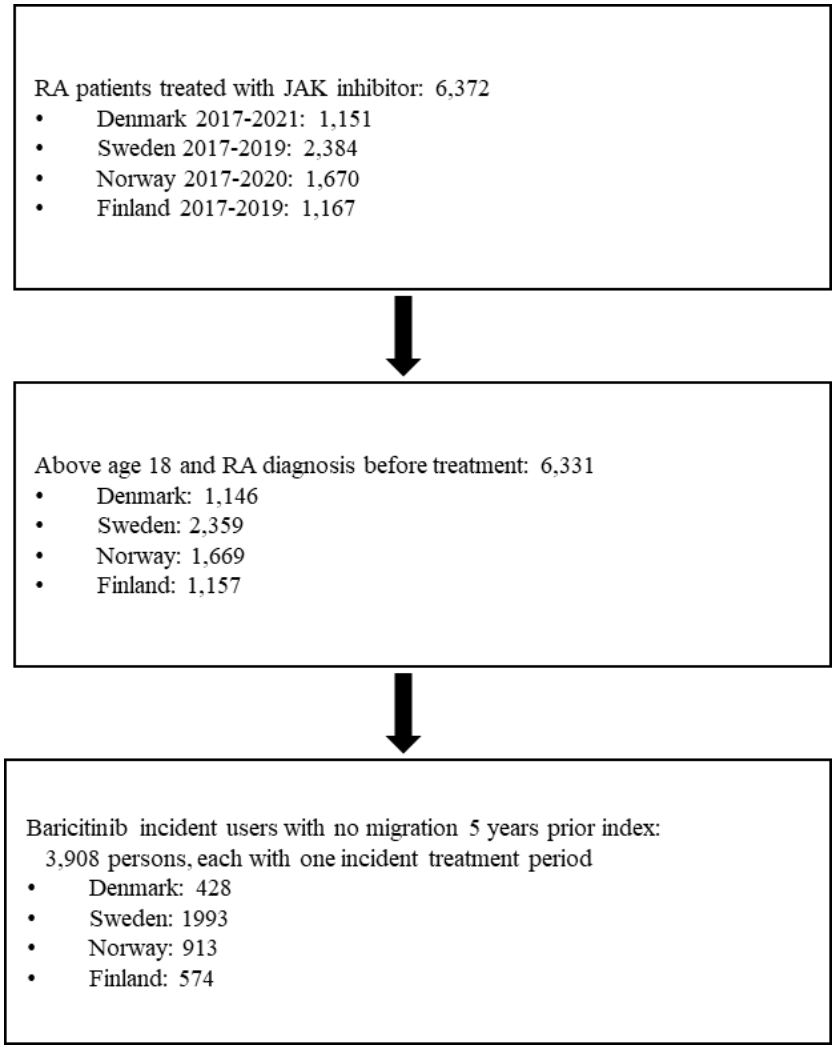
9.10. Quality Control

All data gathering and analyses was overseen by 2 researchers experienced in the field of register-based research. Programming for this project was conducted by a primary analyst and validated by a separate analyst (validation analyst). For all data processing steps, the validation analyst reviewed the programme along with input and output datasets. For the analysis steps of the project, double-programming techniques to reduce the potential for programming errors were employed.

10. Results

10.1. Participants

Figure 1 shows the flowchart. In total, 3908 patients with incident baricitinib treatment were identified.



Abbreviations: JAK = Janus kinase; RA = rheumatoid arthritis.

Figure 1. Flow chart.

10.2. Descriptive data

Number of incident baricitinib users and the total follow-up time available (based on the estimated exposure duration) are presented below. Note that the PY exposure is not censored by any outcome events.

Denmark: 428 patients with a total of 433 PY exposure

Sweden: 1993 patients with a total of 1675 PY exposure

Norway: 913 patients with a total of 732 PY exposure

Finland: 574 patients with a total of 533 PY exposure

In total: 3908 patients with a total of 3373 PY exposure

10.3. Outcome data

Not applicable.

10.4. Main results

10.4.1. Infections

Table 4 shows the number of TB and viral hepatitis infections diagnoses identified prior to and during exposure duration among the 3908 patients with first baricitinib treatment.

Table 4. Tuberculosis and Viral Hepatitis Infections Prior to, and During, Exposure Duration Among 3908 Baricitinib Patients

Tuberculosis 5-year Prior Exposure	Tuberculosis During Exposure	Viral Hepatitis 5-year Prior Exposure	Viral Hepatitis During Exposure
6 (0.2%)	Less than 3	20 (0.5%)	8 (0.2%)

Note: *Less than 3* being 0, 1, or 2.

10.4.2. Pregnancies

10.4.2.1. Estimation of pregnancy duration

As mentioned in Section 9.4.2.2, data from pregnancies ending in an abortion in Denmark were used to estimate duration of pregnancy for those ending in abortion in Norway, Sweden, and Finland. For pregnancies ending in abortions, the following minimum, mean, and maximum pregnancy durations were estimated in data from the Danish RA population, see Table 5. The minimum, mean, and maximum pregnancy duration estimates from Denmark were then used to examine a range of pregnancy duration estimates for considering overlap with baricitinib exposure duration in the other countries.

Table 5. Minimum, Mean, and Maximum Pregnancy Durations (in Days) for Pregnancies Ending in Abortion in Denmark (382 and 593 Pregnancies Ending in Elective and Spontaneous Abortion, Respectively, Informed the Estimates)

Abortion	Minimum Pregnancy Duration (Days)	Mean Pregnancy Duration (Days)	Maximum Pregnancy Duration (Days)
Elective abortion	28	57	147
Spontaneous abortion	7	60	146

10.4.2.2. Potential overlap of pregnancy duration with baricitinib exposure duration

Of the 3908 patients with RA identified as initiating baricitinib, 815 were women considered to be of childbearing age (in other words, between the ages of 18 to 50 years old). Among those, there were 8 (1%) women with evidence of a pregnancy that may have overlapped with baricitinib exposure (Table 6).

Note, that to calculate the percentages, the denominator is the number of women aged between 18 and 50 years within each cohort. The number of pregnancies ending in abortion with potential overlap with baricitinib exposure duration did not change when considering a pregnancy duration informed by either the minimum, mean, or maximum pregnancy duration.

Table 6. Pregnancies Among Women with RA of Childbearing Age Overlapping with Baricitinib Exposure Duration

Pregs[a]	Spontaneous Abortions			Elective Abortions			Still births	Livebirths	Livebirths w/ Malformation	Women[b]
	Using the min preg Duration[c]	Using the mean preg Duration	Using the max preg Duration	Using the min preg Duration	Using the mean preg Duration	Using the max preg Duration				
8 (1%)	<3	<3	<3	4 (0.5%)	4 (0.5%)	4 (0.5%)	<3	3 (0.4%)	<3	815

Abbreviations: max =maximum; min = minimum; preg = pregnancy; RA = rheumatoid arthritis; w/ = with.

[a] Pregs consist of abortions, stillbirths, and livebirths.

[b] Number of women aged 18 to 50 years.

[c] Min, mean, max preg durations were estimated from Denmark (see Table 5).

Note: *<3* being 0, 1 or 2.

As an additional analysis, it was investigated if the number of pregnancies in Table 6 changed when the following criteria were removed: 1) RA diagnosis *before* treatment start, 2) no migration 5 years before treatment start, and 3) only incident baricitinib treatment. In this case, there were 847 women of childbearing age, with 1 additional pregnancy that potentially overlapped with baricitinib treatment. Thus, there were 9 pregnancies instead of 8. The pregnancy resulted in live birth.

10.4.3. Changes in lipid parameters

Table 7 shows number of hyperlipidaemia diagnosis identified prior to and during exposure duration.

Table 7. Hyperlipidaemia Prior to and During Baricitinib Exposure Duration Among 3908 Baricitinib Patients

Hyperlipidaemia 5 years Prior to Exposure	Hyperlipidaemia 1 year Prior to Exposure	Hyperlipidaemia During Exposure
77 (2%)	22 (0.6%)	18 (0.5%)

Table 8 shows number of changes in statin prescription, indicating lipid level assessment.

Table 8. Change in Statin Prescription Among 3908 Baricitinib Patients

Change in Statin Prescription[a]	N (%)
Any change	363 (9.3%)
Initiation of statin	177 (4.5%)
Escalation of statin	At least 9, at most 11
Reduction of statin	175 (4.5%)
Change in statin ATC code	Less than 3

Abbreviations: ATC = Anatomical Therapeutic Chemical Classification; N = number of patients.

[a] Change in statin prescription is initiation, escalation, or reduction in statin dose, or change in statin ATC code, as described in Section 9.4.2.3. Reduction of statin are both patients who reduce dose, but still have a statin prescription after baricitinib initiation, and patients with no statin prescription after baricitinib treatment initiation.

Note: *Less than 3* being 0, 1, or 2. The range in "escalation of statin" row is to maintain blinding of count in "change in statin ATC code" row.

10.5. Other analyses

Not applicable.

10.6. Adverse events/adverse reactions

Not applicable.

11. Discussion

11.1. Key results

The present report describes events pertaining to the additional risk minimisation messages within the baricitinib HCP Educational Materials and the PAC, specifically regarding infection, pregnancy, and changes in lipid parameters. There were 3908 RA patients identified initiating baricitinib in 4 Nordic countries (815 of which were women of childbearing age). From these patients, it was assessed that

- 0.2% had evidence of viral hepatitis infections during baricitinib treatment, which is lower than the 0.5% identified with viral hepatitis diagnoses in the 5 years prior to baricitinib initiation.
    - Counts of patients with TB diagnoses during baricitinib treatment were so low as to require blinding of results.
- 8 pregnancies (1% of women aged 18 to 50 years) had a potential overlap with baricitinib treatment.
- 0.5% had a hyperlipidaemia diagnosis during baricitinib treatment, and 9.3% had a change in statin prescription, suggesting occurrence of lipid level assessment.

11.2. Limitations

One hundred and eighty days were used as the maximum allowed duration between registered baricitinib administrations/dispensations to bridge gaps in data due to lack of registration. Given the short half-life of baricitinib, it is possible that a patient could have a period without baricitinib exposure if the patient stopped taking the medication but appears as continuously treated in the analyses. The benefit from this conservative assignment of an exposure duration is that any events related to infections, pregnancies, and hyperlipidaemia during exposure are unlikely to be overlooked, but consequently this approach may also have overestimated the true number of events. With regard to change in statin prescriptions, this is not affected, because the defined analysis looks for statin prescriptions up to 6 months prior to and between 2 and 8 months after baricitinib start and did not consider the baricitinib exposure period.

The identification of events is inherently limited to registered events only. Consequently, the number of events may be underestimated. As per definition, the infections by TB and viral hepatitis and the hyperlipidaemia were identified in the patient registers. This means that the diagnosis is only included in the present results if the patient with RA was admitted to the hospital (either as in- or outpatient) and had the diagnosis registered. Further, it is assumed this registered diagnosis would equate to "*active TB*" and "*active viral hepatitis*", as it is referred to in the baricitinib aRMM. Consequently, infection and hyperlipidaemia diagnoses managed outside the hospital, for example, by a general practitioner, are not included. Similarly, only abortions registered in the patient registers (in- and outpatient contacts in relation to hospitals) are included. Abortions handled by the women herself (including very early abortions, where the women may not even be aware of a pregnancy) and abortions involving, for example, a general

practitioner and/or gynaecologist in private practice, are not included. Furthermore, in data from Sweden, information about stillbirths and congenital malformations was not available.

According to the protocol, TB and viral hepatitis should be identified as "patients diagnosed with active TB or active viral hepatitis who have prescriptions consistent with such treatment". Due to the low numbers of events, only diagnoses were used to identify TB and viral hepatitis. If TB and viral hepatitis were to be identified with the combination of both diagnosis and treatment, the number of events would be lower than the numbers of identified in present report.

Pregnancy duration was not fully accurate. For pregnancies ending in abortion, data from Sweden, Norway, and Finland did not include dates of pregnancy start. Instead the estimated pregnancy durations from Danish data were used. For Sweden, the exact date of pregnancy end was not provided, only month and year. The 15th was imputed as day. This leads to imprecision that may reduce the ability to correctly identify true overlaps between pregnancy and exposure duration. However, the same number of pregnancies potentially overlapping with baricitinib exposure were identified regardless of whether minimum, mean, or maximum pregnancy durations were used.

In the SAP for this study, the use of statin prescriptions was the predefined approach to identify patients with assessed lipid parameters. However, this was not carried out as specified in the SAP regarding period and change of dose in favour of implementing a more precise approach. According to the SAP, statin prescriptions were to be identified in a period of 90 days. It is the experience of researchers at Phase4CPH that 90 days is too short of a period to identify statin use. Instead, a period of 180 days was used. Statin use was identified 180 days before DMARD exposure start. Statin use after baricitinib exposure start was also identified in a 180-day period, but because it is likely that the patient did not have the lipid level assessed immediately after baricitinib exposure start, statin use after exposure start was identified between Day 60 and Day 240 after baricitinib exposure start. The statin prescription closest to the baricitinib start within the 2 periods, that is, before and after start of baricitinib, was used. When calculating change in dose, according to the SAP, the dose should be grouped in 3 categories (Low [<20 mg/day], Moderate [20 to <80 mg/day], and High [≥80 mg/day] simvastatin-equivalent dose). However, instead Lilly looked at change in dose without grouping, because any change in dose can be interpreted as the lipid level being assessed. Also, the SAP defined only initiation and escalations as proxies for lipid level assessment. However, reduction in dose and a change in ATC code (despite a stable dose) were also considered as proxies for an assessment of the patient's lipid level. Despite these changes, it is important to highlight that patients who had their lipid level assessed, but required no change in statin prescriptions (either continuous nonusers or continues dose) would not be distinguished from patients who did not have their lipid level assessed. Consequently, a more precise interpretation is that a patient who had their lipid level assessed, who required change in statin prescription, and where the change was carried out, was identified. Therefore, the current evaluation is likely an underestimation of the true number of patients who had their lipid level assessed.

The SAP states for the following sensitivity analyses to be carried out:

- Repeat the analyses with prevalent baricitinib users, if too few incident users.
- Repeat the analyses with JAK inhibitor incident users as a drug class analyses.
- Repeat the analyses with JAK inhibitor prevalent users as a drug class analyses, if too few incident users.

These were not included in the present report. In total, 3908 incident baricitinib users were identified and used in the present report. Prevalent baricitinib users would be 3985 (when previous JAK inhibitors are allowed and with no exclusion due to migration or RA diagnosis prior exposure) with 4376 treatment periods. The 3908 incident users identified are a sufficient number of persons to provide reasonable confidence that the observed results describe the treated population. There is not much gain in using the 3985 prevalent users, where events may also be correlated, if the same person experienced multiple events in consecutive baricitinib exposure periods. The use of JAK inhibitor incident and prevalent users was a predefined option if too few baricitinib users were identified. However, given the robust sample size of baricitinib users identified, and the lack of interpretability specific to the baricitinib aRMM, these class level sensitivity analyses were not executed.

The SAP also mentions that pregnancies with a refill of baricitinib would be identified, as a narrower definition of baricitinib and pregnancy overlap. However, due to the low number of pregnancies, this was not considered.

11.3. Interpretation

Identification of infections and pregnancies are considered valid following a hospital contact, while the hyperlipaemia diagnosis may be underused and therefore underestimates the true number of patients with this diagnosis. Use of change in statin prescription as proxy for lipid level assessment will not include patients who had their lipid level assessed, but required no change in statin prescriptions.

In regards to infections, the aRMM state HCPs should "*Screen patients to rule out active tuberculosis and active viral hepatitis before starting Olumiant".* As discussed, the use of patient registers to identify these screenings may miss the screen, as only patients admitted to the hospital with this diagnosis would receive a registered diagnosis code. However, by describing the proportion of new baricitinib users with these diagnosis codes in the period before and after initiating baricitinib, results suggest that there is not a bolus of TB or hepatitis activation, and thus HCPs are aware of these recommendations.

In regards to pregnancy, the aRMM state that "*Olumiant must not be used during pregnancy*". The results from this study suggest that use of baricitinib among women of childbearing age is low, with 815 of the 3908 baricitinib users (20.9%) being women between the ages of 18 and 50 and only 8 (1%) of those women having a suggestion of a potential overlap between pregnancy duration and baricitinib exposure.

In regards to lipid levels, the aRMM state prescribers are to "*Assess lipid parameters approximately 12 weeks following initiation of Olumiant therapy*". While the data sources were

unable to provide evidence of laboratory tests for lipid levels, proxy measures were used instead. Among the incident baricitinib users, a similar but numerically higher number of patients had diagnosis codes of hyperlipidaemia in the period 1-year before baricitinib initiation than during baricitinib exposure, and 9.3% of patients had changes in their statin prescription, suggesting that prescribers adhered to recommendations within the aRMM. However, 1) it is not known whether the monitoring was due to routine clinical care or due to the specific baricitinib aRMM and 2) the use of statin prescriptions as a proxy for lipid level assessment only identifies patients with a change in statin prescription and will not distinguish patients who had their lipid level assessed, but required no change in statin prescriptions (either continuous nonusers of statins or continue dose as is) from patients who did not have their lipid level assessed, thus providing an underestimate of the actual proportion of patients receiving lipid monitoring.

11.4. Generalisability

The data from Denmark, Sweden, Norway, and Finland are all based on nation-wide registers and are thus considered generalisable to the population of patients meeting inclusion criteria for this study.

12. Other information

Not applicable.

13. Conclusions

With national Nordic data, this study was able to describe the occurrence of events relevant to the baricitinib aRMM within a cohort of incident baricitinib users. This study identified low occurrence of selected infections or pregnancies, and 9.3% of patients had their lipids monitored, based on the proxy measure of changes in their statin medication, suggesting that prescribers adhered to recommendations within the aRMM. The current results from Study B011 suggest effective communication of the additional risk minimisation key messages for baricitinib.

14. References

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Annex 1. List of standalone documents

Not applicable.

Annex 2. Additional information

Not applicable.