Rheumatologist and Dermatologist Survey to Assess the Effectiveness of the Risk Minimisation Measures (RMM) for Olumiant (baricitinib), a JAK1/2 Inhibitor

Study I4V-MC-B025

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PASS Information

Title:	Rheumatologist and Dermatologist Survey to Assess the Effectiveness of the Risk Minimisation Measures (RMM) for Olumiant® (baricitinib) a JAK1/2 inhibitor
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Procedure number:	To be added after submission
Marketing authorisation holder(s) (MAH):	Eli Lilly Nederland B.V.
Joint PASS:	Not Applicable (N/A)
Research question and objectives:	This study will assess: 1. The effectiveness of the updated baricitinib healthcare professional (HCP) Educational Materials and Patient Alert Card (PAC) among dermatologists and rheumatologists 2. The effectiveness of a Direct Healthcare Professional Communication (DHPC) distributed to dermatologists and rheumatologists
Countries of study:	At least 3 EU countries: Sweden, France and Germany.

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Marketing Authorisation Holder

Marketing Authorisation Holder(s)	Eli Lilly Nederland B.V. (Lilly) Papendorpseweg 83 3528 BJ Utrecht The Netherlands
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2. List of Abbreviations

Term	Definition
aDCT	Annotated Data Collection Tool
AA	alopecia areata
AD	atopic dermatitis
aRMM	additional risk minimisation measure
ATC	Anatomical Therapeutic Chemical
B025	Study I4V-MC-B025
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CIOMS	Council for International Organisations of Medical Sciences
CI	confidence interval
DHPC	Direct Healthcare Professional Communication
EDC	electronic data capture
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EULAR	European League Against Rheumatism
FDA	United States Food and Drug Administration
GDPR	General Data Protection Regulation
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HCP	healthcare professional
ICD	International Classification of Disease
ICH	International Council for Harmonisation
IEA	International Epidemiological Association
ISPE	International Society for Pharmacoepidemiology
IT	Information Technology
JAK	Janus kinase
JAKi	Janus kinase inhibitor
KRM	Key Risk Message
Lilly	Eli Lilly and Company
MACE	major adverse cardiovascular event
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
NCA	National Competent Authority
NMSC	non-melanoma skin cancer
PAC	Patient Alert Card
PAS	post authorisation study
PASS	post authorisation safety study
PRAC	Pharmacovigilance and Risk Assessment Committee

RA	rheumatoid arthritis
RMM	risk minimisation measures
RMP	Risk Management Plan
SAR	suspected adverse reaction
SAS	Statistical Analysis Software
SDLC	System Development Life Cycle
SmPC	Summary of Product Characteristics
SOPs	Standard Operating Procedures
SSRS	Server Reporting Services
TLFs	tables, listings, and figures
TNFα	Tumour Necrosis Factor alpha
TNFi	Tumour Necrosis Factor inhibitor
UBC	United BioSource LLC
UK	United Kingdom
USA	United States of America
VTE	venous thromboembolism
WHO	World Health Organisation

3. Responsible Parties

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4. Abstract

Title: Rheumatologist and Dermatologist Survey to Assess the Effectiveness of the Risk Minimisation Measures (RMM) for Olumiant® (baricitinib) a JAK1/2 inhibitor.

Rationale and Background:

Baricitinib is a Janus kinase (JAK) 1/JAK2 inhibitor that was first approved for the treatment of rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs. When baricitinib was first authorised for use in the European Union (EU) in February 2017, additional risk minimisation activities were included as part of the EU Risk Management Plan (RMP). These activities include:

(i) the Healthcare Professional (HCP) Educational Materials to inform the initial discussion between the rheumatologist and patient at time of first prescribing about important safety information related to the use of baricitinib during pregnancy or breastfeeding, the potential risk of infection, and changes in lipid parameters associated with the administration of baricitinib, and

(ii) a Patient Alert Card (PAC) with the same important safety information described above.

Additionally, Lilly committed to conduct of a survey of rheumatologists to assess the effectiveness of the above listed risk minimisation activities (Study I4V-MC-B010). The survey was designed to assess rheumatologists' understanding of the important safety information detailed in the HCP Education Materials and assess the communication of the important safety information and distribution of the PAC to patients prescribed baricitinib for the first time.

Subsequently, baricitinib has been approved for the indication of moderate to severe atopic dermatitis (AD) in adult patients who are candidates for systemic therapy and for the treatment of severe alopecia areata (AA) in adult patients.

Additionally, the HCP Educational Materials and the PAC for all indications have been updated to include important safety information on venous thromboembolism (VTE), major adverse cardiovascular events (MACE), lymphoma and other malignancies and dosing recommendations.

Also, a Direct Healthcare Professional Communication (DHPC) has been distributed to dermatologists and rheumatologists to draw attention to the increased incidence of MACE, serious infections, VTE and mortality seen with JAK inhibitor treatment.

Research Questions and Objectives: This study will assess the following:

1. The effectiveness of the updated baricitinib HCP Educational Materials and PAC among dermatologists and rheumatologists
2. The effectiveness of a DHPC distributed to dermatologists and rheumatologists

- **Study Design:** This study uses a multi-national, observational cross-sectional design. Approximately 400 completed surveys will be obtained with approximately 200 from dermatologists and 200 from rheumatologists. No more than 80 completed dermatology surveys and 80 completed rheumatology surveys will be accepted from any individual country.
- **Population:** The survey will be administered to dermatologists and rheumatologists in at least 3 EU countries: Sweden, France and Germany. The targeted respondent population will be dermatologists of whom at least 50% will have prescribed baricitinib and rheumatologists of whom at least 50% will have prescribed baricitinib.

  Screening questions will be used to determine respondent eligibility for the survey. Individuals who have ever worked directly for, or whose immediate family members have ever worked directly for Eli Lilly and Company (Lilly) or any of its affiliates, United BioSource LLC (UBC), IQVIA, the European Medicines Agency (EMA) or any National Competent Authority (NCA) will not be considered for participation.

- **Study Endpoints**: For Objective 1, the study endpoints are the correct understanding of each Key Risk Message (KRM) (Questions 8-16 pertaining to pregnancy, lipid changes, infections and VTE, MACE, lymphoma, and other malignancies and dosing as communicated in the HCP Educational Materials).

  The survey will also assess whether HCPs (a) communicate the important safety information and mitigating actions to patients prescribed baricitinib for the first time, and (b) distribute the PAC to patients prescribed baricitinib for the first time.

  For Objective 2, the study endpoints are the correct understanding of each KRM (Questions 17-19) pertaining to the JAK inhibitor class effects communicated in the DHPC.

- **Variables:** The survey will collect responses to each question required to address the study objectives, in addition to prescriber status (yes/no), demographic information (e.g., country of practice), and clinical experience (e.g., duration of experience treating patients with relevant indication, number of patients for whom they have prescribed baricitinib).

- **Data Sources**: Structured, self-administered surveys comprising closed-ended questions or statements with multiple-choice responses will be used to collect the data.

- **Study Size**: The study will target completion of approximately 400 surveys (approximately 200 dermatologists and approximately 200 rheumatologists), with at least 50% of those from dermatologists who have prescribed baricitinib and 50% from rheumatologists who have prescribed baricitinib. This will provide an estimated precision of ±7% around the observed proportion of correct responses (for each speciality) who answer correctly, assuming the true proportion is 50%. If the true proportion is greater or lesser than 50%, the estimated proportion will be more precise. The maximum number of completed surveys from any individual country will be set to 80 dermatologists and 80 rheumatologists.

- **Data Analysis:** Data collected from the survey will be reported using descriptive statistics. In addition to the overall analysis of the survey data collected, data will also be analysed by country, by speciality (dermatologist or rheumatologist) and prescriber status (has previously prescribed baricitinib [i.e., prescriber], has not previously prescribed baricitinib [i.e., potential prescriber]), by number of patients treated, and by

clinical experience. Responses to each question relating to the understanding of risks will be categorised as "Correct" or "Incorrect". Frequency distributions with 95% confidence intervals (CIs) will be calculated for responses to questions that address the survey objective (excluding demographic questions).

- **Milestones:** Data collection will commence within 3 months after both the DHPC and updated risk minimisation materials have been distributed in each participating country and a positive Committee for Medicinal Products for Human Use (CHMP) opinion on the protocol has been received. Data collection is estimated to start by 31 October 2023 and end when 400 surveys have been completed which is estimated to be 31 October 2024. Findings from the survey results will be reported to regulatory authorities (Section 6) with the study report expected by 30 April 2025.

5. Amendments and Updates

Amendment or Update Identifier	Date	Section of Study Protocol	Amendment or Update	Reason
a	21 April 2023	Title 8. Research Question and Objectives 9. Research Methods Appendix I.1 Survey	Inclusion of Rheumatologists in addition to Dermatologists Total study size increased to 400 participants Changes to Survey questions to test revised KRMs in HCP educational materials and DHCP Communication	Objectives and Survey Target Population expanded consistent with commitment made in the Article 20 referral
		Cover page 9. Research Methods Appendix I.1 Survey	Country change: Belgium replaced by Sweden	Feasibility to perform study
b	See Cover Page	9.7 Data Analysis 9.9 Limitations of the Research Methods	Removal of the target success threshold	Per PRAC review of protocol: Threshold is arbitrary and may not give full justice to study results and limit their interpretation
		9.9 Limitations of the Research Methods	Added limitation of recruitment method	Clarification of survey recruitment methods and how this is related to selection bias
		9.4 Data Sources	Revised methods for target sample size determination to ensure representativeness	Clarification of target sample size
		9.3 Variables 9.7 Data Analysis Survey Questionnaire	Removed Question 8 from survey	Per PRAC review of protocol: Age is not required as a confounder or stratification variable

6. Milestones

Milestone	Planned* Timeline
Submission of protocol	**25 April 2023**
Start of data collection	**Within 3 months after both the DHPC and updated risk minimisation materials have been distributed in each participating country and a positive CHMP opinion of the protocol.** **Estimated by 31 October 2023**
End of data collection	**When at least 400 surveys have been completed (200 dermatologists and 200 rheumatologists), estimated at 31 October 2024**
Registration in the EU PAS Register	**Prior to start of data collection**
Final study report	**6 months after the end of data collection, estimated 30 April 2025**

*The proposed start date for the survey depends on the timing of the CHMP opinion of the protocol (based on EMA timetable for Post Authorisation Measure assessment) as well as the DHPC distribution and implementation of updated risk minimisation materials (i.e., the PAC and HCP Educational materials) in each participating country.

7. Rationale and Background

Baricitinib is a Janus kinase (JAK) 1/JAK2 inhibitor that was first approved for the treatment of rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs. When baricitinib was first authorised for use in the European Union (EU) in February 2017, additional risk minimisation activities were included as part of the EU Risk Management Plan (RMP). These activities included:

(i) the Healthcare Professional (HCP) Educational Materials to inform the initial discussion between the rheumatologist and patient at time of first prescribing about important safety information related to the use of baricitinib during pregnancy or breastfeeding, the potential risk of infection, and changes in lipid parameters associated with the administration of baricitinib, and

(ii) a Patient Alert Card (PAC) with the same important safety information described above.

Eli Lilly and Company (Lilly) conducted a survey of rheumatologists to assess the effectiveness of the above listed risk minimisation activities. The survey was designed to assess rheumatologists' understanding of the important safety information detailed in the HCP education materials and assess the communication of the important safety information and distribution of the PAC to patients prescribed baricitinib for the first time. The final study report for Study B010 concluded that the risk minimisation materials were effective; rheumatologists understood the safety information for baricitinib and communicated these messages to their patients (Procedure EMEA/H/C/004085/II/0017 with Committee for Medicinal Products for Human Use [CHMP] positive opinion 29 October 2020).

Subsequently, baricitinib was approved for the indication of moderate to severe atopic dermatitis (AD) in adult patients who are candidates for systemic therapy in October 2020 and for the treatment of severe alopecia areata (AA) in adult patients in June 2022. With the expansion of marketing authorisation into dermatologic conditions, Lilly originally committed to survey dermatologists to ensure the risk minimisation materials were also effective among dermatologists (Study I4V-MC-B025; committed to in EU RMP v8.1 [Procedure EMEA/H/C/004085/II/0016]).

Implementation of Study B025 was held as part of a safety variation submitted to the Pharmacovigilance and Risk Assessment Committee (PRAC) by Lilly 29 October 2021, and then by the Article 20 referral for Janus kinase inhibitors (JAKi) (10 February 2022). With the completion of the Article 20 referral (10 March 2023), the scope of B025 was expanded to include rheumatologists as well as dermatologists, and to assess the resulting Risk Minimisation Measures (RMMs) which included updated educational materials and a Direct Healthcare Professional Communication (DHPC). The HCP Educational Materials and the PAC for all indications were updated to include additional important safety information on venous thromboembolism (VTE), major adverse cardiovascular events (MACE), lymphoma and other malignancies and dosing recommendations.

The DHPC has been distributed to dermatologists and rheumatologists to communicate the increased incidence of MACE, serious infections, VTE and mortality seen with JAK inhibition treatment compared to Tumour Necrosis Factor inhibitors (TNFi).

8. Research Question and Objectives

This study will assess the following:

Research Questions and Objectives: This study will assess the following:

1. The effectiveness of the updated baricitinib HCP Educational Materials and PAC among dermatologists and rheumatologists. The key risk messages (KRMs) within these materials include those pertaining to:
    a. Pregnancy
    b. Infections
    c. Changes in lipid parameters
    d. VTE
    e. MACE
    f. Lymphoma and other malignancies
    g. Appropriate dosing
2. The effectiveness of a DHPC distributed to dermatologists and rheumatologists.

9. Research Methods

9.1. Study Design

This observational study is a multi-national cross-sectional survey.

9.2. Setting

Eligible dermatologists and rheumatologists from at least 3 EU countries (Sweden, France, and Germany) will be invited. These countries were chosen based upon sufficient market uptake of baricitinib to support target enrolment and sufficient numbers of dermatologists and rheumatologists who have indicated they are willing to participate in this type of research. The survey will be distributed within 3 months after both the DHPC and updated risk minimisation materials have been distributed in each participating country and a positive CHMP opinion of this protocol (see Section 6).

To maximize the generalisability of the survey results, a maximum number of completed surveys will be accepted from each country, so that no individual country is over-represented. No more than 80 completed surveys from each speciality will be accepted from any one country, i.e., a maximum of 80 dermatologists from each country and 80 rheumatologists from each country. Additional EU countries may be considered as necessary to meet target enrolment.

The HCP Educational Materials, the PAC and the DHPC will be sent to HCPs who are prescribers or potential prescribers of baricitinib in each country, as agreed by each National Competent Authority (NCA).

The target population in each selected country will be dermatologists and rheumatologists who have been sent the HCP Educational Materials, the PAC and the DHPC.

The same survey will be used for all participating countries to ensure consistency in testing the target population. As such, variability of survey results based on geography is not anticipated.

Respondents will have the option to complete the survey via the internet, which will allow respondents to participate at a time and location that is convenient for them, or via telephone. The same survey will be offered through both modalities.

9.2.1. Survey Target Population

The target populations for the survey are dermatologists and rheumatologists in the EU who have previously self-identified as being willing to receive invitations for survey research. At survey initiation, this will include dermatologists and rheumatologists in Sweden, France and Germany.

Inclusion criteria

Dermatologists or rheumatologists must meet the following criterion for inclusion in the survey:

- Must identify themselves as being previous prescribers or potential prescribers of baricitinib.

To ensure that survey results adequately reflect the knowledge of the main target of the survey; at least 50% of the total completed surveys for each speciality will be required from prescribers of baricitinib.

Exclusion criteria

Dermatologists or rheumatologists meeting the following criterion will not be permitted to take the survey:

- Current or past employment with Lilly or any of its affiliates, UBC, IQVIA, the European Medicines Agency (EMA) or any NCA.

9.3. Variables

The survey will collect responses to each question required to address the two study objectives:

Objective 1

- Response to questions about important safety information detailed in HCP Educational Materials, including key risk messages pertaining to:
    a. Pregnancy
    b. Infections
    c. Changes in lipid parameters
    d. VTE
    e. MACE
    f. Lymphoma and other malignancies
    g. Appropriate dosing
- Whether or not important safety information and mitigating actions to patients prescribed baricitinib for the first time was communicated, and
- Whether the PAC was distributed to patients prescribed baricitinib for the first time.

Objective 2

- Responses to questions about important safety events observed with JAKi as detailed in the DHPC letter.

In addition, information on the following will be collected:

- Speciality (rheumatologist/dermatologist)
- Prescriber status (yes, have previously prescribed/have not yet prescribed)
- Demographic information: geographic location (country), and
- Clinical experience: duration of experience treating patients with relevant indication (years), number of patients for whom they have prescribed baricitinib (count).

9.4. Data Sources

In order to target the desired population, the data source will be a database of dermatologists and rheumatologists sourced from IQVIA, a subcontractor of UBC, in each of the selected countries who have previously agreed to be contacted for this type of research. Based on feasibility assessments of the list of dermatologists and rheumatologists from each of the

participating countries, invitations will be sent to all rheumatologists in each country's list. There are larger numbers of dermatologists listed in Germany and France. Therefore, a 50% simple random sample will be selected and invited in each of these 2 countries while all dermatologists in Sweden will be invited.

Dermatologists and rheumatologists will receive an invitation letter via email and/or postal mail to participate in the survey. The invitation letter (Appendix I.2) will include: an overview of the rationale for the survey, information on how to access the survey online or by telephone, and a unique invitation code to ensure that the invitation is used only once. Based on survey uptake within each respective country, reminder notices will be sent via email and/or postal mail to those who have been invited but have not yet participated. The database of invitees will be regularly updated with responders and after each invitation mailing, the database will be cross-checked with any correspondence that had an invalid address, was undeliverable or had incorrect contact details. Those who have been sent an invitation, and there is no evidence that it has not been received (e.g., an invalid address), and who do not respond within 2 weeks from the initial mailing, will receive at least 1 reminder invitation.

A structured questionnaire will be used to collect survey data (Appendix I.1). It is comprised of closed-ended questions or statements with multiple response choices.

The survey will be voluntary. The collection of any personal, identifying information (e.g., first name, last name, address) from respondents will only be used for processing of participants' financial compensation, as allowed by local laws and country regulations, and will be stored in a separate database.

Each individual HCP will be randomly assigned a unique code to access the survey. Each unique code will be deactivated upon first use to prevent the code from being used to complete the survey multiple times. Individuals will not have to actively "decline to complete the survey". Therefore, there will be no ability to track those who decline to participate. Individuals who log into the survey and decline to complete the full survey will be presented with two questions relating to whether non-respondents have prescribed baricitinib and whether they are aware of the important safety information communicated in the HCP Educational Materials and in the DHPC communication. Participants who agree to respond to the survey will begin with a screening module with questions to confirm eligibility.

The internet survey will be self-administered. The telephone survey will be administered by a trained interviewer from the Survey Coordinating Centre who will conduct the telephone interviews using a Computer-Assisted Telephone Interview programme and will enter the participants' responses directly into the Electronic Data Capture (EDC) system while in conversation with the participants. For both the internet and telephone modalities, the surveys will be available in the applicable local language.

The survey will include questions in the following categories:

Screening questions:

- *Agreement to participate*
- *Dermatologists or rheumatologists*
- *Current or past employment by Lilly, or any of its affiliates, UBC, IQVIA, the EMA, or any NCA*

Data on demographic characteristics:

- *Geographical location*
- *Years of experience in speciality*
- *Proportion of patients seen with relevant indication for the speciality (ie., proportion of patients seen with either AD or AA for the dermatologists or proportion of patients seen with RA for the rheumatologists)*
- *Prescriber of baricitinib (yes/no)*
- *Number of patients prescribed baricitinib*

Data pertaining to evaluation of the dermatologists and rheumatologists' understanding of the important safety information in the HCP Educational Materials, communication of the important safety information and mitigating actions to patients prescribed baricitinib for the first time, and distribution of the PAC to patients prescribed baricitinib for the first time.

Data pertaining to evaluation of dermatologists' and rheumatologists' understanding of the content of the DHPC.

9.5. Study Size

The target sample size is approximately 200 dermatologists and approximately 200 rheumatologists, leading to a total of approximately 400 completed surveys. This sample size was determined based on providing a precision of ±5% around a response of 50%, based on a two-sided 95% confidence interval (CI) for the full population of 400 surveys. Because precision varies based on the proportion who respond correctly, Table 1 provides a range of expected precision, based on the normal approximation of the binomial CI, for several proportions as well as sample sizes. The greatest variance and, therefore, the least precision, occurs when the observed proportion of responses is 50%, i.e., when p=0.5 in the equation below:

$$p \pm z_{1-\alpha/2}\sqrt{\frac{p(1-p)}{n}}$$

Where p = proportion of interest
α = desired confidence
$z_{1-\alpha/2}$ = 1.96 for 95% confidence
n = sample size

Additional requirements for the same size include:

- Require that at least 50% of respondents from each speciality indicate they have prescribed baricitinib

- The maximum number of completed surveys from any individual country will be set to 80 for each speciality, i.e., maximum of 80 dermatologists from each country and 80 rheumatologists from each country.

Although the sample size is based on the requirements set in the study, the proportion of correct responses cannot be known ahead of time. Since precision depends on both the sample size and the proportion of correct responses, a range of possible precision is presented for different proportions at relevant sample sizes. For analyses by prescriber status, where 200 of each specialty are anticipated, the precision of results will lie within ±7% at worst. For analysis overall, where 400 surveys will be completed, the precision of results will lie within ±5% at worst. Results by country subgroups cannot be estimated since the total number of completed surveys from each country is not yet known. Further stratification is not planned as the resulting sample sizes would have limited precision. For example, 40 responses resulting from stratifying prescriber status by country would have less precision than ±15.5%.

Table 1. Estimated Precision, by Sample Size and Proportion

Sample size	Proportion of Correct Responses Observed (%)	Precision or Margin of Error* (±%)
40	50	15.5
	70	14.2
	80	12.4
	90	9.3
200	50	6.9
	70	6.4
	80	5.5
	90	4.2
400	50	4.9
	70	4.5
	80	3.9
	90	2.9

* 95% confidence interval, two-sided.

9.6. Data Management

All data collected during the survey will be confidential. UBC's secure web-based proprietary EDC system used for data collection does not include any respondent-identifying information. Respondent identifiers are stored in a separate encrypted electronic database from the survey responses.

The survey is programmed to ensure that internet and telephone respondents cannot go back or skip ahead. The survey will time out after 30 minutes of inactivity. Where possible, statements requiring response and response options are presented in a list and are randomised to minimise positional bias. In addition, the ability to mark only one response is part of the programming for the survey administration and will minimise the occurrence of data entry errors. There will be no follow-up questions to respondents for this project.

Throughout the course of the study, a full back-up of the data will be performed on a nightly basis and cumulative back-ups will also be performed on a weekly basis. Back-up files will be stored at a secure off-site location.

Documentation related, but not limited, to the following will be retained:

- Computer software and hardware development, validation, and maintenance records
- Project specific procedures
- Curriculum vitae and training records of personnel
- Team roster
- Organizational charts
- Audit reports/audit certificates

Note: Standard retention policy for documents is at least 2 years following project closure, unless otherwise required per the contract.

Testing and production data extracted from the EDC database-derived analysis datasets, and generated tables, listings, and figures (TLFs), will be validated, documented, and retained by UBC after the data is exported from the EDC system.

The UBC EDC application provides protection and security. The team incorporates processes, automated and manual tools, and experienced security experts to ensure the protection of all stakeholder and sponsor data. These tools and processes are governed by data privacy and protection standard operating procedures (SOPs) to ensure compliance and adherence. Protection of the data requires that audit trails be under application control for all updates and deletions, and that date and time stamps are available. The UBC EDC maintains an audit trail containing date and time stamps at all times. Security of the application requires data centre and application security which is governed by physical and logical security SOPs. The UBC EDC maintains user and group-level security so that only staff on the Lilly baricitinib team will have access to the system. All web-based applications include secure sockets layer, encryption, and authentication protocols for access. Any remote user to the system must obtain a secure username and password that is only assigned after proper training is completed and authorisation is granted by the appropriate personnel. Remote UBC staff must log in via a secure virtual private network, as well as with a secure username and password. Access is available only to personnel who are provided a username and password, or to survey respondents who are provided a unique study-based code.

Dependability of the application requires that the application have validated and documented evidence that the application does what it is purported to do and will continue to do so. The database will be thoroughly validated and documentation of testing will be completed.

UBC's Information Technology (IT) applications are governed by a development approach to ensure compliance to the United States Food and Drug Administration (FDA) Guidance for Industry-Computerized Systems Used in Clinical Trials in the Title 21 Code of Federal Regulations (CFR) Part 11, Electronic Records; Electronic Signatures, and EudraLex Annex 11: Computerized Systems, and international regulations and standards (e.g., EU Guideline on Good Pharmacovigilance Practices [GVP], International Council for Harmonisation [ICH]) and relevant EMA guidelines. Title 21 CFR Part 11 applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted under any records requirements set forth in Agency regulations. Part 11 also applies to

electronic records submitted to the Agency under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act. In accordance with Title 21 CFR Part 11 Department of Health and Human Services Federal Regulations, the EDC application must provide protection, security, and dependability. Protection of the data requires that audit trails be under application control for all updates and deletions, and that date and time stamps are available. Therefore, all associated Title 21 CFR Part 11 requirements are documented including: requirements for data entry, audit trails, date and time stamps, and security. Furthermore, the Title 21 CFR Part 11 checklist, which captures the traceability of the EDC requirements to the requirements set forth in the Title 21 CFR Part 11, *Electronic Records, Electronic Signatures,* is included in the validation summary report.

No respondent contact information will be included in the tables or in the final report.

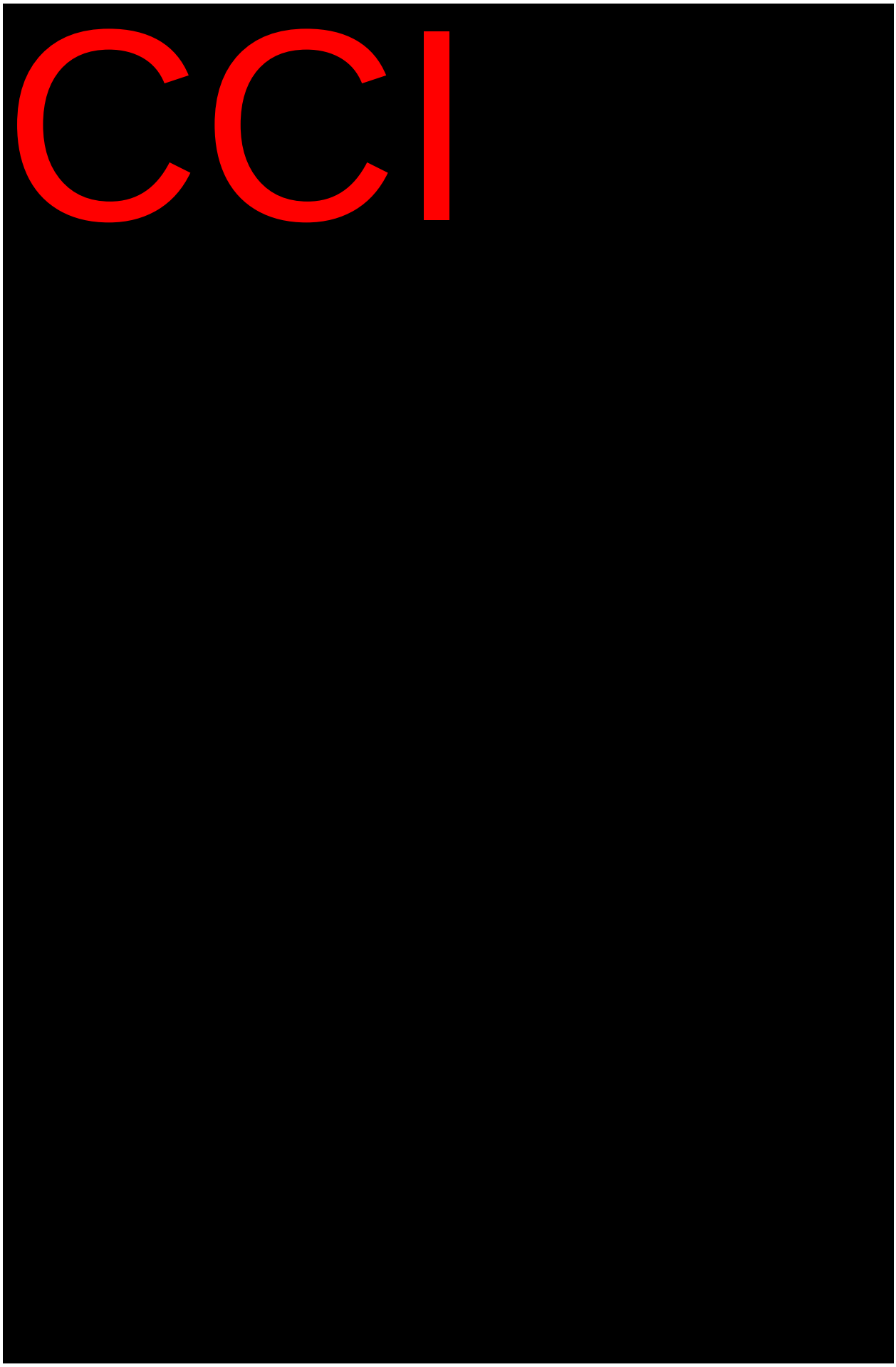
9.7. Data Analysis

Data collected from the survey will be reported as descriptive statistics. Frequency distributions with 95% CIs will be calculated for responses to questions that address the knowledge of the KRMs within the HCP Educational Materials (i.e., excluding demographic questions and general questions concerning the HCP Educational Materials and the DHPC).

Survey data will be analysed overall, and stratified by country, speciality, prescriber status (has previously prescribed baricitinib [i.e., prescriber] or has not previously prescribed baricitinib [i.e., potential prescriber]), and by number of patients treated. The cut-off for stratifying results defined by the number of patients prescribed baricitinib, will be based on the distribution of number of prescriptions in the data. This is to ensure that sufficient numbers are available for each stratum. Analysis by experience treating patients with AD/AA or RA will be based on responses to survey Question 4 (number of years practising in speciality : <5, 5–10, 11–15, >15 years) and Questions 5a and 5b (number of patients who have AD/AA or RA : <5, 5–25, >25), described in Annex 1. The cut-off for stratifying results by “high” or “low” experience will be determined on the distribution of prescribers in the cross-categorisation of experience and proportion of patients with the applicable indication.

Responses will be categorised as “Correct response” and “Incorrect response”. “I do not know” is categorized as an incorrect response.

For Objective 1, Table 2 outlines these 7 key risk messages, the individual questions within each message, and the criteria for success of each message.



For Objective 2, Table 3 outlines the individual questions for the key risk message and the criteria for success.

Among prescribers, the proportion who report the following will be assessed:

- Communication of this information and mitigating actions to patients prescribed baricitinib for the first time, and
- Distribution of the PAC to patients prescribed baricitinib for the first time.

The following information will be reported as part of the analysis using counts and percentages:

- *Survey administration will be performed by country, by speciality and overall:*
  - *The number of survey invitations*
  - *The number of survey invitations/reminders returned due to incorrect mailing/emailing address of dermatologists/rheumatologists invited to participate in the survey*
  - *The number of dermatologists/rheumatologists who responded to the invitation to participate in the survey*
  - *The number of dermatologists/rheumatologists who meet the inclusion criteria for participation in the survey*
  - *The number of dermatologists/rheumatologists who do not meet the inclusion criteria along with the reasons for ineligibility*
  - *The number of dermatologists/rheumatologists who meet the inclusion criteria and completed the survey*
- *Demographic characteristics of participants by country*
  - *Distribution of participants by number of patients currently treated with baricitinib*
- *Responses to questions pertaining to the important safety information (Question 8 to Question 19)*
- *Demonstrated understanding of Key Risk Message 1 to 8.*

For Objective 1, HCPs' understanding of the important safety messages detailed in the HCP Educational Materials, communication of the important safety information and mitigating actions to patients prescribed baricitinib for the first time, and distribution of the PAC to patients prescribed baricitinib for the first time will be analysed by geography, speciality, prescribing status/number of patients treated with baricitinib, and experience with treating patients with the relevant dermatological or rheumatological condition.

A similar analysis will take place for Objective 2.

9.8. Quality Control

Data will be collected using a secure and validated online EDC system designed and built by UBC. A System Development Life Cycle (SDLC) is used for validation that complies with UBC internal IT SOPs. The SDLC is fortified with SOPs addressing validation for all clinical and risk minimisation-related applications. The internet-based repository will be used to store survey data and other relevant programme information. UBC's IT applications are governed by a development approach to ensure compliance with FDA 21 CFR Part 11, international regulations and standards (e.g., EU GVP, ICH) and relevant EMA guidelines. The system is compliant for the entry, storage, handling, analysis and transmission of electronic information. Respondent-identifying information will be stored separately from the survey responses. At the end of each survey cycle, data will be extracted from the EDC.

Programming will be reviewed by UBC Quality Control and simulated users (User Acceptance Testing) prior to implementation.

At the completion of data collection, data will be extracted from the EDC and mapped to Statistical Analysis Software (SAS) datasets (SAS V9.1.3 or higher). The extracted EDC data will be mapped to SAS datasets ("original" production datasets) as defined in the annotated Data Collection Tools (aDCTs) by a SAS programmer/designee. The mapping of raw data will be validated, as will the programming of the analysis tables created from the raw EDC data. Additionally, the EDC data will also be mapped to SAS datasets by a Server Reporting Services (SSRS) programmer as defined in the aDCTs and validated by the UBC Quality Control Team. These original SAS datasets will be validated by double programming and Quality Control. The validated original SAS datasets will then be used by a SAS programmer to create a set of summary tables and listings according to the SAP text and mock-up tables. If derived analysis datasets are required to produce these summary tables, these will be created and independently validated. All TLF output will be independently validated and documented. Summary tables will be reviewed by the appropriate team members and included in the final report sent to Lilly to be submitted to the PRAC.

UBC has an IT Quality Assurance Group that is responsible for managing and overseeing system/application development and validation, as well as related compliance functions.

9.9. Limitations of the Research Methods

The database of dermatologists and rheumatologists in each country from which the recruitment mailing list is derived is a database of prescribers who have previously agreed to participate in survey research. This approach of only contacting HCPs who have consented to be contacted for research purposes has been taken to be compliant with the General Data Protection Regulation (GDPR). However, there is possible selection bias by not reaching out broadly to all practicing rheumatologists or dermatologists in each of the 3 countries. The difficulties of survey research in the EU because of data protection regulations and possible selection bias issues were highlighted in a White Paper by the International Society for Pharmacoepidemiology and presented at the European Medicine Agency's Workshop on Measuring the Impact of Pharmacovigilance Activities (Madison and Sobel 2016). Participants who have agreed to be included in this type of database may differ in their knowledge and prescribing characteristics from the overall group of practicing clinicians in

each country. Given the restrictions of the GDPR that individuals may only be contacted if they have agreed to the contact, it is not possible to contact all HCPs that receive the aRMM materials. Therefore, this type of selection bias is a possibility for all survey-based research where the participants who do respond to the survey may differ from those who do not respond.

The survey recruitment strategies are intended to recruit dermatologists and rheumatologists who report that they are prescribers or potential prescribers of baricitinib. Participants will be self-selected since they will voluntarily respond to the invitation to participate, so the potential exists that those who choose to respond to the survey may differ in their understanding of the important safety information from those who elect not to participate. This is a common limitation of all studies that rely on voluntary participation. A possible approach to address this potential selection bias will be through the use of a limited non-respondent survey, which will be offered to those who decline to respond to the full survey. Subjects who decline to participate may nonetheless elect to respond to 2 questions aimed at understanding whether they differ in important ways from those who volunteer to respond to the survey. Specifically, these questions will request information on whether non-respondents have prescribed baricitinib and whether they are aware of the important safety information communicated in the HCP Educational Materials and in the DHPC communication.

Among those who volunteer to respond to the survey, recall of information is critical. Inherent in survey research is the reliance on the respondent's recall of whether or not the documents were received. If the respondent says she/he did not receive them, the risk minimisation programme is evaluated as not optimally disseminating the materials. It is possible, however, that respondents may simply not recall receiving these documents even thought they were, in fact, received.

It is also possible that the respondents have acceptable understanding of the important safety information despite not receiving or recalling receipt of the documents. The survey can assess the participants' understanding of the important safety information but cannot clearly determine via which channel they gained the information.

All data from the survey are self-reported and therefore susceptible to possible reporting bias.

9.9.1. Controls to Minimise Bias

A number of controls will be in place to ensure that the survey is conducted and minimise bias, including the following:

- Lists of response options will be randomised to minimise the potential for positional bias.
- The internet and telephone surveys will be programmed to ensure that questions are asked in the appropriate sequence, and all questions will be presented in a standard order to reduce exposure bias. Respondents cannot skip ahead or go back to a question once the question has been answered. All questions presented must be answered in order to complete a survey.
- Respondents will be provided with a unique code during the recruitment process in order to gain access to the internet-based systems. The code will be inactivated after use to minimise exposure bias and fraud.

9.10. Other Aspects

Not applicable.

10. Protection of Human Subjects

10.1. Personal Information and Consent

All data collected during the survey will be kept confidential by UBC and used only for the purposes stated in the survey instructions. The collection of any personal, identifying information (first name, last name, address) from respondents will only be used for the processing of the participants' financial compensation. Respondent identifiers are stored in a separate encrypted electronic database from the survey responses. The EDC system used for data collection of the survey responses does not collect any identifiable information. The sponsor will not have access to any personal information collected in relation to this survey.

By answering the first question of the survey ("*Do you agree to participate in this survey?*"), respondents are providing informed consent for participation in the research study.

10.2. Respondent Withdrawal

Respondents can decline to participate or stop taking the survey at any time. Only complete surveys will be included in the analysis.

10.3. Ethics Committee

Approval of this protocol by the respective local Ethics Committee will be sought prior to initiating the survey in each country, where applicable.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor, and follow generally-accepted research practices described in the *Guideline on Good Pharmacovigilance Practices* (*GVP) Module XVI- RMM: Selection of Tools and Effectiveness Indicators* (EMA 2017), *Good Pharmacoepidemiology Practices (GPP)* issued by the International Society for Pharmacoepidemiology (ISPE 2015), *Good Epidemiological Practice* (GEP) guidelines issued by the International Epidemiological Association (Hoffman et al 2019), *International Ethical Guidelines for Epidemiological Research* issued by the Council for International Organisations of Medical Sciences (CIOMS [WWW]), EMA European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology* (ENCePP 2023), and the United States FDA Guidance for Industry: *Good Pharmacovigilance and Pharmacoepidemiologic Assessment* (US FDA 2005).

11. Management and Reporting of Adverse Events/Adverse Reactions

11.1. Primary Data Collection Study

Adverse events will not be actively collected as this study is assessing dermatologists' and rheumatologists' understanding of the important safety information detailed in the HCP Educational Materials, the PAC and the DHPC.

Study personnel and survey respondents are requested to report any suspected adverse reactions (SARs) with any drug to the appropriate party as required in normal practice.

11.2. Product Complaints

Lilly collects product complaints on marketed Lilly products such as drugs, drug/device combinations, medical devices, software as medical device (e.g., mobile medical applications), and comparator product(s) used in post-marketing medical research studies to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

For Lilly products under evaluation and/or Lilly products not under evaluation but discovered during the study, study personnel and survey respondents are instructed to report product complaints as they would for products in the marketplace.

For non-Lilly products, such as comparator drugs or medical devices, or concomitant drugs or medical devices, study personnel are instructed to report product complaints as they would for products in the marketplace.

12. Plans for Disseminating and Communicating Study Results

Final reports will be submitted to regulatory agencies. The study, including the final report, will also be registered in the ENCePP Register. The study findings may be submitted to a scientific congress and/or to a peer-reviewed journal.

13. References

[CIOMS] Council for International Organisations of Medical Sciences. *International Ethical Guidelines for Epidemiological Research*. Accessed 08 Sept 2023. https://cioms.ch/publications/product/international-ethical-guidelines-for-epidemiological-studies/

[ENCePP] European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on methodological standards in pharmacoepidemiology. EMA/95098/2010 Rev. 11. Published July 2023. Accessed 08 Sept 2023. https://www.encepp.eu/standards_and_guidances/documents/01.ENCePPMethodsGuideRev.11.pdf

[EMA] European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) Module XVI – risk minimisation measures: selection of tools and effectiveness indicators. EMA/204715/2012 Rev. 2. Published 28 March 2017. Accessed 08 Sept 2023. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-xvi-risk-minimisation-measures-selection-tools_en-3.pdf

Hoffmann W, Lata U, Baumeister SE, Brunger M, Buttmann-Schweiger N, Hardt J, Offmann V, Karch A, Richter A, Schmidt CO, Schmidtmann I, Swart E, van den Berg N. Guidelines and recommendations for ensuring Good Epidemiological Practice (GEP): a guideline developed by the German Society for Epidemiology. *Eur J Epidemiol*. 2019;34(3):301-317.

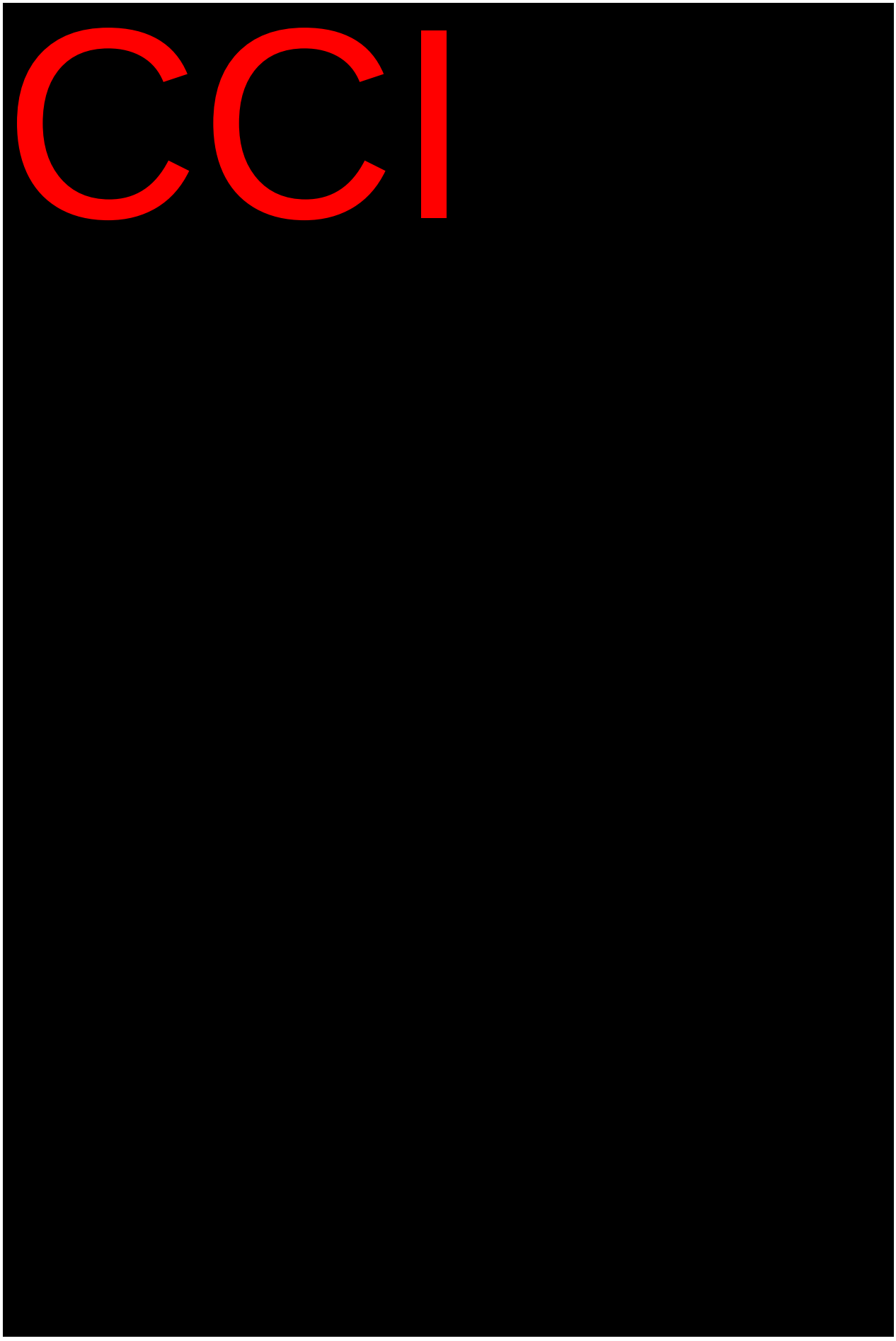
[ISPE] International Society for Pharmacoepidemiology. Guidelines for good pharmacoepidemiology practices (GPP). Rev. 3. Published June 2015. Accessed 08 Sept 2023. https://www.pharmacoepi.org/resources/policies/guidelines-08027/

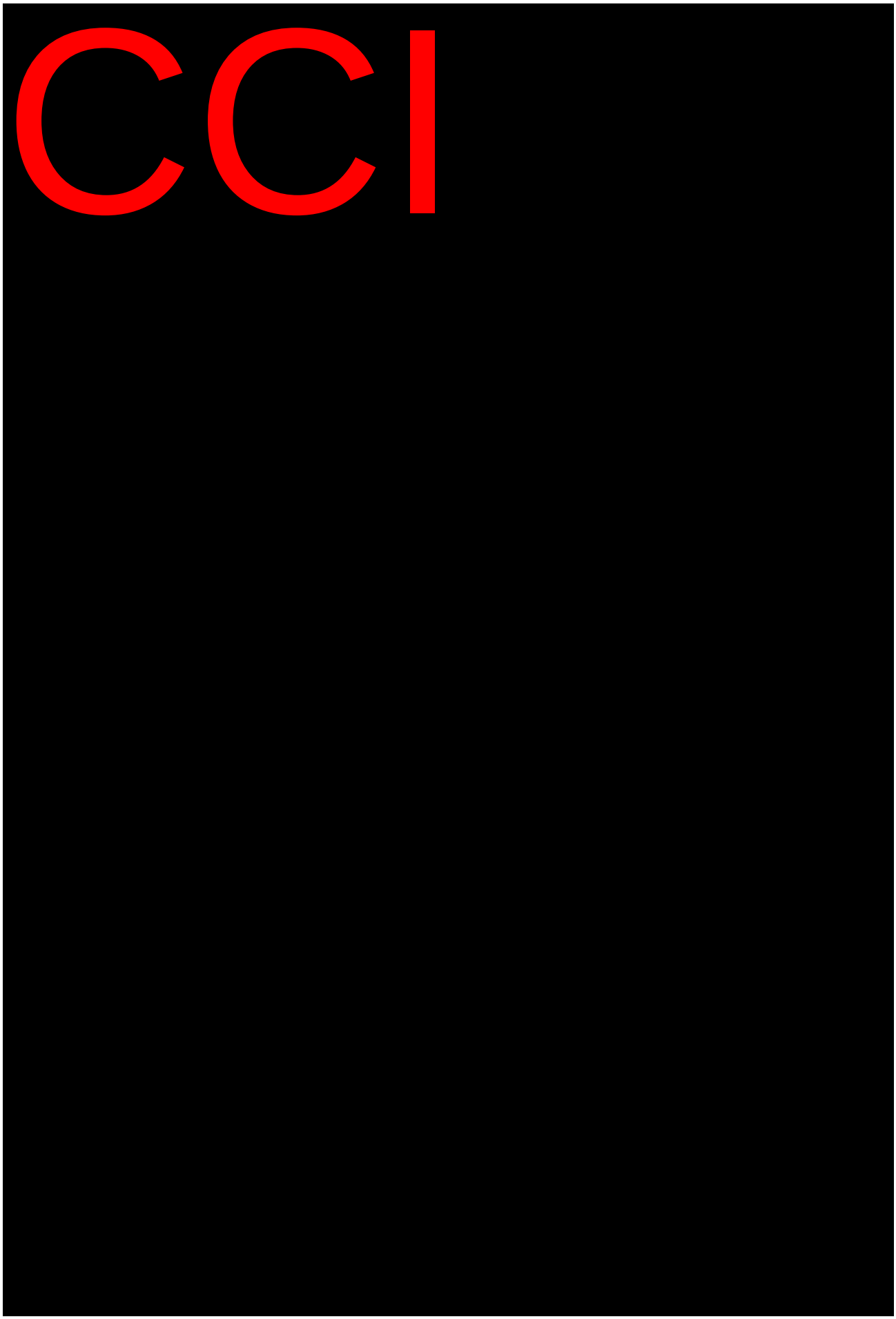
Madison T, Sobel R. Evaluating the effectiveness of additional risk minimisation measures via surveys in Europe: challenges and recommendations. Presented at: European Medicines Agency workshop on measuring the impact of pharmacovigilance activities; 06 December 2016, London, UK. https://www.ema.europa.eu/en/documents/presentation/presentation-ispe-paper-evaluating-effectiveness-additional-risk-minimisation-measures-surveys_en.pdf

[US FDA] United States Food and Drug Administration. Guidance for industry: good pharmacovigilance and pharmacoepidemiologic assessment. Published 22 March 2005. Accessed 08 Sept 2023. https://www.fda.gov/files/drugs/published/Good-Pharmacovigilance-Practices-and-Pharmacoepidemiologic-Assessment-March-2005.pdf

Annex 1. List of Standalone Documents

Number	Document Reference Number	Date	Title
1	Appendix I.1		Proposed Survey
2	Appendix I.2		Sample Draft Survey Invitation Letter
3	Appendix I.3		Healthcare Professional Educational Materials and the Patient Alert Card
4	Appendix I.4		Direct Healthcare Professional Communication [date]





APPENDIX I.2. SAMPLE DRAFT INVITATION LETTER

[Date]
[Addressee's name]
[Title]
[Street address]
[City, State, Post code]
[Country]

Re: Invitation to Participate in Olumiant® (baricitinib) Survey

Dear Dr. [insert LAST NAME],

On behalf of Eli Lilly and Company (Lilly), we would like to invite you to participate in a voluntary safety survey about Olumiant (baricitinib), a Janus kinase (JAK)1/JAK2 inhibitor.

The safety survey is part of a Risk Management Plan (RMP) commitment between Lilly and the European Medicines Agency (EMA) to assess the effectiveness of Lilly's educational materials and communication sent to healthcare professionals to manage the important safety information of Olumiant. The safety survey should take approximately 25 minutes to complete. If you complete the safety survey and provide your contact information, you have the opportunity to receive [**€XX**] as fair compensation of your time, subject to local rules and regulations.

You may be able to participate if you are currently treating patients with atopic dermatitis, alopecia areata or rheumatoid arthritis. For your convenience, the survey can be completed online at https://www.baricitinibsurvey.com or over the telephone at **[TELEPHONE NUMBER].**

You will need the following code when completing the survey: **[UNIQUE CODE]**.

If participating online, it is possible to take the survey via desktop, laptop, or mobile device using a standard web (i.e. Chrome, Firefox) browser. If using an unsupported browser, an error message will display and it will not be possible to log in.

Why is this important?

In accordance with European regulations, Lilly develops RMPs for its medications. The RMP for Olumiant outlines the identified and potential risks associated with use of Olumiant, how these are monitored and what steps are taken to minimise them. In addition to the product labelling, Healthcare Professional Educational Materials, a Patient Alert Card and a Direct Healthcare Professional Communication were developed as additional risk minimisation measures. As part of its regulatory commitment, Lilly is required to assess the effectiveness of these additional risk minimisation measures and report back to the regulatory authorities.

Participating in this safety survey is entirely voluntary. All information that is collected during the course of the safety survey will be kept strictly confidential. Results will be reported in aggregate only. Your participation in the safety survey and your answers to the survey questions will not affect your ability to prescribe or currently treat patients who are prescribed Olumiant. You will not be contacted for marketing purposes. Neither Lilly nor its contractors will sell, transfer, or rent your information.

Your assistance with this safety survey is greatly appreciated. Thank you for your participation in this important research.

Sincerely,

{Note: Signatory to be determined for each country and customised accordingly}

APPENDIX I.3 Healthcare Professional Educational Materials and the Patient Alert Card

Healthcare Professional Educational Materials - Dermatologists

Information Material for Healthcare Professionals Prescribing Olumiant® (baricitinib)

This document contains important information to assist the initial discussion with your patients when prescribing Olumiant. It should be read in conjunction with the enclosed Summary of Product Characteristics (SmPC).

Olumiant is a selective and reversible janus kinase (JAK)1/2 inhibitor indicated for the treatment of moderate to severe atopic dermatitis (AD) in adult patients who are candidates for systemic therapy and severe alopecia areata (AA) in adult patients.

As part of the initial discussion with your patients, please:
- Provide a **Patient Alert Card** to each patient
- Advise them that the Card should be read in conjunction with the **Patient Information Leaflet**.

The recommended dose of baricitinib is 4 mg once daily.
A dose of 2 mg once daily is recommended for patients:
- at higher risk of venous thromboembolism, major adverse cardiovascular events (MACE), and malignancy,
- aged 65 years and older, and
- with a history of chronic or recurrent infections.

A dose of 4 mg once daily may be considered for patients who do not achieve adequate control of disease activity with 2 mg once daily dose.
A dose of 2 mg once daily should be considered for patients who have achieved sustained control of disease activity with 4 mg once daily and are eligible for dose tapering.

Infections

Olumiant increases the potential risk of infections.

Patients should be instructed to seek immediate medical attention if signs or symptoms suggesting infection appear.

As there is a higher incidence of infections in the elderly and in the diabetic populations in general,

- **caution** should be used when treating the elderly and patients with diabetes.

Changes in Lipid Parameters

Olumiant use is associated with hyperlipidaemia.

Prescribers should monitor the patient's lipid parameters and manage the hyperlipidaemia, if detected.

Venous Thromboembolism

Olumiant increases the risk of venous thrombosis and pulmonary embolism (PE). Olumiant should be used with caution in patients with known risk factors for deep vein thrombosis/PE other than cardiovascular or malignancy risk factors.

Patients should be instructed to seek immediate medical attention if signs or symptoms of deep vein thrombosis/PE appear.

Major Adverse Cardiovascular Events

There is a potentially increased risk of MACE in patients with certain risk factors using JAK inhibitor treatment, including Olumiant.

Thus, Olumiant should only be used if no suitable treatment alternatives are available, in patients:
- 65 years of age and older,
- who are current or past long-term smokers, and
- with other cardiovascular risk factors.

Lymphoma and Other Malignancies

Lymphoma and other malignancies have been reported in patients receiving JAK inhibitors, including Olumiant.

Thus, Olumiant should only be used if no suitable treatment alternatives are available, in patients:
- over 65 years of age,
- who are current or past long-term smokers, or

• Olumiant should only be used in patients 65 years of age and older if no suitable treatment alternatives are available. **Advise the patients that** • Olumiant use should be stopped in case of herpes zoster or any other infection that doesn't respond to standard treatment until the event resolves. • they should not be immunised using live attenuated vaccines shortly before or during treatment with Olumiant. Prescribers should screen the patients for viral hepatitis before commencing Olumiant treatment. Active tuberculosis should also be ruled out.	• with other malignancy risk factors (for example, current malignancy or history of malignancy). **Pregnancy and Breast Feeding** Olumiant is contraindicated in pregnancy, as pre-clinical data showed reduced foetal growth and malformations. **Thus,** • physicians should **advise** women of child-bearing potential to use contraception during treatment and for a week after its ending. • Olumiant treatment should be stopped if a planned pregnancy is considered.

Healthcare Professional Educational Materials: Rheumatologists

Information Material for Healthcare Professionals Prescribing Olumiant® (baricitinib)

This document contains important information to assist the initial discussion with your patients when prescribing Olumiant. It should be read in conjunction with the enclosed Summary of Product Characteristics (SmPC).

Olumiant is a selective and reversible janus kinase (JAK)1/2 inhibitor indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti -rheumatic drugs.

As part of the initial discussion with your patients, please:

- Provide a **Patient Alert Card** to each patient
- Advise them that the Card should be read in conjunction with the **Patient Information Leaflet**.

The recommended dose of baricitinib is 4 mg once daily.

A dose of 2 mg once daily is recommended for patients:

- at higher risk of venous thromboembolism, major adverse cardiovascular events (MACE), and malignancy
- aged 65 years and older, and
- with a history of chronic or recurrent infections.

A dose of 4 mg once daily may be considered for patients who do not achieve adequate control of disease activity with 2 mg once daily dose.

A dose of 2 mg once daily should be considered for patients who have achieved sustained control of disease activity with 4 mg once daily and are eligible for dose tapering.

Infections

Olumiant increases the potential risk of infections.

Patients should be instructed to seek immediate medical attention if signs or symptoms suggesting infection appear.

As there is a higher incidence of infections in the elderly and in the diabetic populations in general,

- **caution** should be used when treating the elderly and patients with diabetes.
- Olumiant should only be used in patients 65 years of age and older if no suitable treatment alternatives are available.

Changes in Lipid Parameters

Olumiant use is associated with hyperlipidaemia.

Prescribers should monitor the patient's lipid parameters and manage the hyperlipidaemia, if detected.

Venous Thromboembolism

Olumiant increases the risk of venous thrombosis and pulmonary embolism (PE). Olumiant should be used with caution in patients with known risk factors for deep vein thrombosis/PE other than cardiovascular or malignancy risk factors.

Patients should be instructed to seek immediate medical attention if signs or symptoms of deep vein thrombosis/PE appear.

Major Adverse Cardiovascular Events

There is a potentially increased risk of MACE in patients with certain risk factors using JAK inhibitor treatment, including Olumiant.

Thus, Olumiant should only be used if no suitable treatment alternatives are available, in patients:

- 65 years of age and older,
- who are current or past long-term smokers, and
- with other cardiovascular risk factors.

Lymphoma and Other Malignancies

Lymphoma and other malignancies have been reported in patients receiving JAK inhibitors, including Olumiant.

Thus, Olumiant should only be used if no suitable treatment alternatives are available, in patients:

- over 65 years of age,
- who are current or past long-term smokers, or
- with other malignancy risk factors (for example, current malignancy or history of malignancy).

Advise the patient that • Olumiant use should be stopped in case of herpes zoster or any other infection that doesn't respond to standard treatment until the event resolves. • they should not be immunised using live attenuated vaccines shortly before or during treatment with Olumiant. Prescribers should screen the patients for viral hepatitis before commencing Olumiant treatment. Active tuberculosis should also be ruled out.	**Pregnancy and Breast Feeding** Olumiant is contraindicated in pregnancy, as pre-clinical data showed reduced foetal growth and malformations. **Thus,** • physicians should **advise** women of child-bearing potential to use contraception during treatment and for a week after its ending. • Olumiant treatment should be stopped if a planned pregnancy is considered. These points are in line with independent expert European League Against Rheumatism (EULAR) recommendations* *Götestam Skorpen C, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann Rheum Dis*. 2016;75(5):795-810. https://doi.org/10.1136/annrheumdis-2015-208840

Patient Alert Card:

Information for Patients about OLUMIANT® (baricitinib)

This document contains important information you should be aware of before and during treatment with Olumiant.

Keep this information with you and share it with other healthcare professionals involved in your medical care or treatment.

Your name:

_____

Doctor's name (who prescribed Olumiant)**:**

_____

Doctor's phone number:

_____

Pregnancy

- Do not take Olumiant if you are pregnant or suspect you may be pregnant.
- Use effective contraception while taking Olumiant (and for 1 week after if you stop treatment).
- Tell your doctor immediately if you become (or wish to become) pregnant.

Infections

Olumiant may make an existing infection worse or increase the chance of you getting a new infection or increase the chance of viral reactivation. If you have diabetes or are older than 65, you may have an increased chance of getting infections. The infection can become serious if not treated. Inform your doctor immediately if you get symptoms of infection, such as:

- Fever, wounds, feeling more tired than usual, or dental problems.
- A cough that won't go away, night sweats, and weight loss. These could be symptoms of tuberculosis (an infectious disease of the lungs).
- A painful skin rash with blisters. This could be a sign of a herpes zoster infection.

Non-melanoma skin cancer

Non-melanoma skin cancer has been observed in patients taking Olumiant. If new skin lesions appear during or after therapy or if existing lesions change appearance, tell your doctor.

Blood clots

Olumiant may cause a condition in which a blood clot forms in your leg that may travel to your lungs. Inform your doctor

	immediately if you experience any of the following symptoms: • Swelling or pain in one leg or arm • Warmth or redness in one leg or arm • Shortness of breath which is unexpected • Rapid breathing • Chest pain **Heart attack or stroke** Inform your doctor immediately if you experience any of the following: • Severe chest pain or tightness (that may spread to arms, jaw, neck, back) • Shortness of breath • Cold sweat • One-sided weakness in arm and/or leg • Slurred speech

APPENDIX I.4 Direct Healthcare Professional Communication

<date>

Cibinqo (abrocitinib), Jyseleca (filgotinib), Olumiant (baricitinib), Rinvoq (upadacitinib) and Xeljanz (tofacitinib) – Updated recommendations to minimise the risks of malignancy, major adverse cardiovascular events, serious infections, venous thromboembolism and mortality with use of Janus kinase inhibitors (JAKi).

Dear Healthcare Professional,

AbbVie, Galapagos, Lilly and Pfizer in agreement with the European Medicines Agency and the <National Competent Authority> would like to inform you of the following:

Summary

- An increased incidence of malignancy, major adverse cardiovascular events (MACE), serious infections, venous thromboembolism (VTE) and mortality has been observed in patients with rheumatoid arthritis (RA) with certain risk factors using JAKi treatment com**pared to TNFα inhibitors.**
- These risks are considered class effects and relevant across all approved indications of JAKi in inflammatory and dermatologic diseases.
- These JAKi should only be used if no suitable treatment alternatives are available in patients:
    - 65 years of age and older;
    - who are current or past long-time smokers;
    - with other cardiovascular or malignancy risk factors.
- JAKi should be used with caution in patients with VTE risk factors other than those listed above.
- Dosing recommendations are revised for some patient groups with risk factors.
- Periodic skin examination is recommended for all patients.
- Prescribers should discuss with patients the risks associated with the use of JAKi.

Background on the safety concern

The JAKi Cibinqo (abrocitinib), Jyseleca (filgotinib), Olumiant (baricitinib), Rinvoq (upadacitinib) and Xeljanz (tofacitinib) are approved for the treatment of several chronic inflammatory disorders (rheumatoid arthritis (RA), psoriatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, ulcerative colitis, atopic dermatitis, and alopecia areata). The approved use differs for the different products, as outlined in the respective product information.

In March 2021, a Direct Healthcare Professional Communication (DHPC) for Xeljanz (tofacitinib)[1] was sent to healthcare professionals, informing them that data from a completed clinical trial (A3921133)[2] in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, suggest a higher risk of major adverse cardiovascular events (MACE) and malignancies (excluding non-melanoma skin cancer (NMSC)) with tofacitinib as compared to patients treated with a TNF-alpha inhibitor.

An additional DHPC[3] was sent in July 2021 to inform about an increased incidence of myocardial infarction, lung cancer, and lymphoma with tofacitinib compared to TNF-alpha inhibitors observed in the same clinical trial, as well as adopted recommendations for the product information of tofacitinib.

Preliminary findings from an observational study (B023) involving another JAK inhibitor, Olumiant (baricitinib), also suggest an increased risk of major cardiovascular events and VTE in patients with RA treated with Olumiant compared with those treated with TNF-alpha inhibitors.

Following the finalization of the review procedure of the available data across these five JAKi by EMA, recommendations have been adopted as specified in the "summary" above. The product information and the educational materials for healthcare professional and patients is being updated accordingly.

This letter is not intended as a complete description of the benefits and risks related to the use of these products. For further details, please refer to the updated SmPC for the respective products.

Call for reporting

< to be filled nationally>

Healthcare providers and patients are encouraged to report adverse reactions in accordance with the national spontaneous reporting system. <to be filled nationally> Please find the relevant contact for each product in the table below.

Product	Cibinqo (abrocitinib)	Jyseleca (filgotinib)	Olumiant (baricitinib)	Rinvoq (upadacitinib)	Xeljanz (tofacitinib)
MAH	Pfizer	Galapagos	Lilly	AbbVie	Pfizer
Telephone number					
Email address					

Company contact point

< to be filled nationally>

[1] https://www.ema.europa.eu/en/medicines/dhpc/xeljanz-tofacitinib-initial-clinical-trial-results-increased-risk-major-adverse-cardiovascular
[2] Ytterberg, Steven R., et al. "Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis." *New England Journal of Medicine* 386.4 (2022): 316-326.
[3] https://www.ema.europa.eu/en/medicines/dhpc/xeljanz-tofacitinib-increased-risk-major-adverse-cardiovascular-events-malignancies-use-tofacitinib

Product	Cibinqo (abrocitinib)	Jyseleca (filgotinib)	Olumiant (baricitinib)	Rinvoq (upadacitinib)	Xeljanz (tofacitinib)
MAH	Pfizer	Galapagos	Lilly	AbbVie	Pfizer
Website address					
Postal address					

Annex 2. ENCePP Checklist for Study Protocols

Study title: Survey to Assess the Effectiveness of the Risk Minimisation Measures (RMM) for Olumiant® (baricitinib) a JAK1/2 inhibitor

EU PAS Register® number: EUPAS43239
Study reference number (if applicable): I4V-MC-B025

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[4]	☒	☐	☐	9
1.1.2 End of data collection[5]	☒	☐	☐	9
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	9
1.1.6 Final report of study results.	☒	☐	☐	9

Comments:

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.3
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

The study will be descriptive and there will not be hypothesis testing

[4] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[5] Date from which the analytical dataset is completely available.

Section 3: Study design	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Healthcare Professionals' answers will be categorised as "correct" or "incorrect". The frequency of "correct" answers will be calculated for each question that addresses the study objective.

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	6 & 9.2
4.2.2 Age and sex	☐	☒	☐	9.4
4.2.3 Country of origin	☒	☐	☐	9.4
4.2.4 Disease/indication	☒	☐	☐	9.4
4.2.5 Duration of follow-up	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1 & 9.4

Comments:

4.2.2 – HCP participant age will not be collected per PRAC feedback.

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.7
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.5
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.4 & 9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9.1

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☐	☐	☒	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☐	☐	☒	
9.1.3 Covariates and other characteristics?	☐	☐	☒	
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☒	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

Only completed, surveys will be included in the analysis, therefore there would not be missing data

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.2 & 9.4

Comments:

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10.1

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: _____

Date: dd/Month/year

Signature: _____

Annex 3. Additional Information

Not applicable.