PASS Information

Title	Study I4V-MC-B010: Rheumatologist Survey to Assess the Effectiveness of the Risk Minimisation Measures (RMM) for Olumiant® (baricitinib) a JAK1/2 inhibitor
Version identifier of the final study report	Version 1.0
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Product reference:	EMEA/H/C/004085
Procedure number:	
Marketing authorisation holder(s)	Eli Lilly Nederland B.V.
Joint PASS	Not Applicable
Research question and objectives	This study assessed: a) Rheumatologists' understanding of the important safety information detailed in the Healthcare Professional Educational Material, that is, information relating to: - Pregnancy and breast feeding - Infections - Changes in lipid parameters b) Communication of the important safety information and mitigating actions to patients prescribed baricitinib for the first time c) Distribution of the Patient Alert Card (PAC) to patients prescribed baricitinib for the first time.
Countries of study	France, Germany, Sweden, and the United Kingdom.
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Signature of principal investigator	PPD Signature on file/see approval date below

Approval Date: 17-Mar-2020 GMT

Marketing Authorisation Holder

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

Title: Study I4V-MC-B010: Rheumatologist Survey to Assess the Effectiveness of the Risk Minimisation Measures (RMM) for Olumiant® (baricitinib) a JAK1/2 inhibitor

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Keywords: Olumiant®, baricitinib, JAK1/2 inhibitor, rheumatoid arthritis

Rationale and background:

Eli Lilly and Company (Lilly) conducted a survey to evaluate the effectiveness of RMM associated with the use of baricitinib for the treatment of rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to 1 or more disease-modifying anti-rheumatic drugs. The additional risk minimisation materials for baricitinib include a Healthcare Professional (HCP) Educational Material and a Patient Alert Card (PAC). The intent of the HCP Educational Material is to facilitate the initial discussion between the HCP and patient on important safety information and mitigating actions related pregnancy and breastfeeding, infections, and changes in lipid parameters.

This survey was designed to assess rheumatologists' understanding of the important safety information detailed in the HCP Educational Material with respect to use during pregnancy and breast feeding, potential risk of infection, and changes in lipid parameters. It also assessed the communication of the important safety information and distribution of the PAC to patients prescribed baricitinib for the first time. As agreed with each National Competent Authority (NCA), the HCP Educational Material and the PAC were distributed to rheumatologists who were expected to prescribe baricitinib in each European Union (EU) country prior to launch.

Research question and objectives:

This study assessed the following:

a) Rheumatologists' understanding of the important safety information detailed in the HCP Educational Material, that is, information relating to: pregnancy and breastfeeding, infections, and changes in lipid parameters;

b) Communication of the important safety information and mitigating actions to patients prescribed baricitinib for the first time;

c) Distribution of the PAC to patients prescribed baricitinib for the first time.

Study design:

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

Setting:

The surveys were administered to rheumatologists in France, Germany, Sweden, and the United Kingdom (UK). Countries were selected based on whether the survey was feasible and informative, timing of product launch, and market uptake.

Subjects and study size, including dropouts:

Rheumatologists who identified themselves as currently treating patients with RA and have prescribed or are potential prescribers of baricitinib were eligible to participate. To ensure that survey results adequately reflect the knowledge of the main target of the survey, at least 50% of the total completed surveys were required from prescribers of baricitinib. The target sample size was at least 200 completed surveys.

Variables and data sources:

The survey collected information about rheumatologists' understanding of the key safety messages in the risk minimisation communication and information about potential behaviour with regard to communicating important safety information to patients for the first time, as well as demographic characteristics and clinical experience information.

In this survey, the data source was a list of rheumatologists that was developed based on criteria used to compile the distribution list of recipients for the HCP Educational Material and the PAC. This list consisted of rheumatologists who had previously agreed to be contacted for this type of research.

Results:

A total of 5,943 rheumatologists were invited to participate in the survey. Of those, 271 (4.6%) responded to the invitation. Of the 271 respondents, 226 (83.4%) were eligible and completed the survey (58 from Germany, 39 from Sweden, 81 from UK, and 48 from France). A similar number of rheumatologists indicated they had been treating patients with RA for 5 to 10 years (29.6%), 11 to 15 years (23.0%), or more than 15 years (35.8%). The majority of rheumatologists (58.0%) indicated 26% to 50% of their patients had RA and almost all rheumatologists (93.4%) had prescribed baricitinib. Most rheumatologists indicated treating 1 to 5 patients (47.3%) or 6 to 10 patients (25.2%) with baricitinib within the last 6 months.

Each of the individual survey questions pertaining to important safety information were answered correctly by greater than 79% of rheumatologists who completed the survey. The question specific to safety in breastfeeding had a lower percentage of correct responses (79.2%) while all other questions resulted in greater than 84% correct responses.

The individual questions in the survey were arranged into 4 key risk messages, each corresponding to the key safety topics outlined in the HCP Educational Materials. To be counted

as demonstrating understanding of a specific key risk message, rheumatologists were required to answer all questions/items of the key risk message correctly. The RMM were considered effective if at least 70% of respondents demonstrated understanding of each key risk message.

- 164 rheumatologists (72.6%) demonstrated understanding of Key Risk Message 1 (pregnancy and breastfeeding),
- 206 (91.2%) demonstrated understanding of Key Risk Message 2 (lipid parameters),
- 179 (79.2%) demonstrated understanding of Key Risk Message 3 (management of infections), and
- 163 (72.1%) demonstrated understanding of Key Risk Message 4 (reactivation of viral infections).

There were no differences in the understanding of any key risk messages when analysed by the following subgroups: country, prescriber status, prescriber frequency, and prescriber experience.

In regards to the descriptive objectives assessing communication of the risk messages, the results showed nearly all (94.8%) rheumatologists indicated that they, or someone in their practice/hospital, communicates the important information to their patients when prescribing baricitinib for the first time. About 2/3 of rheumatologists (67.3%) indicated that they were aware of the PAC for baricitinib, and of those who were aware of the PAC and had prescribed baricitinib, 67.4% indicated that when prescribing baricitinib for the first time their patient was provided with a PAC.

Discussion:

The current survey was completed quickly (approximately 6 months ahead of plan), with more than the intended sample size (226 respondents when targeting 200), with reasonable response rates from all 4 countries included, and over 90% of respondents were prescribers of baricitinib. This suggests the baricitinib prescribing rheumatologist population is motivated and engaged in safety messaging.

Results confirm that more than 70% of rheumatologists understood each of the key risk messages pertaining to use in pregnancy and breastfeeding, lipids, and infections. Based upon this current evaluation, the RMM were determined effective as shown by at least 70% of rheumatologists demonstrating understanding of each key risk message. In addition to understanding of the safety information, nearly all rheumatologists (94.8%) indicated that they, or someone in their practice/hospital, communicates the important safety information to their patients when prescribing baricitinib for the first time. Thus, while awareness and distribution of the PAC to patients directly from the rheumatologist was lower (67.4%), the communication regarding the important safety information between rheumatologists and patients is occurring. It is worth noting that the PAC is also attached to the Patient Information Leaflet (PIL) in each baricitinib pack and as such is provided to every patient dispensed baricitinib.

Conclusion:

The results of this survey indicate that rheumatologists understand the safety information for baricitinib and communicate these messages to the patient. Therefore, based on the current evaluation, the RMM were deemed effective, and no changes are warranted to the RMM.

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2. List of abbreviations

Term	Definition
aDCTs	annotated Data Collection Tools
CFR	Code of Federal Regulations
CIs	confidence intervals
EDC	Electronic Data Capture
EMA	European Medicines Agency
EU	European Union
FDA	(US) Food and Drug Administration
GVP	Good Pharmacovigilance Practices
HCP	Healthcare Professional
ICH	International Council for Harmonisation
JAK	Janus kinase
KRM	Key Risk Message
Lilly	Eli Lilly and Company
NCA	National Competent Authority
PAC	Patient Alert Card
PAS	Post Authorisation Study
PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
RA	rheumatoid arthritis
RMM	risk minimisation measures
SAP	Survey Analysis Plan
SDLC	System Development Life Cycle
SOPs	standard operating procedures
UBC	United BioSource LLC
UK	United Kingdom

3. Investigators

Principal Investigator(s) of the Protocol

Name, degree(s)	Role in Study	Affiliation
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4. Other responsible parties

All Main Responsible Parties

Name, degree(s)	Role in Study	Affiliation
PPD	Principal Investigator	Eli Lilly and Company
PPD	Co-investigator	Eli Lilly and Company

5. Milestones

Milestone	Planned date	Actual date
Start of data collection	Estimated at Quarter 1 of 2019	19Mar2019
End of data collection	When at least 200 surveys have been completed, estimated at Quarter 1 of 2020	18Nov2019
Registration in the EU PAS register	Prior to start of data collection, estimated at Quarter 1 of 2019	02Feb2019
Final report of study results	4 months after the end of data collection, estimated Quarter 3 2020	See date stamp on bottom of Page 1

Abbreviations: EU = European Union; PAS = Post Authorisation Study;

*The planned timeline was contingent upon approval of the Healthcare Professional Educational Material and the Patient Alert Card (PAC) by the National Competent Authority (NCA), and protocol review and approval by PRAC (Pharmacovigilance Risk Assessment Committee). The end of data collection was dependent on launch and market uptake.

6. Rationale and background

Baricitinib is a Janus kinase (JAK)1/JAK2 inhibitor used for the treatment of rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to 1 or more disease-modifying anti-rheumatic drugs. Baricitinib was authorised for use in the European Union (EU) by the European Medicines Agency (EMA) in February 2017, and additional risk minimisation measures (RMM) were included as part of the risk management plan. These activities consist of (i) the Healthcare Professional (HCP) Educational Material, which is intended to inform the initial discussion between the rheumatologist and patient at the 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) which is provided to patients by both the prescribing physician as well as directly attached to the Patient Information Leaflet (PIL) included with every package of baricitinib.

In order to assess the effectiveness of the additional risk minimisation activities, this survey was designed to assess rheumatologists' understanding of the important safety information detailed in the HCP Educational Material with respect to the risks of use during pregnancy and breast feeding, potential risk of infection, and changes in lipid parameters. It also assessed the communication of the important safety information and distribution of the PAC to patients prescribed baricitinib for the first time. The HCP Educational Material and the PAC were distributed to rheumatologists who were expected to prescribe baricitinib, in each country prior to launch and available post-launch, as agreed by each National Competent Authority (NCA).

7. Research question and objectives

This study assessed the following:

- Rheumatologists' understanding of the important safety information detailed in the HCP Educational Material, that is, information relating to: pregnancy and breastfeeding, infections, and changes in lipid parameters;
- Communication of the important safety information and mitigating actions to patients prescribed baricitinib for the first time;
- Distribution of the PAC to patients prescribed baricitinib for the first time.

8. Amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
None				

9. Research methods

9.1. Study design

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

9.2. Setting

The assessment survey was initiated within 21 months of market availability in France, Germany, Sweden, and the United Kingdom (UK). These EU Member State countries were chosen based upon:

- Whether the survey was feasible and informative;
- The timing of product launch;
- Having sufficient market uptake of baricitinib to support target enrolment.

At the time of initial study planning, Germany and the UK were selected as predominant markets in the EU, and Sweden was selected to complement the information collected in Study I4V-MC-B011; A Retrospective Cohort Study to Assess the Safety of Baricitinib Compared with Other Therapies Used in the Treatment of Rheumatoid Arthritis in Nordic countries. The survey was initiated in these 3 countries (Germany, Sweden, and UK). The survey was extended to rheumatologists in France approximately 8 months later when responses from the other 3 countries appeared exhausted following the reminder letters, and the target sample size of 200 respondents (see Section 9.7) had not yet been achieved. To maximise the generalisability of the survey results, a maximum number of 80 completed surveys was accepted from each country.

As agreed with each NCA, the HCP Educational Material and the PAC were sent to rheumatologists who were expected to prescribe baricitinib in each EU country. The survey used in this study included questions that assessed rheumatologists' understanding of the important safety information detailed in the HCP Educational Material, communication of the important safety information and the related risk mitigation actions to patients prescribed baricitinib for the first time, and distribution of the PAC to patients prescribed baricitinib for the first time. In addition to receiving the same risk minimisation materials, the same survey was used for all participating countries to ensure consistency. As such, variability of survey results based on geography was not anticipated and, therefore, a minimum of 3 countries were considered representative of the EU.

The survey was administered via the internet, which allowed respondents to participate at a time and location that was convenient for them, or via telephone to allow participation of respondents without internet access or who preferred the telephone. The same survey was offered through both modalities.

9.3. Subjects

Eligible rheumatologists who responded to the survey invitation made up the study population. Rheumatologists were expected to be the prescribing HCP in the EU Member State countries participating in this survey.

9.3.1. Inclusion criteria

Rheumatologists were required to meet the following criterion for inclusion in the survey:

- Must identify themselves as currently treating patients with RA and must be previous 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 were required from those who had already prescribed baricitinib at the time of survey participation.

9.3.2. Exclusion criteria

Rheumatologists meeting the following criterion were not permitted to take the survey:

- Current or past employment with Eli Lilly and Company (Lilly) or any of its affiliates, United BioSource LLC (UBC), the EMA or any NCA.

9.4. Variables

The survey contained a total of 22 questions (Q) relating to: eligibility (Q1-3), demographics (Q4-8), understanding of safety information (Q9-15), awareness and behaviours pertaining to HCP Educational Materials (Q16-18), awareness and behaviours pertaining to the Patient Alert Card (Q19-21), and administrative information relating to financial compensation for time to complete survey (Q22). The survey is provided in Annex 1, Appendix 1.1 of the protocol [Annex 1, Appendix 1.1 of this document].

These survey questions provided the variables needed to address the study objectives:

- Response to questions about important safety information detailed in the HCP Educational Material (Q9-15). The analysis and arrangement of the individual safety questions into "key risk messages" is detailed further in Section 9.9.2.
- Whether or not important safety information and related risk mitigation actions were communicated to patients prescribed baricitinib for the first time (Q20, and Q6 to assess whether they prescribe baricitinib), and
- Whether the PAC was distributed to patients prescribed baricitinib for the first time (Q21, along with Q6 and Q19 to assess whether they were aware of the PAC).

In addition, information on the following was collected:

- Baricitinib prescriber status (yes, have previously prescribed/have not yet prescribed),
- Demographic information: age (years), geographic location (country), and

- Clinical experience: duration of experience treating patients with RA (years), number of patients for whom they have prescribed baricitinib (count).

9.5. Data sources

In order to target the desired population, the data source consisted of rheumatologists in each country who had previously agreed to be contacted for this type of research.

Rheumatologists received an invitation letter via the postal mail to participate in the survey. The invitation letter included: 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 was used only once. Based on survey uptake within each respective country, reminder notices were sent via email and/or postal mail to rheumatologists who had been invited, but had not yet participated. Participating rheumatologists' identifying information was collected for the purposes of providing financial compensation, as allowed by local laws and country regulations. The database of invited rheumatologists was regularly updated with responders and after each invitation mailing; the database was cross-checked with any correspondence that had an invalid address, was undeliverable or had incorrect contact details. Rheumatologists who received an invitation and who had no evidence of not receiving it (e.g., an invalid address), but who did not respond within 2 weeks from the initial mailing, received at least 1 reminder invitation.

A structured questionnaire was used to collect survey data (Annex 1, Appendix 1.1 of the protocol [Annex 1, Appendix 1.1 of this document]). It was comprised of closed-ended questions or statements with multiple response choices. User testing was performed on the survey questions by sampling 10 rheumatologists who were known to be actively treating patients with RA and who were independent of the sponsor and UBC (Annex 1, Appendix 1.2). The final draft version of the survey incorporates feedback from this User Testing and is available in (Annex 1, Appendix 1.1 of the protocol [Annex 1, Appendix 1.1 of this document]). Some of the survey questions and associated answer options were amended where required as a result of the feedback from the user testing.

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

Each individual was given a randomly assigned unique code to access the survey. Each unique code was deactivated upon first use to prevent the code from being used to complete the survey multiple times. Individuals did not have to actively "decline to complete the survey". Therefore, there was no ability to track those who declined to participate, but who had not actively opted out. Individuals who logged into the survey and did not agree to participate in the survey (answered "No" to survey Question 1) were presented with 2 questions relating to whether they had prescribed baricitinib and whether they were aware of the important safety information communicated in the HCP Educational Material. Participants who agreed to respond to the survey began with a screening module with questions to confirm eligibility.

The internet survey was self-administered. The telephone survey was administered by a trained interviewer from the Survey Coordinating Centre who conducted the telephone interviews using a Computer Assisted Telephone Interview programme and entered the participants' responses directly into the Electronic Data Capture (EDC) system while in conversation with the participants.

9.6. Bias

A number of controls were in place to ensure that the survey was conducted in a professional manner and to minimise bias, including the following:

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

9.7. Study size

The target sample size was at least 200 completed surveys. This sample size was determined based on providing a precision of ±7% around a response of 50%, based on a 2-sided 95% confidence interval (CI). Because precision varies based on the proportion who respond correctly, Table 9-1 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

For 200 completed surveys, results would be precise to within ±7%. Note that although the sample size was based on the requirements set in the study, the proportion of correct responses could not be known ahead of time. Since precision depends on both the sample size and the proportion of correct responses, a range of possible precision was presented for different

proportions at relevant sample sizes. For analyses by prescriber status, where 100 prescribers were anticipated, the precision of results would lie within ±10% at worst. Results by country subgroups could not be estimated since the total number of completed surveys from each country was not yet known; however, based on the maximum number permitted for each country, results would be precise to within ±11% at worst (with maximum of 80 completed surveys from each country). If fewer surveys were returned in each country, then precision would fall. Further stratification was 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 9-1: Estimated Precision, by Sample Size and Proportion

Sample size	Proportion of Correct Responses Observed (%)	Precision or Margin of Error* (±%)
40	20	12.4
	50	15.5
	70	14.2
80	20	8.8
	50	11.0
	70	10.0
100	20	7.8
	50	9.8
	70	9.0
200	10	4.2
	20	5.5
	50	6.9
	70	6.4
	80	5.5
	90	4.2

*95% confidence interval, 2-sided.

9.8. Data transformation

All data collected during the survey were held confidentially by UBC. The EDC system used for data collection encrypted all respondent-identifying information, and respondent identifiers were stored separately from the survey responses. The data from the surveys collected were stratified by country as well as combined for analysis in this final study report. Details on management and protection of survey data are provided in the survey protocol (Annex 1, Appendix 1.1).

9.9. Statistical methods

9.9.1. Main summary measures

Statistical analyses were descriptive, that is, no formal hypothesis was tested. Counts and percentages of the correct response were calculated for each question/item in the questionnaire. All CIs around the percentages are exact 2-sided 95% CIs calculated according to the method of Clopper-Pearson (Clopper and Pearson, 1934). The survey contained skip patterns, that is, some questions were skipped depending on the answer of a previous question. Percentages were based on the population to whom a specific question was presented.

The analysis populations included:

All Respondents – The All Respondents population consisted of respondents that had accessed the survey using a unique code (see Section 9.5 for further details). These respondents were used as the denominator for percentages in survey administration statistics, unless otherwise specified, and in the survey eligibility results analysis.

Completed Surveys (Primary Population) – The population for all remaining analyses included only those with completed surveys. "Completed" was defined as an eligible respondent who had no missing data with the exception of data from skip patterns. An eligible respondent was defined as one who completed all eligibility questions and met all inclusion criteria and none of the exclusion criteria.

9.9.2. Main statistical methods

Analysis of the Primary Objectives:

All responses to questions around the primary objectives were summarised by counts and percentages. Exact binomial 2-sided 95% CIs were calculated for the proportion of respondents who gave the correct or desired responses. The primary objectives of the study are listed in Section 7.

The relevant questions to define success of understanding important safety information were combined into 4 key risk messages (Table 9-2). To be counted as demonstrating understanding of a specific key risk message, rheumatologists were required to answer all questions/items of the key risk message correctly. The number and percentages, including exact binomial 2-sided 95% CIs, of respondents demonstrating understanding were calculated for each individual key risk message and for all key risk messages.

The RMM were considered effective if at least 70% of respondents demonstrated understanding of each key risk message.

Table 9-2: Key Risk Messages Informing Understanding of Important Safety Messages

Key Risk Message (KRM)	Desired Response
KRM 1: Pregnancy and breastfeeding	
Question 9: Please answer True, False, or I don't know for each of the following statements	
9a: CCI [redacted]	False
9b: CCI [redacted]	True
Question 10: *Please select one option.* Which statement is correct regarding Olumiant (baricitinib)?	CCI [redacted] CCI [redacted]
KRM 2: Lipid parameters	
Question 11: *Please select one option.* According to the information in the Healthcare Professional Educational Material for Olumiant (baricitinib).	CCI [redacted]
KRM 3: Management of infections	
Question 12: *Please select one option.* What should you do if the patient develops Herpes Zoster infection?	CCI [redacted]
Question 13: *Please select one option.* What should you do if the patient develops an infection which does not respond to standard treatment?	CCI [redacted] .
Question 14: *Please select one option.* Which statement is correct regarding Olumiant (baricitinib)?	CCI [redacted]
KRM 4: Reactivation of viral infection	
Question 15: Please answer True, False, or I don't know for each of the following statements regarding Olumiant (baricitinib).	
15a: CCI [redacted]	True
15b: CCI [redacted] nt.	True

Table 9-2: Key Risk Messages Informing Understanding of Important Safety Messages

Key Risk Message (KRM)	Desired Response
15c: CCI [redacted]	False
15d: CCI [redacted]	False

Analysis of Additional Survey Questions:

Additional questions in the survey included questions to determine respondent eligibility, prescribing status, demographic information, and clinical experience. The number and percentage of respondents were summarised by their responses to each question.

Subgroup Analysis:

The following subgroup analyses were performed for each of the questions related to the primary objectives of the study for all completed surveys as applicable.

Subgroup analysis: Country of Practice:

- France
- Germany
- Sweden
- United Kingdom

Subgroup analysis: Prescribing status

- Active Prescriber (has previously prescribed)
- Potential prescriber (has not previously prescribed baricitinib)

Subgroup analysis: Prescribing frequency

- High prescribers (≥6 patients in last 6 months)
- Low prescribers (≤5 patients in the last 6 months)

Note that the cut-off between low and high prescribers was not determined a priori and was instead based on the distribution of the prescribing frequency in the completed surveys. The goal was to have similar sample sizes in both subgroups.

Subgroup analysis: Prescriber experience

- High experience
- Medium experience
- Low experience

Prescriber experience was based on the responses to survey Question 4 (number of years treating patients with RA: <5, 5-10, 11-15, >15 years) and Question 5 (proportion of patients who have RA: 0-25%, 26-50%, 51-75%, 76-100%). High experience was defined as prescriber with >15 years' experience and 51-75% or 76-100% RA patients. Low experience was defined as prescribers with <5 years' experience and 0-25% or 26 to 50% RA patients. All other prescribers were counted as medium experience.

9.9.3. Missing values

In order to minimise bias, the survey was programmed to ensure respondents could not skip ahead and only allowed for missing data when caused by skip patterns. In instances where there was missing data not due to skip patterns (that is, respondent did not complete the survey), the respondent was not considered in the analysis.

9.9.4. Sensitivity analyses

There were no pre-defined sensitivity analyses. A post-hoc sensitivity analysis was conducted to assess sensitivity of results to the 81st respondent from the UK. See Section 10.4.1 for detail.

9.9.5. Amendments to the Survey Analysis Plan

There were no unforeseen analyses or deviations from the Survey Analysis Plan (SAP). No analysis was completed until survey collection had ended from all 4 participating countries (France, Germany, Sweden, and UK).

9.10. Quality control

Data were collected using a secure and validated online EDC system designed and built by UBC. A System Development Life Cycle (SDLC) was used for validation that complies with UBC internal Information Technology standard operating procedures (SOPs). The SDLC is fortified with SOPs addressing validation for all clinical and risk minimisation-related applications. The internet-based repository was used to store survey data and other relevant programme information.

The UBC Information Technology application developed and manner of its deployment was in compliance with EMA Good Pharmacovigilance Practice (GVP) Module V (Risk management systems) and GCP Module XVI (Risk minimization: selection of tools and effectiveness indicators).

The UBC Information Technology applications developed for this study are compliant with the US Food and Drug Administration (FDA) guidance for Industry-Computerized Systems Used in the Guidance for Industry 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 GVP, International Council for Harmonisation [ICH]. The system is compliant for the entry, storage, handling, analysis and transmission of electronic information. Respondent-identifying information was stored separately from the survey responses. At the end of each survey cycle, data were extracted from the EDC.

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

At the completion of data collection, data were extracted from the EDC and mapped to SAS® datasets (SAS V9.3 ("original" production datasets) as defined in the annotated Data Collection Tools (aDCTs) by a SAS programmer/designee. The mapping of raw data was independently validated by the UBC Quality Control Team. The raw EDC data were used to create derived analysis datasets which were independently validated according to the SAP. The validated analysis SAS datasets were then used by a SAS programmer to create a set of summary tables and listings according to the SAP text and mock-up tables. All output was programmatically validated by an independent programmer and validation was documented. Summary tables were reviewed by the appropriate team members and included in the final report sent to Lilly to be submitted to the Pharmacovigilance Risk Assessment Committee (PRAC).

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

10. Results

10.1. Participants

Survey administration statistics for rheumatologists invited to participate in the survey are presented by country and overall in Table 10-1.

A total of 5,943 rheumatologists involved in the treatment and management of patients with RA were invited to participate in the survey. Survey reminder/invitation letters were sent to rheumatologists in Germany, Sweden, and the UK on 2 separate occasions following the mailing of the initial invitation. No reminder letters were sent to rheumatologists in France since the target sample size was reached following the first invitation.

Of those invited, 271 (4.6%) responded to the invitation using their unique identification. Of the 271 respondents, 236 (87.1%) were eligible for participation and of those, 226 respondents (83.4%) completed the survey (58 from Germany, 39 from Sweden, 81 from UK, and 48 from France). Most rheumatologists completed the survey via internet versus telephone (Germany 54 vs. 4, Sweden 35 vs. 4, UK 79 vs. 2, and France 43 vs. 5, respectively).

As outlined in the protocol and Section 9.2, no more than 80 respondents were to respond from any 1 country. Of the 226 rheumatologists who completed the survey, 81 were from the UK. Because this was 1 more respondent for a country than the protocol allowed, a post-hoc analysis was conducted limiting the UK respondents to the first 80 respondents to determine if the results from this additional respondent had any effect on the results of this survey. This analysis resulted in no difference in results and is detailed in Section 10.4.1.

Table 10-1: Survey Administration Statistics

Parameter, n (%)	Germany	Sweden	United Kingdom	France	Overall
Number of Rheumatologists invited[a]	1,481	335	1,424	2,703	5,943
All Respondents[b]	72 (4.9)	44 (13.1)	93 (6.5)	62 (2.3)	271 (4.6)
Eligible Respondents[d]	63 (87.5)	41 (93.2)	83 (89.2)	49 (79.0)	236 (87.1)
Completed the survey[d]	58 (80.6)	39 (88.6)	81 (87.1)	48 (77.4)	226 (83.4)
Did not complete the survey[d]	5 (6.9)	2 (4.5)	2 (2.2)	1 (1.6)	10 (3.7)
Respondents not eligible[c, d]	9 (12.5)	3 (6.8)	10 (10.8)	13 (21.0)	35 (12.9)

[a] The number of rheumatologists invited to participate in the survey excludes the number of invitations that were undeliverable.

[b] Number of respondents who accessed the survey. Percentages are based on the number of invitations provided to HCPs excluding the number of invitations undeliverable.

[c] Number of respondents who did not meet eligibility criteria or did not complete eligibility questions. The responses to the eligibility criteria with the reason for ineligibility are presented in Table 10-2

[d] Percentages are based on the number of all respondents.

Survey participant eligibility results for rheumatologists who responded to the survey are presented by country and overall in Table 10-2.

Of the 271 rheumatologists who responded to the survey, 35 were not eligible because they either did not meet eligibility criteria or did not complete the eligibility questions. Of these 35, 1 respondent did not agree to participate in the survey, 6 indicated that they or an immediate family member had worked directly for Lilly or its affiliates, UBC, the EMA, or any NCA; and 28 respondents discontinued the survey before answering the eligibility questions.

Table 10-2: Survey Participant Eligibility Results

Question	Germany (N=72) n (%)	Sweden (N=44) n (%)	United Kingdom (N=93) n (%)	France (N=62) n (%)	Overall (N=271) n (%)
Question 1: Do you agree to take part in this survey about Olumiant® (baricitinib)?					
Yes	66 (91.7)	43 (97.7)	87 (93.5)	50 (80.6)	246 (90.8)
No[a]	0	0	0	1 (1.6)	1 (0.4)
Discontinued	6 (8.3)	1 (2.3)	6 (6.5)	11 (17.7)	24 (8.9)
Question 2: Have you or any of your immediate family members ever worked directly for Eli Lilly and Company (Lilly) or its affiliates, United BioSource Corporation (UBC), the European Medicines Agency (EMA), or any National Competent Authority (NCA)?					
Yes[a]	2 (2.8)	1 (2.3)	2 (2.2)	1 (1.6)	6 (2.2)
No	63 (87.5)	42 (95.5)	84 (90.3)	49 (79.0)	238 (87.8)
Question not asked[b]	0	0	0	1 (1.6)	1 (0.4)
Discontinued	7 (9.7)	1 (2.3)	7 (7.5)	11 (17.7)	26 (9.6)
Question 3: Are you a rheumatologist currently treating patients with rheumatoid arthritis?					
Yes	63 (87.5)	41 (93.2)	83 (89.2)	49 (79.0)	236 (87.1)
No[a]	0	0	0	0	0
Question not asked[b]	2 (2.8)	1 (2.3)	2 (2.2)	2 (3.2)	7 (2.6)
Discontinued	7 (9.7)	2 (4.5)	8 (8.6)	11 (17.7)	28 (10.3)

[a] Ineligible to participate in the survey.
[b] Question not asked due to the skip pattern in the survey or previous question termination.
Note: Respondents were counted as discontinued if they did not answer all eligibility questions without being identified as ineligible in a previous question. Once respondents were counted as discontinued, they were counted as discontinued in all subsequent eligibility questions.

10.2. Descriptive data

Description of eligible rheumatologists who completed the survey by country and overall is presented in Table 10-3.

Of the 226 rheumatologists who completed the survey, a similar number indicated they had been treating patients with RA for 5 to 10 years (29.6%), 11 to 15 years (23.0%), or more than 15 years (35.8%). The majority of rheumatologists (58.0%) indicated 26% to 50% of their patients had RA and almost all rheumatologists (93.4%) had prescribed baricitinib. Most rheumatologists had treated 1 to 5 patients (47.3%) or 6 to 10 patients (25.2%) with baricitinib within the last 6 months. The majority of rheumatologists (59.3%) were 40 to 59 years of age.

Table 10-3: Description of Rheumatologists

Question	Germany (N=58) n (%)	Sweden (N=39) n (%)	United Kingdom (N=81) n (%)	France (N=48) n (%)	Overall (N=226) n (%)
Question 4: In total, how many years have you been treating patients with rheumatoid arthritis?					
Less than 5 years	5 (8.6)	5 (12.8)	9 (11.1)	7 (14.6)	26 (11.5)
5 - 10 years	8 (13.8)	13 (33.3)	30 (37.0)	16 (33.3)	67 (29.6)
11 - 15 years	14 (24.1)	6 (15.4)	26 (32.1)	6 (12.5)	52 (23.0)
More than 15 years	31 (53.4)	15 (38.5)	16 (19.8)	19 (39.6)	81 (35.8)
Question 5: Approximately, what proportion of your patients that you see have rheumatoid arthritis?					
0-25%	5 (8.6)	0	7 (8.6)	16 (33.3)	28 (12.4)
26-50%	40 (69.0)	17 (43.6)	47 (58.0)	27 (56.3)	131 (58.0)
51-75%	12 (20.7)	20 (51.3)	23 (28.4)	5 (10.4)	60 (26.5)
76-100%	1 (1.7)	2 (5.1)	4 (4.9)	0	7 (3.1)
Question 6: Have you prescribed Olumiant (baricitinib)?					
Yes	58 (100.0)	37 (94.9)	71 (87.7)	45 (93.8)	211 (93.4)
No	0	2 (5.1)	10 (12.3)	3 (6.3)	15 (6.6)
Question 7: Approximately, how many patients have you treated in the last six months with Olumiant (baricitinib)?					
None	0	0	0	0	0
1-5	20 (34.5)	27 (69.2)	31 (38.3)	29 (60.4)	107 (47.3)
6-10	20 (34.5)	7 (17.9)	16 (19.8)	14 (29.2)	57 (25.2)
More than 10	18 (31.0)	3 (7.7)	24 (29.6)	2 (4.2)	47 (20.8)
Question not asked[a]	0	2 (5.1)	10 (12.3)	3 (6.3)	15 (6.6)
Question 8: Which of the following groups best describes your age?					
Less than 40	7 (12.1)	10 (25.6)	27 (33.3)	23 (47.9)	67 (29.6)
40-59	41 (70.7)	23 (59.0)	50 (61.7)	20 (41.7)	134 (59.3)
60 or older	9 (15.5)	5 (12.8)	3 (3.7)	3 (6.3)	20 (8.8)
Prefer not to answer	1 (1.7)	1 (2.6)	1 (1.2)	2 (4.2)	5 (2.2)

[a] Question not asked due to the skip pattern in the survey or previous question termination.

Responses to questions about the HCP Educational Material for baricitinib by eligible rheumatologists who completed the survey are presented in Table 10-4.

Of the 226 rheumatologists who completed the survey, the majority (65.9%) indicated prior to today, they were aware of the Health Professional Educational Material for baricitinib. Of those, 73.2% received a copy of the Health Professional Educational Material for baricitinib. Of those who received a copy, 80.7% indicated reading it.

Table 10-4: Responses to Questions about Healthcare Professional Educational Material for Baricitinib – Completed Surveys

Question	Overall (N=226) n (%)
Question 16: Prior to today, were you aware of the Healthcare Professional Educational Material for Olumiant (baricitinib)?	
Yes	149 (65.9)
No	77 (34.1)
Question 17: Did you receive a copy of the Healthcare Professional Educational Material for Olumiant (baricitinib)?[a]	
Yes	109 (73.2)
No	13 (8.7)
I don't remember	27 (18.1)
N/A (Answered 'No' to Question 16)	77
Question 18: Have you read the Healthcare Professional Educational Material for Olumiant (baricitinib)?[a]	
Yes	88 (80.7)
No	10 (9.2)
I don't remember	11 (10.1)
N/A (Answered 'No' to Question 16 or 'No' or 'I don't remember' to Question 17)	117

[a] Percentages are calculated based on the sample presented with this question because of the skip logic in the survey.

10.3. Main results

10.3.1. Individual questions about important safety information

Responses to the individual questions related to the understanding of the important safety information by eligible rheumatologists who completed the survey are presented in Table 10-5.

Of the 226 eligible rheumatologists who completed the survey, most correctly indicated as “False” that baricitinib is safe to be used in pregnancy (88.1%) and correctly indicated as “True”

that baricitinib is not safe for use in pregnancy (87.2%). In addition, most rheumatologists (79.2%) correctly responded that baricitinib cannot be used in women who are breastfeeding.

A high percentage of rheumatologists (91.2%) correctly indicated that according to the information in the HCP Educational Material for Olumiant (baricitinib) lipid parameters should be assessed approximately 12 weeks after the first dose of baricitinib. Similarly, a high percentage of rheumatologists correctly indicated that baricitinib therapy is to be temporarily interrupted and not resumed until the infection has resolved if a patient develops Herpes Zoster infection (94.2%) and if a patient develops an infection that does not respond to standard treatment (91.6%). In addition, 210 rheumatologists (92.9%) correctly indicated that it is important to instruct patients to seek immediate medical attention if signs or symptoms suggesting infection appear.

A high percentage of rheumatologists also correctly indicated that baricitinib increases the potential risk of viral reactivation (91.6%) and that prescribers should screen their patients to rule out active viral hepatitis before starting baricitinib treatment (96.9%). Most rheumatologists correctly identified as “False” that it is not necessary to screen patients to rule out active tuberculosis before starting baricitinib treatment (84.1%), and correctly identified as “False” that live attenuated vaccines can be used during, or immediately prior to baricitinib therapy (88.5%).

Table 10-5: Questions Related to the Understanding of the Important Safety Information – Completed Surveys

Question	Overall (N=226) n (%) [95% CI][b]
Question 9: Please answer True, False, or I don't know for each of the following statements.	
9a: CCI [redacted]	
True	2 (0.9)
False[a]	199 (88.1) [83.1-92.0]
I don't know	25 (11.1)
9b: CCI [redacted].	
True[a]	197 (87.2) [82.1-91.2]
False	5 (2.2)
I don't know	24 (10.6)
Question 10: *Please select one option.* Which statement is correct regarding Olumiant (baricitinib)?	
CCI [redacted].	5 (2.2)
CCI [redacted]	179 (79.2) [73.3-84.3]
I don't know.	42 (18.6)

Table 10-5: Questions Related to the Understanding of the Important Safety Information – Completed Surveys

Question	Overall (N=226) n (%) [95% CI][b]
Question 11: *Please select one option.* According to the information in the Healthcare Professional Educational Material for Olumiant (baricitinib).	
CCI	206 (91.2) [86.7-94.5]
CCI	7 (3.1)
I don't know.	13 (5.8)
Question 12: *Please select one option.* What should you do if the patient develops Herpes Zoster infection?	
CCI	213 (94.2) [90.4-96.9]
CCI	7 (3.1)
CCI	4 (1.8)
I don't know.	2 (0.9)
Question 13: *Please select one option.* What should you do if the patient develops an infection which does not respond to standard treatment?	
CCI	207 (91.6) [87.2-94.9]
	17 (7.5)
	0
I don't know.	2 (0.9)
Question 14: *Please select one option.* Which statement is correct regarding Olumiant (baricitinib)?	
CCI	CCI
	15 (6.6)
	1 (0.4)
I don't know.	0
Question 15: Please answer True, False, or I don't know for each of the following statements regarding Olumiant (baricitinib).	
15a: CCI	
True[a]	207 (91.6) [87.2-94.9]
False	6 (2.7)
I don't know	13 (5.8)

Table 10-5: Questions Related to the Understanding of the Important Safety Information – Completed Surveys

Question	Overall (N=226) n (%) [95% CI][b]
15b: CCI [redacted]	
True[a]	219 (96.9) [93.7-98.7]
False	4 (1.8)
I don't know	3 (1.3)
15c: CCI [redacted]	
True	32 (14.2)
False[a]	190 (84.1) [78.6-88.6]
I don't know	4 (1.8)
15d: CCI [redacted]	
True	16 (7.1)
False[a]	200 (88.5) [83.6-92.3]
I don't know	10 (4.4)

[a] Correct response.
[b] 95% exact 2-sided confidence intervals are calculated using the Clopper-Pearson method.

10.3.2. Understanding of Key Risk Messages

The important safety information within Questions 9 through 15 and summarized above were combined into 4 key risk messages:

- Key Risk Message #1: Pregnancy and breastfeeding (2 items of Q9, Q10)
- Key Risk Message #2: Lipid parameters (Q11)
- Key Risk Message #3: Management of infections (Q12, Q13, Q14)
- Key Risk Message #4: Reactivation of viral infections (4 items of Q15).

As described in Section 9.9.2, to be counted as demonstrating understanding of a specific key risk message, rheumatologists were required to answer all questions/items of the key risk message correctly and RMM were determined effective if at least 70% of rheumatologists demonstrated understanding of each key risk message.

As shown in Table 10-6,

- 164 rheumatologists (72.6%) demonstrated understanding of Key Risk Message 1,
- 206 (91.2%) demonstrated understanding of Key Risk Message 2,

- 179 (79.2%) demonstrated understanding of Key Risk Message 3, and
- 163 (72.1%) demonstrated understanding of Key Risk Message 4.

Overall, 99 rheumatologists (43.8%) demonstrated understanding of all key risk messages. Demonstrating understanding of a single key risk message required answering all questions/items of the respective key message correctly. Therefore, demonstrating understanding of all key risk messages required the respondent to have answered all elements of all key risk messages correctly. In other words, this reflects the proportion of rheumatologists that scored perfectly for all elements of Questions 9 through 15.

Table 10-6: Understanding the Key Risk Messages – Completed Surveys

	Rheumatologists (N=226) n (%) [95% CI][e]
KRM#1 Pregnancy and breastfeeding (Q9, Q10)[a]	
Yes	164 (72.6) [66.3-78.3]
No	62 (27.4)
KRM#2 Lipid parameters (Q11)[b]	
Yes	206 (91.2) [86.7-94.5]
No	20 (8.8)
KRM#3 Management of infections (Q12, Q13, Q14)[c]	
Yes	179 (79.2) [73.3-84.3]
No	47 (20.8)
KRM#4 Reactivation of viral infections (Q15)[d]	
Yes	163 (72.1) [65.8-77.9]
No	63 (27.9)
Understanding all KRMs[f]	
Yes	99 (43.8) [37.2-50.5]
No	127 (56.2)

[a] To be counted as understanding of Key Risk Message (KRM) #1, both items of Q9 and Q10 must be answered correctly.
[b] To be counted as understanding of KRM#2, Q11 must be answered correctly.
[c] To be counted as understanding of KRM#3, Q12, Q13, and Q14 must be answered correctly.
[d] To be counted as understanding of KRM#4, all 4 items of Q15 must be answered correctly.
[e] 95% exact 2-sided confidence intervals are calculated using the Clopper-Pearson method.
[f] To be counted as understanding of all KRMs, all items of Q9 through Q15 must be answered correctly.

10.3.3. Communication of important safety information

Responses to questions about the communication of important safety information to patients prescribed baricitinib by eligible rheumatologists who completed the survey are presented in Table 10-7.

Nearly all rheumatologists (94.8%) indicated that someone in their practice/hospital communicates the important safety information to their patients when prescribing baricitinib for the first time.

Table 10-7: Communication of the Important Safety Information to Patients Prescribed Baricitinib for the First Time – Completed Surveys

Question	Overall (N=226) n (%)
Question 20: Do you or someone in your practice/hospital communicate the important safety information to your patients when prescribing Olumiant (baricitinib) for the first time?[a]	
Yes	200 (94.8)
No	7 (3.3)
I don't remember	4 (1.9)
N/A (Answered 'No' to Question 6 (Have you prescribed Olumiant (baricitinib)?)	15

[a] Percentages are calculated based on the sample presented with this question because of the skip logic in the survey.

10.3.4. Distribution of the Patient Alert Card

Responses to questions about the PAC for baricitinib by eligible rheumatologists who completed the survey are presented in Table 10-8.

The majority of rheumatologists (67.3%) indicated that prior to today (day of survey participation), they were aware of the PAC for baricitinib. Of the 144 rheumatologists who were aware of the PAC (Question 19 Table 10-8) and indicated prescribing baricitinib (Question 6, Table 10-3), 97 (67.4%) indicated that when prescribing baricitinib for the first time, their patient would be provided with a PAC.

Table 10-8: Responses to Questions about the Patient Alert Card for Baricitinib – Completed Surveys

Question	Overall (N=226) n (%)
Question 19: Prior to today, were you aware of the Patient Alert Card for Olumiant?	
Yes	152 (67.3)
No	74 (32.7)
Question 21: When prescribing Olumiant (baricitinib) for the first time is your patient provided with a Patient Alert Card?[a]	
Yes	97 (67.4)
No	19 (13.2)
I don't remember	28 (19.4)
N/A (Answered 'No' to Question 19 or 'No' to Question 6 (Have you prescribed Olumiant (baricitinib)?)	82

[a] Percentages are calculated based on the sample presented with this question because of the skip logic in the survey.

10.4. Subgroup analyses

10.4.1. Individual questions about important safety information and understanding of key risk messages

Subgroup analysis of responses to each individual question related to the understanding of the important safety information and of understanding of the key risk messages were conducted by stratifying according to country of practice, prescribing status, prescribing frequency, and prescriber experience (as described in Section 9.9.2). The full set of tables are provided in Annex 1, Appendix 1.3.

In the analysis of individual questions by country, the only difference by country was noted for Question 13 (as shown in Table 3.1 in Appendix 1.3). When stratifying rheumatologists' responses by country of practice, a difference (based on non-overlapping CIs) between responses of rheumatologists from Germany and the UK was noted for Question 13 (*Please select one option. What should you do if the patient develops an infection which does not respond to standard treatment?* Response: CCI [redacted] favouring rheumatologists from the UK (correct response rate 98.8% [93.3%-100.0%]) over rheumatologists from Germany (correct response rate 82.8% [70.6%-91.4%]).

In the analysis of individual questions by prescriber status, a difference was only noted for Question 10 (as shown in Table 3.2 in Appendix 1.3). When stratifying rheumatologists' responses by prescribing status, a difference (based on non-overlapping CIs) between responses of rheumatologists who were active prescribers (n=211) and potential prescribers (n=15) was noted for Question 10 (*Please select one option. Which statement is correct regarding Olumiant (baricitinib)?* Response*:* CCI [redacted] favouring active prescribers (correct response rate 81.5% [75.6%-86.5%]) over potential prescribers (correct response rate 46.7% [21.3%-73.4%]). However, due to the low sample size of N=15 potential prescribers, limited conclusions can be drawn from this subgroup analysis.

Similarly, in the analysis of individual questions by prescribing frequency, a difference was noted only for Question 10 (as shown in Table 3.3 in Appendix 1.3). When stratifying rheumatologists' responses by prescribing frequency, a difference (based on non-overlapping CIs) between responses of rheumatologists who were high prescribers (n=104) and potential prescribers (n=15) was noted for Question 10 (*Please select one option. Which statement is correct regarding Olumiant (baricitinib)?* Response*:* CCI [redacted] favouring high prescribers (correct response rate 86.5% [78.4%-92.4%]) over potential prescribers (correct response rate 46.7% [21.3%-73.4%]). However, due to the low sample size of N=15 potential prescribers, limited conclusions can be drawn from this subgroup analysis.

No differences were noted among the subgroups based on prescriber experience. In addition, no difference in any of the subgroup analyses were noted for understanding of the key risk messages.

A post-hoc analysis was completed to assess the sensitivity of results to the extra respondent from the UK. Per the protocol, a maximum number of 80 completed surveys was to be accepted from each country to maximise the generalisability of the survey results. Of the 226 rheumatologists who completed the survey, 48 were from France, 58 from Germany, 39 from Sweden, and 81 were from the UK. A post-hoc analysis excluding the responses from the 81st respondent in the UK indicated there was no change in understanding each of the key risk messages; therefore the inclusion of 1 respondent more than allowed by protocol did not alter our results.

10.4.2. Communication of important safety information

Subgroup analysis of responses to questions about the communication of important safety information to patients prescribed baricitinib showing stratification of rheumatologists' responses by country of practice, prescribing status, prescribing frequency, and prescriber experience are described in Section 9.9.2, and the full set of tables are provided in Annex 1, Appendix 1.3. These analyses were descriptive in nature. No confidence intervals or statistical tests were used to assess differences between subgroups.

In the analysis by country, among the rheumatologists that have prescribed baricitinib, 100% from Sweden and the UK responded "Yes" to Question 20 (*Do you or someone in your practice/hospital communicate the important safety information to your patients when prescribing Olumiant (baricitinib) for the first time?*), 93.3% of rheumatologists from France who indicated prescribing baricitinib responded "Yes", and 86.2% of rheumatologists from Germany that have prescribed baricitinib responded "Yes".

The percentages of rheumatologists communicating safety information were similar when stratified by prescribing frequency (high vs. low prescribers), and prescriber experience.

10.4.3. Distribution of the Patient Alert Card

Subgroup analysis of responses to questions about the Patient Alert Card for Olumiant showing stratification of rheumatologists' responses by country of practice, prescribing status, prescribing frequency, and prescriber experience are described in Section 9.9.2, and the full set of tables are provided in Annex 1, Appendix 1.3. These analyses were descriptive in nature. No confidence intervals or statistical tests were used to assess differences between subgroups.

In general, rheumatologists from Germany and Sweden more frequently responded "Yes" to Question 19 (*Prior to today, were you aware of the Patient Alert Card for Olumiant?*), 74.1% and 71.8%, respectively, and Question 21 (*When prescribing Olumiant (baricitinib) for the first time is your patient provided with a Patient Alert Card?*), 74.4% and 74.1%, respectively, compared with rheumatologists from France and the UK (64.6% and 61.7% for Question 19 and 58.6% and 62.2% for Question 21, respectively for France and UK).

Stratification by prescriber status demonstrated that 68.2% of active prescribers responded "Yes" to Question 19 (*Prior to today, were you aware of the Patient Alert Card for Olumiant?*) and that 53.3% of potential prescribers had the same answer. High and low prescribers similarly responded "Yes" to this question of PAC awareness (66.4 and 70.2%, respectively). Among those aware of it, distribution of the PAC for high and low prescribers was 63.4 and 71.2%, respectively (Question 21).

10.5. Adverse events/adverse reactions

Adverse event and product complaint information was not collected during this survey.

11. Discussion

11.1. Key results

This observational study assessed the following objectives:

- Rheumatologists' understanding of the important safety information detailed in the HCP Educational Material, that is, information relating to: pregnancy and breastfeeding, infections, and changes in lipid parameters;
- Communication of the important safety information and mitigating actions to patients prescribed baricitinib for the first time;
- Distribution of the PAC to patients prescribed baricitinib for the first time

The relevant questions to define success of understanding important safety information were combined into 4 key risk messages:

- Key Risk Message #1: Pregnancy and breastfeeding (2 items of Q9, Q10)
- Key Risk Message #2: Lipid parameters (Q11)
- Key Risk Message #3: Management of infections (Q12, Q13, Q14)
- Key Risk Message #4: Reactivation of viral infections (4 items of Q15).

Each of the individual survey questions pertaining to important safety information were answered correctly by greater than 79% of rheumatologists who completed the survey. Question 10 regarding safety in breastfeeding had the lowest percentage of correct responses, with 79.2% of rheumatologists responding correctly that baricitinib should not be used in women who are breastfeeding. This lower percentage, compared to the other questions, could be explained by 2 factors. First, the age of RA patients makes breastfeeding an infrequent occurrence in this target population. Second, there was a poor response to this question by the subgroup of 15 potential baricitinib prescribers, where only 46.5% correctly answered this question on breastfeeding safety. All of the remaining questions elicited greater than 84% correct responses (Table 10-5).

To be counted as demonstrating understanding of a specific key risk message, rheumatologists were required to answer all questions/items of the key risk message correctly. Overall, 72.6% of rheumatologists demonstrated understanding of the risk message pertaining to pregnancy and breastfeeding, 91.2% demonstrated understanding of risk message pertaining to lipids, 79.2% demonstrated understanding of the risk message pertaining to management of infections, and 72.1% demonstrated understanding of the risk message pertaining to reactivation of viral infections. Therefore, based upon this current evaluation, the RMM were determined effective as shown by at least 70% of rheumatologists demonstrating understanding of each key risk message.

It was noted that only 43.8% of rheumatologists demonstrated understanding of all 4 key risk messages. This is equivalent to the percentage of rheumatologists that scored perfectly for all elements of Questions 9 through 15. Given that each of the 4 key risk messages achieved greater than 70% demonstrated understanding, the low percentage demonstrating understanding of all key risk messages indicates that rheumatologists were getting different key risk messages wrong. In other words, there was no systematic misunderstanding of any 1 key risk message.

Differences were noted in subgroup analysis for select individual questions (Section 10.4.1). For Question 13 ([redacted] rheumatologists in UK had more favorable responses with 98.8% [93.3%-100.0%] answering correctly, where as in Germany, 82.8% [70.6%-91.4%] answered correctly. While this difference was statistically significant based on non-overlapping confidence intervals, the percent correct in each country is still high and this difference did not impact the country subgroup analysis of Key Risk Message 3. Differences were also noted in the subgroup analysis by prescriber status and prescriber frequency for Question 10 (*Please select one option. Which statement is correct regarding Olumiant (baricitinib)?* Response: [redacted]. This finding was driven by the low percent correct for potential prescribers (n=15), where 46.7% [21.3%-73.4%] responded correctly. Generalisability and interpretation of this finding is tempered by the low number of respondents in this subgroup. Furthermore, and similar to above, this difference in subgroups for an individual question did not translate into a difference in the understanding of Key Risk Message 1 by subgroups.

A high percentage of rheumatologists (94.8%) indicated that someone in their practice/hospital communicates the important information to their patients when prescribing baricitinib for the first time. About 2/3 of rheumatologists (67.3%) indicated that they were aware of the PAC for baricitinib, and of those who were aware of the PAC and had prescribed baricitinib, 67.4% indicated that when prescribing baricitinib for the first time their patient is provided with a PAC. There was no pre-determined threshold for success in regards to these 2 objectives pertaining to communication of safety information and distribution of the PAC. The analysis was descriptive in nature. Taken together, the results from these questions suggest communication of safety information to the patient from the rheumatologist is occurring in some form, just not necessarily through the delivery of the PAC. It is worth noting that the PACs are also distributed directly to the patient, as they are attached to the PIL which is provided with every package of baricitinib.

11.2. Limitations

Medical research in the form of surveys is inherently difficult to conduct in the EU, primarily due to the data protection regulations which pose significant challenges in recruiting participants. This was highlighted in a White Paper by the International Society for Pharmacoepidemiology and presented at the European Medicines Agency's Workshop on Measuring the Impact of Pharmacovigilance Activities (Sobel and Madison, 2016). There are difficulties in targeting the specific HCP audience required to be studied which could lead to selection bias, as there are constraints on the sharing of personal information between sponsor and vendors who administer the surveys. Additionally, experience from other surveys suggests that participation rates among

recruited HCPs are generally poor (Bester et al, 2016). This could reflect a low interest in participating in such studies. Reasons for low interest in participation could be numerous and include limited availability, low monetary compensation, lack of understanding of their importance, or lack of mandate from regulatory body. It has been cited elsewhere that there may be a perception that these surveys are too burdensome and of little scientific interest (Banerjee et al, 2014).

11.3. Interpretation

Despite these limitations for these types of surveys in general, it is worth noting that the current survey was completed quickly, with more than the intended sample size (226 respondents when targeting 200), with reasonable response rates from all 4 countries included, and over 90% of respondents were prescribers of baricitinib. For the current survey, 4.6% of invited rheumatologists responded to the invitation, and 3.8% of invited rheumatologists completed the survey. The typical response rate for these types of surveys in the US are between 3 to 5% based on the experience of the vendor that conducted the study, and the most recent survey conducted in the EU reported a response rate of 3.1%. Therefore, despite the noted limitations of low response rates for these types of surveys, the observed response rate of 4.6% is above what we have previously experienced in the EU. Also notable for the current survey was the speed at which the survey responses were achieved; the survey was completed within 8 months from when the initial invitation letters were sent out. In France for example, the target number of 48 completed surveys to reach the overall target was achieved within a space of 13 days. Overall, the speed of survey completion resulted in a final report available nearly 6 months ahead of original planned date of the third quarter of 2020, as reflected in the protocol Milestones. Finally, over 90% of respondents were prescribers of baricitinib. All of these metrics suggest the baricitinib prescribing rheumatologist population from the sampled countries are motivated and engaged in the safety messaging.

The objective of this study was to assess rheumatologists' understanding of the important safety information detailed in the HCP Educational material for baricitinib. Results confirm that more than 70% of rheumatologists understood each of the key risk messages pertaining to use in pregnancy and breastfeeding, lipids, and infections. While there were some differences in correct response frequencies for individual questions in the subgroup analyses, the correct response frequencies were still high, or in the case of the potential prescribers response to safety in breastfeeding, the low correct responses were based on a very small subgroup (n=15). Furthermore, the question with the lowest percentage of correct responses overall was for breastfeeding (79.2%) but this may not be unexpected given the older average age of RA patients and the infrequency of breastfeeding exposures. Despite the small number of subgroup differences in individual questions, there were no differences in key risk message understanding by subgroups.

In addition to understanding of the safety information, nearly all rheumatologists (94.8%) indicated that they, or someone in their practice/hospital, communicates the important safety information to their patients when prescribing baricitinib for the first time. Thus, while

awareness and distribution of the PAC to patients directly from the rheumatologist was lower, the communication regarding the important safety information between rheumatologists and patients is occurring.

Based upon this current evaluation of knowledge understanding and behaviours, the RMM were determined effective.

11.4. Generalisability

Although the choice of EU countries to participate in the survey was limited by product launch timings, access challenges, and market uptake, it is believed that the results are generalisable. At the time of initial study planning, Germany and the UK were selected as predominant markets in the EU, and Sweden was selected to complement the information collected in Study I4V-MC-B011; A Retrospective Cohort Study to Assess the Safety of Baricitinib Compared with Other Therapies Used in the Treatment of Rheumatoid Arthritis in Nordic countries. Response rates within these 3 initial countries were monitored, along with market uptake and feasibility of expanding the survey into additional EU countries. France was later added as it is a large market for baricitinib and additional respondents were needed to meet the survey target of 200. In addition, to maximise the generalisability of the survey results, a maximum number of 80 completed surveys was accepted from each country. Survey results were generally similar across the countries with exception of Question 13 CCI [redacted] which had a lower correct response rate in Germany compared to UK. However, the correct response rate in Germany of 82.8% was well above the pre-defined threshold of 70% and this statistically significant difference has no impact on the overall interpretation of the results or understanding of the pregnancy and breastfeeding key risk message country subgroup analyses.

Further contributing to the generalisability was that over 93% of respondents were prescribers of baricitinib. Therefore, this survey is reflective of the main target for assessing knowledge and behaviour, that is rheumatologists treating patients with RA and prescribing baricitinib.

12. Other information

Not applicable.

13. Conclusions

The results of this survey showed that:

- The 4 key safety messages were effectively communicated to rheumatologists (each key message had demonstrated understanding >70%),
- important safety information is communicated to patients when they are prescribed baricitinib for the first time (94.8%), and
- About 2/3 (67.4%) of the rheumatologists were aware of and provide the PAC to patients prescribed baricitinib for the first time.

Taken together, these results indicate that rheumatologists understand the safety information for baricitinib and communicate these messages to the patient in some form, just not necessarily through the delivery of the PAC from the rheumatologist. It is worth noting that the PACs are also distributed directly to the patient, as they are attached to the PIL which is provided with every package of baricitinib.

Based upon this current evaluation of knowledge understanding and behaviours, the RMM were determined effective. No changes to the RMM are warranted based on the results of this study.

14. References

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Annex 1. List of standalone documents

No.	Document Reference No	Date	Title
1.	Appendix 1.1	23 Jul 2018	Study I4V-MC-B010: Rheumatologist Survey to Assess the Effectiveness of the Risk Minimisation Measures (RMM) for Olumiant® (baricitinib) a JAK1/2 inhibitor
2.	Appendix 1.2		User Testing/Qualitative Topline Report
3.	Appendix 1.3		Final Tables and Listings

Rheumatologist Survey to Assess the Effectiveness of the Risk Minimisation Measures (RMM) for Olumiant® (Baricitinib) a JAK1/2 Inhibitor

PASS Information

Title:	Study I4V-MC-B010: Rheumatologist Survey to Assess the Effectiveness of the Risk Minimisation Measures (RMM) for Olumiant® (baricitinib) a JAK1/2 inhibitor
Version identifier:	Version 1.0
Date of last version:	23 Jul 2018
European Union (EU) Post Authorisation Study (PAS) Register No:	EUPAS25154
Active substance:	Baricitinib ATC Code: L04AA37
Medicinal product(s):	Baricitinib
Product reference:	EMEA/H/C/004085
Procedure number:	
Marketing authorisation holder(s) (MAH):	Eli Lilly Nederland B.V.
Joint PASS:	N/A
Research question and objectives:	This study will assess: a) Rheumatologists' understanding of the important safety information detailed in the Healthcare Professional Educational Material, that is, information relating to: - Pregnancy and breast feeding - Infections - Changes in lipid parameters b) Communication of the important safety information and mitigating actions to patients prescribed baricitinib for the first time c) Distribution of the Patient Alert Card (PAC) to patients prescribed baricitinib for the first time.
Countries of study:	At least 3 EU countries: Germany, Sweden, and the United Kingdom. EU countries were selected based on timing of product launch and market uptake of baricitinib.

Approval Date: 03-Dec-2018 GMT

Authors:	PPD PPD Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285, USA Email:PPD Tel: PPD

Marketing Authorisation Holder

Marketing Authorisation Holder(s)	Eli Lilly Nederland B.V. (Lilly) Papendorpseweg 83 3528 BJ Utrecht The Netherlands
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1. Table of Contents

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List of Annexes

2. List of Abbreviations

Term	Definition
aDCTS	annotated Data Collection Tools
CFR	Code of Federal Regulations
CIOMS	Council for International Organisations of Medical Sciences
CIs	confidence intervals
EDC	Electronic Data Capture
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	(US) Food and Drug Administration
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practices
GVP	Guideline on Good Pharmacovigilance Practices
HCP	Healthcare Providers
ICH	International Council for Harmonisation
IEA	International Epidemiological Association
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ISPE	International Society for Pharmacoepidemiology
JAK	Janus kinase
Lilly	Eli Lilly and Company
NCA	National Competent Authority
PAC	Patient Alert Card
RA	rheumatoid arthritis
RMM	risk minimisation measures
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

3. Responsible Parties

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Contract Research Organization

PPD

4. Abstract

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

- **Rationale and Background:** The additional risk minimisation activities for baricitinib include a Healthcare Professional Educational Material and a Patient Alert Card (PAC) to be distributed to patients prior to prescribing the product. The PAC is also included in the patient information leaflet. These materials will be distributed prior to launch to all healthcare providers (HCPs) who are expected to prescribe baricitinib, as agreed to with each National Competent Authority (NCA). The intent of the Healthcare Professional Educational Material is to facilitate the initial discussion between the HCP and patient on the important safety information and mitigating actions related to pregnancy and breastfeeding, infections, and changes in lipid parameters. A patient survey to directly assess the effectiveness of the PAC was not considered feasible, so the proposed assessment will evaluate the HCP's understanding of the important safety information in the Healthcare Professional Educational Material, 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. In the European Union (EU) Member State countries participating in this survey, the prescribing HCPs are expected to be rheumatologists per the provisions provided in the Summary of Product Characteristics (SmPC). Data from a second study (I4V-MC-B011; A Retrospective Cohort Study to Assess the Safety of Baricitinib Compared with Other Therapies Used in the Treatment of Rheumatoid Arthritis in Nordic countries), will aim to describe drug utilisation patterns and outcomes among patients using baricitinib.

- **Research Questions and Objectives:** This study will assess the following:
  a) Rheumatologists' understanding of the important safety information detailed in the Healthcare Professional Educational Material, that is, information relating to: pregnancy and breastfeeding, infections, and changes in lipid parameters;
  b) Communication of the important safety information and mitigating actions to patients prescribed baricitinib for the first time;
  c) Distribution of the PAC to patients prescribed baricitinib for the first time.

- **Study Design:** This study uses a multi-national, observational cross-sectional design. A survey will be administered to rheumatologists who are currently treating patients with rheumatoid arthritis (RA). No more than 80 completed surveys will be accepted from any individual country.

- **Population:** The survey will be administered to rheumatologists in at least 3 EU countries: Germany, Sweden, and the United Kingdom (UK), based on product launch and anticipated market uptake. The targeted respondent population will be rheumatologists who are currently treating patients with RA, at least 50% of whom will have prescribed baricitinib. The timing of the survey initiation and implementation in each country will depend on launch dates and the extent of baricitinib uptake after launch. 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, UBC, the European Medicines Agency (EMA) or any NCA will not be considered for participation.

- **Study Endpoints**: The risk minimisation measures (RMM) will be considered effective if at least 70% of respondents understand the key safety messages (Questions 9-15 pertaining to pregnancy and breastfeeding, lipid changes, and infections) communicated in the Healthcare Professional Educational Material. Among prescribers, we will also assess whether they, (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.

- **Variables:** The survey will collect responses to each question required to address th9e study objectives, in addition to prescriber status (yes/no), demographic information (e.g., age, country of practice), and clinical experience (e.g., duration of experience treating patients with RA, 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 from a random sample of rheumatologists who have previously agreed to be contacted for such studies.

- **Study Size**: The study will target completion of at least 200 surveys, with at least 50% of those from rheumatologists who have prescribed baricitinib. A maximum number of surveys will be required in each country, with no more than 80 completed surveys from Germany, Sweden, and the UK. Overall, the planned study size of 200 will provide an estimated precision of +/- 7% around the observed proportion of respondents 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.

- **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 and prescriber status (has previously prescribed baricitinib [i.e., prescriber], 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 baricitinib prescriptions will be based on the distribution of number of prescriptions in the data. Responses to each question relating to the understanding of risks will be categorised as "Correct" or "Incorrect". Frequency distributions with 95% confidence intervals will be calculated for responses to questions that address the survey objective (excluding demographic questions).

- **Milestones:** The study will be initiated within 21 months of market availability in the applicable EU country. Findings from the survey results will be reported to regulatory authorities (Section 6).

5. Amendments and Updates

Not applicable.

6. Milestones

Milestone	Planned Timeline*
Start of data collection	**Estimated at Q1 of 2019**
End of data collection	**When at least 200 surveys have been completed, estimated at Q1 of 2020**
Registration in the EU PAS Register	**Prior to start of data collection, estimated at Q1 of 2019**
Final study report	**4 months after the end of data collection, estimated Q3 2020**

Abbreviations: EU = European Union; NCA = National Competent Authority; PAC = Patient Alert Card; PAS = Post Authorisation Study; Q4 = quarter.

*The planned timeline is contingent upon approval of the Healthcare Professional Educational Material and the PAC by the NCA, and protocol review and approval by PRAC (Pharmacovigilance Risk Assessment Committee). The end of data collection is dependent on launch and market uptake.

7. Rationale and Background

Baricitinib is a Janus kinase (JAK)1/JAK2 inhibitor used 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. Baricitinib was authorised for use in the European Union (EU) by the EMA in February 2017, and additional risk minimisation activities were included as part of the risk management plan. These activities consist of (i) the Healthcare Professional Educational Material, which is intended to inform the initial discussion between the rheumatologist and patient at the 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 (ii) a Patient Alert Card (PAC).

In order to assess the effectiveness of the additional risk minimisation activities, this survey is designed to assess rheumatologists' understanding of the important safety information detailed in the Healthcare Professional Educational Material with respect to the risks of use during pregnancy and breast feeding, potential risk of infection, and changes in lipid parameters. It will also assess the communication of the important safety information and distribution of the PAC to patients prescribed baricitinib for the first time. The Healthcare Professional Educational Material and the PAC will be distributed to healthcare providers (HCPs) who are expected to prescribe baricitinib, in each country prior to launch, as agreed by each National Competent Authority (NCA).

8. Research Question and Objectives

This study will assess the following:

a) Rheumatologists' understanding of the important safety information detailed in the Healthcare Professional Educational Material, that is, information relating to: pregnancy and breastfeeding, infections, and changes in lipid parameters;

b) Communication of the important safety information and mitigating actions to patients prescribed baricitinib for the first time;

c) Distribution of the PAC to patients prescribed baricitinib for the first time.

9. Research Methods

9.1. Study Design

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

9.2. Setting

The assessment survey will be initiated within 21 months of market availability in at least 3 countries in the EU including Germany, Sweden, and the United Kingdom (UK). These Member States were chosen based upon:

- Providing the most timely information in countries where the survey is feasible and informative;
- The timing of product launch;
- Having sufficient market uptake of baricitinib to support target enrolment.

Germany and the UK are the predominant markets in the EU, and Sweden was selected to complement the information collected in Study I4V-MC-B011. Timing of survey launch and delivery of final study report are listed in Section 6. Market uptake across the EU will be monitored, and additional EU countries may be added, as required. The timing of survey initiation and implementation will vary according to the individual country launch plans and the extent of baricitinib uptake after launch. Surveys will be initiated in each country after reaching a market uptake of at least 300 patients exposed to baricitinib. Although this requirement has the potential to impact milestones by delaying survey launch, this risk is warranted given that it increases the likelihood of successful enrolment in each country. In addition, to maximize the generalisability of the survey results, a maximum number of completed surveys will be accepted from each country. No more than 80 completed surveys each will be accepted from Germany, Sweden, and the UK. Additional EU countries, such as Belgium or The Netherlands, may be considered as necessary to meet target enrolment.

The Healthcare Professional Educational Material and the PAC will be sent, prior to launch, to HCPs who are expected to prescribe baricitinib in each country, as agreed by each NCA. The target population in each selected country will have received the Healthcare Professional Educational Material and the PAC. 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 and, therefore, a minimum of 3 countries will be representative of the EU.

The survey will be administered via the internet, which will allow respondents to participate at a time and location that is convenient for them, and via telephone to allow participation of respondents without internet access. The same survey will be offered through both modalities. The survey includes questions that will assess rheumatologists' understanding of the important safety information detailed in the Healthcare Professional Educational Material, 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.

9.3. Survey Target Population

Eligible rheumatologists who respond to the survey invitation will make up the study population. Per the provisions in the SmPC, rheumatologists are expected to be the prescribing HCP in the EU Member State countries participating in this survey.

9.3.1. Inclusion criteria

Rheumatologists must meet the following criterion for inclusion in the survey:

- Must identify themselves as currently treating patients with RA and must be 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 will be required from prescribers of baricitinib.

9.3.2. Exclusion criteria

Rheumatologists meeting the following criterion will not be permitted to take the survey:

- Current or past employment with Eli Lilly and Company (Lilly) or any of its affiliates, United BioSource LLC (UBC), the EMA or any NCA.

9.4. Variables

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

- Response to questions about important safety information detailed in the Healthcare Professional Educational Material,
- 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.

In addition, information on the following will be collected:

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

9.5. Data Sources

In order to target the desired population, the data source will be a list of rheumatologists that is based on criteria used for the distribution list of recipients for the Healthcare Professional Educational Material and the PAC. This list consists of rheumatologists who have previously agreed to be contacted for this type of research. If there are more rheumatologists on the list than the number of invitations required for this study, a random sample will be invited to participate in the survey. The same sampling procedure will be used across all countries where participants have been identified and may be invited to take the survey.

Rheumatologists will receive an invitation letter via the 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 rheumatologists who have been invited, but have not yet participated. Participating rheumatologists' identifying information will be collected for the purposes of providing financial compensation, as allowed by local laws and country regulations. The database of invited rheumatologists will be regularly updated with responders and after each invitation mailing, the database will be crosschecked with any correspondence that had an invalid address, was undeliverable or had incorrect contact details. Rheumatologists who receive an invitation and who have no evidence of not receiving it (e.g., an invalid address), but who do not respond within 2 weeks from the initial mailing, will receive at least 1 reminder invitation.

A structured, self-administered questionnaire will be used to collect survey data (APPENDIX I.**1**). It is comprised of closed-ended questions or statements with multiple response choices. User testing has been performed on the survey questions by sampling 10 rheumatologists who were known to be actively treating patients with RA and who were independent of the sponsor and UBC. The final draft version of the survey incorporates feedback from this User Testing and is available in APPENDIX I.1.

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 rheumatologists' financial compensation, as allowed by local laws and country regulations, and will be stored in a separate database.

Each individual will be given a 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, but who have not actively opted out. 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 Healthcare Professional Educational Material. 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.

Screening questions:

- *Agreement to participate*
- *Rheumatologists who are currently treating patients with RA*

- *Current or past employment by Lilly, or any of its affiliates, UBC, the EMA, or any NCA*

Data on demographic characteristics:

- *Age*
- *Geographical location*
- *Experience in treating patients with RA*
- *Number of patients prescribed baricitinib*

Data pertaining to evaluation of the rheumatologists' understanding of the important safety information in the Healthcare Professional Educational Material, 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.

9.6. Study Size

The target sample size is at least 200 completed surveys. This sample size was determined based on providing a precision of ±7% around a response of 50%, based on a two-sided 95% confidence interval (CI). 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

For 200 completed surveys, results will be precise to within ±7%. Note that 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 100 prescribers are anticipated, the precision of results will lie within ±10% at worst. Results by country subgroups cannot be estimated since the total number of completed surveys from each country is not yet known; however, based on the maximum number permitted for each country, results would be precise to within ±11% at worst (Germany, Sweden, and the UK, with maximum 80 completed surveys each). If fewer surveys are returned in each country, then precision will fall. 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	20	12.4
	50	15.5
	70	14.2
80	20	8.8
	50	11.0
	70	10.0
100	20	7.8
	50	9.8
	70	9.0
200	10	4.2
	20	5.5
	50	6.9
	70	6.4
	80	5.5
	90	4.2

*95% confidence interval, two-sided.

9.7. 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. 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 1 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.

The UBC's Information Technology applications are governed by a development approach to ensure compliance to the Food and Drug Administration's (FDA) guidance for Industry-Computerized Systems Used in the Guidance for Industry 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. The 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 the 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 21 CFR Part 11 requirements are documented including: requirements for data entry, audit trails, date and time stamps, and security. Furthermore, the 21 CFR Part 11 checklist, which captures the traceability of the EDC requirements to the requirements set forth in the 21 CFR Part 11, *Electronic Records, Electronic Signatures,* is included in the validation summary report.

For the EDC information provided, the following UBC SOPs are followed for the relevant processes:

S-IT-10005	Report development lifecycle
S-STAT-10010	SAS file format conversion
S-STAT-10008	Development of derived datasets
S-STAT-10009	Development of tables, listings, and figures
S-STAT-10011	SAS program production and validation tracking
S-STAT-10012	Derived data sets, tables, listing and figures client release
S-REG-10002	Trial Master File Management

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

9.8. 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 survey objectives (i.e., excluding demographic questions).

Survey data will be analysed overall, and stratified by country, 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 baricitinib prescriptions, 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. At least 1 stratum is expected for each of: 1 previous baricitinib prescription, and >1 previous baricitinib prescription, but additional strata may be considered if they will. Analysis by experience treating patients with RA will be based on responses to survey Question 4 (number of years spent treatment patients with RA: <5, 5-10, 11-15, >15 years) and Question 5 (proportion of patients who have RA: 0-25%, 26-50%, 51-75%, 76-100%), described in Annex 1. Depending on the distribution of responses to Questions 4 and 5, i.e., there must be at least 5 respondents per category, strata may be collapsed for the purposes of presenting results. Responses will be categorised as “Correct response” and “Incorrect response”. Each question will be assessed individually.

The risk minimisation measures (RMM) will be considered to be successful if at least 70% of rheumatologists:

- Demonstrate understanding of the important safety information (Questions 9-15),

Among prescribers, we will also assess the proportion who report:

- 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.

Separate thresholds will not be used for individual questions.

The following information will be reported as part of the analysis:

Rheumatologists:

- *Survey administration will be performed by country and overall:*
  - *The number of survey invitations*
  - *The number of survey invitations/reminders returned due to incorrect mailing/emailing address of rheumatologists invited to participate in the survey*
  - *The number of rheumatologists who responded to the invitation to participate in the survey*
  - *The number of rheumatologists who meet the inclusion criteria for participation in the survey*
  - *The number of rheumatologists who do not meet the inclusion criteria along with the reasons for ineligibility*
  - *The number of rheumatologists who meet the inclusion criteria who completed the survey*
- *Demographic characteristics of participants by country*
  - *Distribution of participants by age groups*
  - *Distribution of participants by number of patients currently treated with baricitinib*
- *Responses to questions pertaining to the important safety information (Question 9 to Question 15)*

Rheumatologists' understanding of the important safety messages detailed in the Healthcare Professional Educational Material, 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, prescribing status/number of patients treated with baricitinib, and experience with treating patients with RA.

9.9. 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 Information Technology 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. The UBC's Information Technology applications are governed by a development approach to ensure compliance to FDA's guidance for Industry-Computerized Systems Used in the Guidance for Industry 21 CFR Part 11, Electronic Records; Electronic Signatures, and EudraLex Annex 11: Computerized Systems, and 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. The raw EDC data is used to populate analysis tables that are programmed by SQL Server Reporting Services (SSRS) according to the Survey Analysis Plan. Additionally, the EDC data will also be mapped to SAS datasets by a 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 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.

9.10. Limitations of the Research Methods

The survey recruitment strategies are intended to recruit rheumatologists who are identified as those treating patients with RA, and 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 Healthcare Professional Educational Material.

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 Healthcare Professional Educational Material and the PAC were received. If the respondent says she/he did not receive the Healthcare Professional Educational Material, the risk minimisation programme is evaluated as not optimally disseminating the material. It is possible, however, that respondents may simply not recall receiving the Healthcare Professional Educational Material and the PAC that 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 Healthcare Professional Educational Material and the PAC. The survey can assess the rheumatologists' understanding of the important safety information but cannot clearly determine via which channel the rheumatologists gained the information.

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

9.10.1. 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.

9.11. 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 rheumatologists' 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, *Good Pharmacoepidemiology Practices* (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), *Good Epidemiological Practice* (GEP) guidelines issued by the International Epidemiological Association (IEA), *Good Outcomes Research Practices* issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), *International Ethical Guidelines for Epidemiological Research* issued by the Council for International Organisations of Medical Sciences (CIOMS), EMA European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology*, and the United States FDA Guidance for Industry: *Good Pharmacovigilance and Pharmacoepidemiologic Assessment*.

11. Management and Reporting of Adverse Events/Adverse Reactions

Adverse Events

Adverse events will not be actively collected as this study is assessing rheumatologists' understanding of the important safety information detailed in the Healthcare Professional Educational Material, 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.

Survey respondents and other study personnel are requested to report any suspected adverse reactions with baricitinib to the regulators or the MAH as they would in normal practice as required by applicable laws, regulations, and practices.

Product Complaints

Survey respondents are instructed to report product complaints as they would for products in the marketplace.

12. Plans for Disseminating and Communicating Study Results

The study will be registered in the Post Authorisation Study Register hosted by ENCePP. The final report of the study results will be submitted as described in Section 6. Additionally, the study findings may be presented at a scientific congress and/or submitted to a peer-reviewed journal.

13. References

[CIOMS] Council for International Organisations of Medical Sciences. *International Ethical Guidelines for Epidemiological Research*.

Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika* 1934;26(4):404–413.

[EMA ENCePP] European Medicines Agency European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. *Guide on Methodological Standards in Pharmacoepidemiology*.

[GVP] Guideline on Good Pharmacovigilance Practices Module XVI- RMM: Selection of Tools and Effectiveness Indicators.

[IEA] International Epidemiological Association. *Good Epidemiological Practice*.

[ISPE] International Society for Pharmacoepidemiology. *Good Pharmacoepidemiology Practices.*

[ISPOR] International Society for Pharmacoeconomics and Outcomes Research. *Good Outcomes Research Practices*.

[US FDA] United States Food and Drug Administration. Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment.

Annex 1. List of Standalone Documents

Number	Document Reference Number	Date	Title
1	Appendix I.1		Proposed Rheumatologist Survey
2	Appendix I.2		Sample Draft Survey Invitation Letter for Rheumatologist
3	Appendix I.3		Healthcare Professional Educational Material and the Patient Alert Card

APPENDIX I.1. PROPOSED RHEUMATOLOGIST SURVEY

Survey Legend

- **[PROGRAMMER]** is used to indicate directions to the programmer and is set in bold, red, uppercase letters between square brackets.

- **(INTERVIEWER)** is used to indicate directions to the phone interviewer and is set in bold, blue, text between parentheses. This text appears when content is to be administered by phone only (for example, spontaneous adverse event reporting).

- **[BEGIN ONLINE/TELEPHONE SURVEY CONTENT]** and **[END ONLINE/TELEPHONE SURVEY CONTENT]** are used to indicate to the programmer the type of survey administration and the beginning and end of the survey or sections within the survey content, for example, **[BEGIN SAFETY EVENT SECTION]** and **[END SAFETY EVENT SECTION]**.

- **[TERMINATE]** is displayed next to responses that should cause the survey to end. The following termination language will be programmed into the survey or read by the interviewer.

  "Thank you very much for your time today. Based on your answer, you are not able to take this survey. We appreciate your interest in the survey."

- **[RANDOMISE LIST]** is inserted before questions to indicate to the programmer that the responses should be randomised. Responses such as "I don't know," "Prefer not to answer", or "None of the above" will always appear at the end of the randomised responses.

- **[GO TO Qx]** (skip logic) is inserted after a response to indicate to the programmer that the survey should skip to the indicated question (for example, **[GO TO Q17]** skips to Question 17). If no skip logic is indicated, the survey continues to the next question in the sequence.

- **[MULTILINE INPUT]** indicates to the programmer that multiple lines should be provided for data entry.

- **[FREE TEXT]** indicates to the programmer that 1 line should be provided for data entry.
- **[AMOUNT/TYPE]/[€XX/£XX]** information will be provided by the European Union Project Manager.

Survey Legend

- **[DROP-DOWN LIST INPUT WITH COUNTRIES TABLE]** indicates to the programmer that the response should be a drop-down list containing the countries in the table below.

TBD	TBD	TBD

[WELCOME PAGE]

This survey should take approximately 20 minutes to complete. If you cannot complete the survey at this time, please return when you can. Once you begin the survey you will need to answer all questions; you will not be able to access the survey again if you exit.

Thank you in advance for your participation. Please note the application will time out after xx minutes of inactivity.

If you are ready to begin the survey at this time, please click continue. If not, click Return Later.

Please note: Do not use the browser's back button during this survey.

[END WELCOME PAGE]

[BEGIN ONLINE PREAMBLE 1]

Disclaimer

Thank you for your interest in this voluntary research survey about Olumiant® (baricitinib) which is being conducted by United BioSource LLC(UBC) on behalf of the sponsor, Eli Lilly and Company (Lilly), the marketing authorisation holder of Olumiant. Taking part in this survey is voluntary; you are under no obligation to participate. You may refuse to take the survey or stop taking the survey at any time.

This survey should take approximately 20 minutes to complete. If you cannot complete the survey at this time, please come back when you can. Once you begin the survey, you will need to answer all questions during the same sitting; you will not be able to access the survey again if you exit the survey before answering all survey questions.

How We Use Your Information

This survey is part of a post marketing commitment between Lilly and the European Medicines Agency (EMA) to assess the effectiveness of the material sent to you to manage the key risks of Olumiant. Your answers to the survey questions will be combined with those from other respondents and reported in anonymous form to Lilly, the EMA, and any other locally applicable regulatory organisations. Your name will not be used in any report. If you are able to complete all inclusion questions as presented, complete all the important safety information questions, and provide your contact information; you will receive financial compensation based on your local

rules and regulations. This financial compensation represents the fair market value for your time in connection with completion of the survey. The amount of the financial compensation was not determined by the volume or value of any referrals or business otherwise generated by you. Your name and address will only be used to send the financial compensation to you once you complete the survey. This survey is voluntary; you are under no obligation to participate.

How We Protect Your Privacy

We respect that the privacy of your personal information is important to you. All the information you provide will be kept strictly confidential. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Your privacy will be protected; however, research survey records may be inspected by the EMA or other regulatory agencies. Your choice to allow Lilly to use your answers to the survey questions is entirely voluntary but necessary to participate.

How to Learn More about the Online Survey

If you have questions about or problems with the survey, please contact the Help Desk at:

Websitelink@ubc.com.

[END ONLINE PREAMBLE 1]

[BEGIN TELEPHONE PREAMBLE 1]

Disclaimer

Thank you for your interest in this voluntary research survey about Olumiant® (baricitinib), which is being conducted by United BioSource LLC (UBC) on behalf of the sponsor, Eli Lilly and Company (Lilly), the marketing authorisation holder of Olumiant. Taking part in this survey is voluntary; you are under no obligation to participate. You may refuse to take the survey or stop taking the survey at any time.

This survey should take approximately 20 minutes to complete. If you cannot complete the survey at this time, please call back when you can. Once you begin the survey, you will need to answer all questions during the same telephone call; you will not be able to access the survey again if you end this call.

How We Use Your Information

This survey is part of a post marketing commitment between Lilly and the European Medicines Agency (EMA) to assess the effectiveness of the material sent to you to manage the key risks of Olumiant. Your answers to the survey questions will be combined with those from other respondents and reported in anonymous form to Lilly, the EMA, and any other locally applicable regulatory organisations. Your name will not be used in any report. If you are able to complete all inclusion questions as presented, complete all the important safety message questions, and provide your contact information; you will receive financial compensation based on your local

rules and regulations. This financial compensation represents the fair value for your time in connection with completion of the survey. The amount of the financial compensation was not determined by the volume or value of any referrals or business otherwise generated by you. Your name and address will only be used to send the financial compensation to you once you complete the survey. This survey is voluntary; you are under no obligation to participate.

How We Protect Your Privacy

We respect that the privacy of your personal information is important to you. All the information you provide will be kept strictly confidential. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Your privacy will be protected; however, research survey records may be inspected by the EMA or other regulatory agencies. Your choice to allow Lilly to use your answers to the survey questions is entirely voluntary but necessary to participate.

How to Learn More about the Online Survey

If you have questions about or problems with the survey, please contact the Help Desk at:

Websitelink@ubc.com.

[END TELEPHONE PREAMBLE 1]

[BEGIN SCREENING QUESTIONS]

[BEGIN PREAMBLE 2 AND DISPLAY PREAMBLE 2 AND Q1 ON SAME PAGE]

Please provide a response to all questions and statements as they are presented.

[END PREAMBLE 2]

1. Do you agree to take part in this survey about Olumiant® (baricitinib)?

   - ○ Yes **[GO TO QUESTION 2]**
   - ○ No **[IF RESPONDENT ANSWERS "NO" DISPLAY Q1a and Q1b ON SAM PAGE]**

[BEGIN PREAMBLE 3 AND DISPLAY PREAMBLE 3 AND Q1a and Q1b ON SAME PAGE]

We understand you are not interested in taking the survey and recognise that your time is valuable; however, we would ask that you consider responding to two brief questions to help assure the scientific generalisability of the survey.

1a. **[END PREAMBLE 3]**

Have you ever prescribed Olumiant?

- o Yes
- o No
- o Prefer not to answer

1b. Are you familiar with the important safety information included in the Olumiant Healthcare Professional Educational Material?

- o Yes **[TERMINATE]**
- o No **[TERMINATE]**
- o Prefer not to answer **[TERMINATE]**

2. Have you or any of your immediate family members ever worked directly for Eli Lilly and Company (Lilly) or its affiliates, United BioSource Corporation (UBC), the European Medicines Agency (EMA), or any National Competent Authority (NCA)?

- o Yes **[TERMINATE]**
- o No

3. Are you a rheumatologist currently treating patients with rheumatoid arthritis?

- o Yes
- o No **[TERMINATE]**

[END SCREENING QUESTIONS]

[BEGIN SURVEY CONTENT]

4. In total, how many years have you been treating patients with rheumatoid arthritis?

   - ○ Less than 5 years
   - ○ 5 – 10 years
   - ○ 11 – 15 years
   - ○ More than 15 years

5. Approximately, what proportion of your patients that you see have rheumatoid arthritis?

   - ○ 0-25%
   - ○ 26-50%
   - ○ 51-75%
   - ○ 76-100%

6. Have you prescribed Olumiant (baricitinib)?

   - ○ Yes
   - ○ No **[GO TO QUESTION 8] [TERMINATE IF 100COMPLETE RESPONDENTS HAVE ANSWERED NO, WHERE X IS A CONFIGURABLE NUMBER]**

7. Approximately, how many patients have you treated in the last six months with Olumiant (baricitinib)?

   - ○ None
   - ○ 1-5
   - ○ 6-10
   - ○ More than 10

8. Which of the following groups best describes your age?

   - ○ Less than 40
   - ○ 40-59
   - ○ 60 or older
   - ○ Prefer not to answer

[BEGIN PREAMBLE 4 DISPLAY ON SAME PAGE AS Q9]

The following questions are about the important safety information associated with the use of Olumiant (baricitinib) as communicated in the Healthcare Professional Educational Material.

[END PREAMBLE 4]

9. *Please answer True, False, or I don't know for each of the following statements.*

[RANDOMISE LIST]

		True	False	I don't know
9a.	CCI [redacted]	○	○	○
9b.	CCI [redacted]	○	○	○

10. *Please select one option.* Which statement is correct regarding Olumiant (baricitinib)?

[RANDOMISE LIST WITH I DON'T KNOW ALWAYS AT THE BOTTOM]

10a. ○ CCI [redacted]

10b. ○ CCI [redacted]

10c. ○ I don't know

11. *Please <u>select one option</u>* according to the information in the Healthcare Professional Educational Material for Olumiant (baricitinib),.

11a. CCI ○

11b. ○

11c. I don't know ○

12. *Please select one option.* What should you do if the patient develops Herpes Zoster infection?

[RANDOMISE LIST WITH I DON'T KNOW ALWAYS AT THE BOTTOM]

12a. ○ CCI

12b. ○

12c. ○

12d. ○ I don't know

13. *Please select one option.* What should you do if the patient develops an infection which does not respond to standard treatment?

[RANDOMISE LIST WITH I DON'T KNOW ALWAYS AT THE BOTTOM]

13a. ○ CCI

13b. ○

13c. ○

13d. ○ I don't know

14. *Please select one option*. Which statement is correct regarding Olumiant (baricitinib)?

[RANDOMISE LIST]

14a. ○ CCI [redacted]

14b. ○

14c. ○

14d. ○ I don't know

15. *Please answer True, False, or I don't know for each of the following statements regarding Olumiant (baricitinib).*

[RANDOMISE LIST]

15a	CCI [redacted]	○	○	○
15b.		○	○	○
15c.		○	○	○
15d.		○	○	○

[BEGIN PREMABLE 5 DISPLAY ON SAME PAGE AS Q16]

The next set of questions is about the Healthcare Professional Educational Material for Olumiant (baricitinib). This document contains important information to assist the initial discussion with your patients when prescribing Olumiant.

To reference the Healthcare Professional Educational Material click here. [FOR ONLINE ONLY DISPLAY Healthcare Professional Educational Material.JPG WHEN HYPERLINK IS CLICKED]

[END PREAMBLE 5]

16. Prior to today, were you aware of the Healthcare Professional Educational Material for Olumiant (baricitinib)?

- ○ Yes
- ○ No **[GO TO PREAMBLE 6]**

17. Did you receive a copy of the Healthcare Professional Educational Material for Olumiant (baricitinib)?

- ○ Yes
- ○ No **[GO TO PREAMBLE 6]**
- ○ I don't remember **[GO TO PREAMBLE 6]**

18. Have you read the Healthcare Professional Educational Material for Olumiant (baricitinib)?

- ○ Yes
- ○ No
- ○ I don't remember

[BEGIN PREAMBLE 6 DISPLAY ON SAME PAGE AS Q19]

The next set of questions is about the Patient Alert Card. This Patient Alert Card was enclosed with the Healthcare Professional Educational Material for Olumiant (baricitinib).

To reference the Patient Alert Card click here. [FOR ONLINE ONLY DISPLAY Patient Alert Card.JPG WHEN HYPERLINK IS CLICKED]

[END PREAMBLE 6]

19. Prior to today, were you aware of the Patient Alert Card for Olumiant?

- ○ Yes
- ○ No **[DISPLAY Q20 AND THAN GO TO PREAMBLE 7]**

[ONLY RESPONDENTS WHO ANSWERED YES TO Q6 SHOULD BE PRESENTED WITH Q20 AND Q21]

20. Do you or someone in your practice/hospital communicate the important safety information to your patients when prescribing Olumiant (baricitinib) for the first time?

- ○ Yes
- ○ No
- ○ I don't know

21. **[DO NOT DISPLAY Q21 IF Q19 = NO]** When prescribing Olumiant (baricitinib) for the first time is your patient provided with a Patient Alert Card?

- ○ Yes
- ○ No
- ○ I don't know

[BEGIN PREAMBLE 7 DISPLAY ON SAME PAGE AS Q22]

We would like to send you [AMOUNT/TYPE] as financial compensation for your time and effort, but need your name and address to do so.

[END PREAMBLE 7]

22. Do you agree to provide your contact information for this purpose?

- o Yes **[GO TO PAYMENT TEXT/PAYMENT URL PREAMBLE]**
- o No **[GO TO CLOSING]**

[BEGIN PAYMENT TEXT/PAYMENT URL]

You are entitled to claim [€XX/£XX] to compensate you for the time taken to complete this survey. Please click on the link below to be taken to a secure portal, where you will be asked to enter your contact information to receive financial compensation for participation in this survey about Olumiant (baricitinib).
[www.PAYMENT.com]
[END PAYMENT TEXT/PAYMENT URL]

[BEGIN CLOSING]
This completes the survey. Thank you again for your participation.

[END CLOSING]
[END SURVEY CONTENT]

APPENDIX I.2. SAMPLE DRAFT INVITATION LETTER FOR RHEUMATOLOGISTS

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

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

Dear Dr. [insert rheumatologist's 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, indicated for the treatment of rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs.

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 communication sent to healthcare professionals to manage the important safety information of Olumiant. The safety survey should take approximately 20 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 rheumatoid arthritis. For your convenience, the survey can be completed online at **[www.surveyURL.com]** or over the telephone at **[TELEPHONE NUMBER].**

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

If participating online, you must take the survey on a desktop or laptop computer. The survey will not function correctly on other devices (such as: tablets, smart phones or e-notebooks).

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, a Healthcare Professional Educational Material and a Patient Alert Card were developed as risk minimisation measures. As part of its regulatory commitment, Lilly is required to assess the effectiveness of these 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 Material and the Patient Alert Card

Healthcare Professional Educational Material:

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 JAK1/2 inhibitor indicated for the treatment of rheumatoid arthritis.

The background information and points for discussion here provide context and appropriate risk management for key safety aspects of the prescribing information, namely:

- **Pregnancy and breast feeding**
- **Infections**
- **Changes in lipid parameters**

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**.

Pregnancy and Breast Feeding

Please discuss these points with your female patients if they are of child bearing potential:
- **Olumiant must not be used during pregnancy.** There is insufficient experience with Olumiant at this time to determine whether it can be safely used in pregnancy.
- **Olumiant should not be used in women who are breast feeding or intend to breast feed**. As there is no information on the excretion of Olumiant into human milk, it is unknown if it is safe to use during breast feeding.

As a result, it is important to:

- **Ask** patients if they are, might be, or intend to become pregnant, or are breast feeding prior to prescribing Olumiant.
- **Advise** women to use effective contraception both during treatment and for at least 1 week after discontinuing treatment, taking into account the short half-life of Olumiant.

Background pre-clinical safety information

As described in sections 4.6 and 5.3 of the SmPC, animal studies showed reduced foetal growth and skeletal malformations at exposures ≥10 times the human exposure.

As there are no adequate data on the use of Olumiant in human pregnancy, the implications of these non-clinical findings on use in women are not known. Therefore, the advice provided on use in pregnancy is given as a precautionary measure**.**

EULAR recommendations

The EULAR "Points to Consider for Use of Antirheumatic Drug Before Pregnancy, and During Pregnancy and Lactation" provides independent expert advice to support family planning discussions and could provide another useful reference source.

Infections

Olumiant increases the potential risk of infections, and viral reactivation.

Consistent with usual practice in treating patients with RA, it is important to instruct patients to seek immediate medical attention if signs or symptoms suggesting infection appear, in order to ensure rapid evaluation and appropriate treatment.

If an infection develops, monitor the patient carefully and:

- Temporarily interrupt Olumiant in case of herpes zoster infection or for any infection that is not responding to standard therapy. Do not resume Olumiant treatment until the infection resolves.

• **Advise** patients to inform you immediately if they think they could be pregnant or if pregnancy is confirmed in order to facilitate the appropriate discussions on the potential risks. These points are in line with independent expert EULAR recommendations* (See overleaf) * Götestam Skorpen C 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	• Screen patients to rule out active tuberculosis and active viral hepatitis before starting Olumiant. • Do not use live, attenuated vaccines during, or immediately prior to, Olumiant therapy. **Changes in Lipid Parameters** In clinical trials, dose-dependent increases in LDL and HDL cholesterol were observed at 12 weeks with no change in the LDL/HDL ratio. Lipid levels remained stable after 12 weeks. The long term consequences of these changes are unknown. **As a result of these considerations, it is important to:** • Assess lipid parameters approximately 12 weeks following initiation of Olumiant therapy. • Manage patients according to clinical guidelines for hyperlipidaemia thereafter. • Correct elevations in LDL cholesterol with statin treatment, if necessary.

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. 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.

Blood fat

Your doctor may check for levels of fat in the blood, such as cholesterol, while you are taking Olumiant.

Annex 2. ENCePP Checklist for Study Protocols

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

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	12
1.1.2 End of data collection[2]	☒	☐	☐	12
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	12
1.1.6 Final report of study results.	☒	☐	☐	12

Comments:

[1] 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.
[2] Date from which the analytical dataset is completely available.

Section 2: Research questions	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
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)	☒	☐	☐	13
2.1.2 The objective(s) of the study?	☒	☐	☐	14
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	15
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.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g., cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	15
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	16
3.3 Does the protocol specify measures of occurrence? (e.g., incidence rate, absolute risk)	☒	☐	☐	17
3.4 Does the protocol specify measure(s) of association? (e.g., relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm [NNH] per year)	☐	☐	☒	
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)	☒	☐	☐	27

Comments:

Rheumatologists' answers will be categorized 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**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	16
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?				
4.2.2 Age and sex?	☒	☐	☐	15
4.2.3 Country of origin?	☒	☐	☐	9.2
4.2.4 Disease/indication?	☒	☐	☐	15
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)	☒	☐	☐	18

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
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)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g., current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	16
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	18
6.3 Does the protocol address the validity of outcome measurement? (e.g., precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	23
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g., HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Page Numbers(s)**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g., healthy user bias)	☒	☐	☐	22
7.2.2. Information biases (e.g., misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	22
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Page Number(s)**
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**	**Page Number(s)**
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, etc.)	☐	☐	☒	
9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☐	☐	☒	
9.1.3 Covariates?	☐	☐	☒	
9.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g., date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
8.2.2 Outcomes? (e.g., date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
8.2.3 Covariates? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☐	☒	

Section 9: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
9.3 Is a coding system described for:				
9.3.3 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates?	☐	☐	☒	
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**	**Page Number(s)**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	21
10.2 Are descriptive analyses included?	☒	☐	☐	21
10.3 Are stratified analyses included?	☒	☐	☐	21
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	18

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**	**Page Number(s)**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	19
11.2 Are methods of quality assurance described?	☒	☐	☐	22
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	24
12.1.2 Information bias?	☒	☐	☐	24-25
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, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	18

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board been described?	☒	☐	☐	25
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	26

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	11

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	27
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	27

Comments:

Name of the main author of the protocol: _____

Date: / /

Signature: _____

Annex 3. Additional Information

Not applicable.

	A	B	C	D	E	F	G
1	*This detailed findings and recommendations grid reports feasibility research conducted on the Lilly OlumiantTM (baricitinib) Survey for Healthcare Professionals (HCPs) in the EU. Web-enabled telephone-depth interviews were conducted in the United Kingdom (UK) with ten (10) rheumatologists currently treating patients with rheumatoid arthritis. The rheumatologists represented a mix of practice settings. Interviews were conducted 30 June- 6 July 2017 and findings will be reported to Lilly on 13 July 2017. Verbatim comments are intended to further illustrate overall rheumatologist reactions and comments as needed. These are derived from moderator notes and direct transcription. In addition, clarifying content [in brackets] is sometimes added to verbatim comments to clarify comments or assist readers in understanding the full discussion context.*						
2	**Question**	**Survey Question**	**Answer**	**Qualitative Research Finding**	***HCP Verbatim Comments***	**UBC Recommendations**	**Lilly Decision:**
3	**Question 2**	Have you or any of your immediate family members ever worked for Eli Lilly and Company (Lilly) or its affiliates, United BioSource Corporation (UBC), the European Medicines Agency (EMA), or any National Competent Authorities (NCA)?		This is perceived as a standard and reasonable survey question. It is very clear for the majority of HCPs, however a small minority report its excessive length. A couple of developmental comments were shared by a minority of respondents:	*"It's a very common question"* *"I think it would be better if it said have you or any of your immediate family ever worked for the following:* *- Lilly and Company (Lilly) or its affiliates* *- United BioSource Corporation (UBC)* *- The European Medicines Agency (EMA)* *-Or any National Competent Authorities (NCA)* *So 1,2, 3, 4 bullet points will be make it clearer"*	No revisions recommended	No revisions needed
4	**Response Option 1**	Yes		Very clear and reasonable		No revisions recommended	No revisions needed
5	**Response Option 2**	No		Very clear and reasonable		No revisions recommended	No revisions needed
6							
7	**Question 3**	Are you a rheumatologist currently treating patients with rheumatoid arthritis?		There is a general endorsement for this question as it perceived as clear, well presented and reasonable	*"Straightforward. It's as clear as it can be".* *"It is clear again because some rheumatologists don't treat rheumatoid arthritis. They treat other conditions. So, this is a*	No revisions recommended	No revisions needed
8	**Response Option 1**	Yes		Very clear		No revisions recommended	No revisions needed
9	**Response Option 2**	No		Very clear		No revisions recommended	No revisions needed
10							
11	**Question 4**	Approximately, what proportion of your patients are being treated for rheumatoid arthritis (RA)?		This question appears to be unclear and may cause confusion. A minority of HCPs do not relate to percentages and tend to think about patients in absolute numbers instead. Most importantly, this question may be open to misunderstanding as it's unclear whether the HCPs are asked to focus on their whole cohort of patients (and how many of those have RA) or whether they need to report on the % of RA patients within the cohort of their rheumatoid patients.	*"I mean, I don't think percentages (...). So, it should be phrased in a different way (...). 'Approximately, what proportion of your patients are being treated for rheumatoid arthritis?' It's not clear. I would say, 'What proportion of your whole cohort of patients have rheumatoid arthritis?'"* *"To make it relevant the question has to be, 'Over the last three months how many patients have you treated with rheumatoid arthritis?' and that will give you a magnitude of numbers (...). Somebody could be seeing 1,000 patients and 25% are rheumatoid, and the other one will be seeing 20 patients and 100% of them are rheumatoid arthritis (...) So, I think important information will be, 'How many patients have you treated with rheumatoid arthritis over the last three months? ' "*	Recommend changing to 'Approximately, what proportion of patients that you see have rheumatoid arthritis (RA)?'	Revise to "Approximately, what proportion of patients that you see have rheumatoid arthritis (RA)?"
12	**Response Option 1**	0-25%		Very clear and reasonable		No revisions recommended	No revisions needed
13	**Response Option 2**	26-50%		Very clear and reasonable		No revisions recommended	No revisions needed
14	**Response Option 3**	51-75%		Very clear and reasonable		No revisions recommended	No revisions needed
15	**Response Option 4**	76-100%		Clear but perhaps unreasonable to		No revisions recommended	No revisions needed
16							

	A	B	C	D	E	F	G
2	**Question**	**Survey Question**	**Answer**	**Qualitative Research Finding**	***HCP Verbatim Comments***	**UBC Recommendations**	**Lilly Decision:**
17	**Question 6**	Approximately, how many patients have you treated in the last six months with Olumiant?		Universal feedback requesting baricitinib to be presented right next to the brand name (Olumiant) in order to ease understanding and facilitate recognition. This also reflects professional practice in the UK as pharmacists will manage the prescription process and will dispense the most appropriate product depending on guidelines.	*" I don't know. You have to define Olumiant. Is it the brand name or is it the scientific name, or is it both? Olumiant is actually the brand name, also known as baricitinib. Baricitinib is more clear between brackets: Olumiant (baricitinib). I don't know Olumiant. I know baricitinib".* *"Well, it's very straightforward. In the UK we would tend not to use brand names and I would also put in baricitinib because our prescriptions will have to be for baricitinib. We are, in most situations, encouraged not to use brand names because the pharmacist will choose the cheapest brand".*	Recommend changing to 'Approximately, how many patients have you treated in the last six months with Olumiant (baricitinib)?'	Revise to "Approximately, how many patients have you treated in the last six months with Olumiant (baricitinib)?"
18	**Response Option 1**	None		Very clear and relevant		No revisions recommended	No revisions needed
19	**Response Option 2**	1-5		Very clear and relevant		No revisions recommended	No revisions needed
20	**Response Option 3**	6-10		Very clear and relevant		No revisions recommended	No revisions needed
21	**Response Option 4**	More than 10		Very clear and relevant		No revisions recommended	No revisions needed
22							
23	**Question 7**	In total, how many years have you been treating patients with rheumatoid arthritis?		Very clear question, although some respondents suggest a clearer focus on the level/seniority of the rheumatologist (whether Consultant or Registrar level). In terms of the survey flow, it may make sense to place this question before question 4.	*"That's fine and clear. I don't think there is ambiguity in this question" .* *"I thought that should have come earlier, before, 'How many patients with rheumatoid arthritis are you treating?' I would have expected that to have come much earlier in the survey, but it doesn't matter. That is perfectly legitimate, quite clear, the distribution of the years is quite reasonable. I wouldn't add much to it. Nothing"*	Recommend moving to before Question 4	Question 7 to be moved to before Question 4
24	**Response Option 1**	Less than 5 years		Very clear		No revisions recommended	No revisions needed
25	**Response Option 2**	5 – 10 years		Very clear		No revisions recommended	No revisions needed
26	**Response Option 3**	11 – 15 years		Very clear		No revisions recommended	No revisions needed
27	**Response Option 4**	More than 15 years		Very clear		No revisions recommended	No revisions needed
28							
29	**Question 10A**	Please answer True, False, or I don't know for each of the following statements. CCI		CCI			
30	**Response Option 1**	True		Very clear		No revisions recommended	No revisions needed
31	**Response Option 2**	False		Very clear		No revisions recommended	No revisions needed
32	**Response Option 3**	I don't know		Very clear and relevant		No revisions recommended	No revisions needed

	A	B	C	D	E	F	G
2	**Question**	**Survey Question**	**Answer**	**Qualitative Research Finding**	***HCP Verbatim Comments***	**UBC Recommendations**	**Lilly Decision:**
33							
34	**Question 10B**	CCI		Overall this is considered to be a clear statement	CCI	No revisions recommended	No revisions needed
35	**Response Option 1**			Very clear		No revisions recommended	No revisions needed
36	**Response Option 2**	False		Very clear		No revisions recommended	No revisions needed
37	**Response Option 3**	I don't know		Very clear and appropriate		No revisions recommended	No revisions needed
38							
39	**Question 11**	Please select one option. Which statement is correct?		Very clear		No changes recommended	Revise to "Please select one option. Which statement is correct regarding Olumiant?"
40	**Statement A**	CCI		CCI			
41	**Statement B**	CCI		Clear and relevant, however there is a typo as "breastfeeding" is one word.	CCI		
42	**Statement C**	None of the above		Clear but perhaps redundant		No revisions recommended	No revisions needed
43							

	A	B	C	D	E	F	G
2	**Question**	**Survey Question**	**Answer**	**Qualitative Research Finding**	***HCP Verbatim Comments***	**UBC Recommendations**	**Lilly Decision:**
44	**Question 12A**	Please answer True, False, or I don't know for each of the following statements. CCI		CCI		No revisions recommended	No revisions needed
45	**Response Option 1**	True		Very clear		No revisions recommended	No revisions needed
46	**Response Option 2**	False		Very clear		No revisions recommended	No revisions needed
47	**Response Option 3**	I don't know		Very clear		No revisions recommended	No revisions needed
48							
49	**Question 12B**	CCI therapy.		CCI		No changes recommended	CCI
50	**Statement A**	True		Very clear		No revisions recommended	No revisions needed
51	**Statement B**	False		Very clear		No revisions recommended	No revisions needed
52	**Statement C**	I don't know		Very clear		No revisions recommended	No revisions needed
53							
54	**Question 12C**	CCI					
55	**Statement A**	True		Very clear		No revisions recommended	No revisions needed
56	**Statement B**	False		Very clear		No revisions recommended	No revisions needed
57	**Statement C**	I don't know		Very clear		No revisions recommended	No revisions needed
58							
59	**Question 13**	Please select one option. What should you do if the patient develops Herpes Zoster infection?		Very clear and relevant in the context of contemporary medicine	*"This is fine and a commonly encountered scenario with biologics"*	No revisions recommended	No revisions needed
60	**Statement A**	CCI					No revisions needed
61	**Statement B**	CCI		Very clear		No revisions recommended	No revisions needed
62	**Statement C**	None of the above		Redundant option/not relevant	*"It's either continue or withhold. That's it here. Very clear, but*	No revisions recommended	No revisions needed

	A	B	C	D	E	F	G
2	**Question**	**Survey Question**	**Answer**	**Qualitative Research Finding**	***HCP Verbatim Comments***	**UBC Recommendations**	**Lilly Decision:**
63							
64	**Question 14**	Please select one option. What should you do if the patient develops an infection which does not respond to standard treatment?		Very clear opening		No revisions recommended	No revisions needed
65	**Statement A**	CCI					
66	CCI						No revisions needed
67	**Statement C**	CCI		Very clear		No revisions recommended	No revisions needed
68	**Statement D**	I don't know		Very clear		No revisions recommended	No revisions needed
69							
70	**Question 15**	Please select one option. Which statement is correct?				No revisions recommended	No revisions needed
71	**Statement A**	CCI					
72	CCI						
73	CCI					No revisions recommended	No revisions needed
74							
75	**Question 16A**	Please answer True, False, or I don't know for each of the following statements. CCI		CCI		No revisions recommended	No revisions needed
76	**Response Option 1**	True		Very clear		No revisions recommended	No revisions needed
77	**Response Option 2**	False		Very clear		No revisions recommended	No revisions needed
78	**Response Option 3**	I don't know		Very clear		No revisions recommended	No revisions needed
79							
80	**Question 16B**	CCI				No revisions recommended	No revisions needed
81	**Response Option 1**	True		Very clear		No revisions recommended	No revisions needed
82	**Response Option 2**	False		Very clear		No revisions recommended	No revisions needed
83	**Response Option 3**	I don't know		Very clear		No revisions recommended	No revisions needed
84							
85	**Question 16C**	CCI				No revisions recommended	No revisions needed

	A	B	C	D	E	F	G
2	**Question**	**Survey Question**	**Answer**	**Qualitative Research Finding**	***HCP Verbatim Comments***	**UBC Recommendations**	**Lilly Decision:**
86	**Response Option 1**	True		Very clear		No revisions recommended	No revisions needed
87	**Response Option 2**	False		Very clear		No revisions recommended	No revisions needed
88	**Response Option 3**	I don't know		Very clear		No revisions recommended	No revisions needed
89							
90	**Question 16D**	CCI [redacted]		CCI [redacted] to" is redundant.	CCI [redacted] *vaccines can be used during Olumiant therapy"*	CCI [redacted]	CCI [redacted]
91	**Response Option 1**	True		Very clear		No revisions recommended	No revisions needed
92	**Response Option 2**	False		Very clear		No revisions recommended	No revisions needed
93	**Response Option 3**	I don't know		Very clear		No revisions recommended	No revisions needed
94							
95	**Question 17**	Prior to today, were you aware of the Healthcare Professional Educational Material for Olumiant?		Very clear		No revisions recommended	UBC to follow up internally regarding a pop up of the educational material as requested by Lilly. UBC will follow up separately with Lilly regarding this query.
96	**Response Option 1**	Yes		Very clear		No revisions recommended	No revisions needed
97	**Response Option 2**	No		Very clear		No revisions recommended	No revisions needed
98							
99	**Question 18**	Did you receive a copy of the Healthcare Professional Educational Material for Olumiant?		Very clear question		No revisions recommended	No revisions needed
100	**Response Option 1**	Yes		Very clear		No revisions recommended	No revisions needed
101	**Response Option 2**	No		Very clear		No revisions recommended	No revisions needed
102	**Response Option 3**	I don't know		Clear, however this statement could also reflect the ability to immediately remember these materials	*"We get bombarded with educational materials, we receive so much that sometimes we don't know"*	Recommend changing to "I don't remember"	Revise to "I don't remember"
103							
104	**Question 19**	When prescribing Olumiant to a patient for the first time how often do you provide the patient with a copy of the Patient Alert Card?		Very clear question, however it could be perceived as unnecessary and perhaps even slightly unexpected to some HCPs	*"I think it's reasonable. I mean, I'll be honest with you, because these drugs in this country are probably going to be delivered by the healthcare companies who do the delivery, I think a better question would be, 'Where do the patients get the Patient Alert Card from, the doctor, the nurses or the delivery company?' but anyway, I think for what you want this question is clear"*	No revisions recommended	Revise to "When prescribing Olumiant to a patient for the first time, do you or does someone in your office provide the patient with a copy of the Patient Alert Card?"
105	**Response Option 1**	Always		Very clear		No revisions recommended	No revisions needed
106	**Response Option 2**	Sometimes		Very clear		No revisions recommended	No revisions needed
107	**Response Option 3**	Never		Unnecessary		Suggest change to 'Rarely' as it would never 'never' happen	Response option to be removed
108							
109	**Question 20**	Prior to today, were you aware of the Patient Alert Card for Olumiant?		Very clear for all respondents with minor commentary around	*"I think it's reasonable. I mean, I'll be honest with you, because these drugs in this country are probably going to be delivered by the healthcare companies who do the delivery, I think a*	No revisions recommended	No revisions needed
110	**Response Option 1**	Yes		Very clear		No revisions recommended	No revisions needed
111	**Response Option 2**	No		Very clear		No revisions recommended	No revisions needed

	A	B	C	D	E	F	G
2	**Question**	**Survey Question**	**Answer**	**Qualitative Research Finding**	***HCP Verbatim Comments***	**UBC Recommendations**	**Lilly Decision:**
112	**Response Option 3**	I don't know		Unnecessary		Recommend deleting this response option	Response option to be removed
113							
114							
115							
116							
117	**Source Document:**						
118							
119							
120	Lilly Baricitinib HCP Survey.pptx						
121							

Table 1.1: Survey Administration Statistics

Parameter, n (%)	Germany	Sweden	United Kingdom	France	Overall
Number of Rheumatologists invited	1,481	335	1,424	2,703	5,943
All Respondents[a]	72 (4.9)	44 (13.1)	93 (6.5)	62 (2.3)	271 (4.6)
Eligible Respondents[c]	63 (87.5)	41 (93.2)	83 (89.2)	49 (79.0)	236 (87.1)
Completed the survey[c]	58 (80.6)	39 (88.6)	81 (87.1)	48 (77.4)	226 (83.4)
Did not complete the survey[c]	5 (6.9)	2 (4.5)	2 (2.2)	1 (1.6)	10 (3.7)
Respondents not eligible[b, c]	9 (12.5)	3 (6.8)	10 (10.8)	13 (21.0)	35 (12.9)

[a] Number of respondents who accessed the survey. Percentages are based on the number of invitations provided to HCPs excluding the number of invitations undeliverable.
[b] Number of respondents who did not meet eligibility criteria or did not complete eligibility questions. The responses to the eligibility criteria with the reason for ineligibility are presented in Table 1.2.
[c] Percentages are based on the number of all respondents.

Table 1.2: Survey Participant Eligibility Results - All Respondents

Question	Germany (N=72) n (%)	Sweden (N=44) n (%)	United Kingdom (N=93) n (%)	France (N=62) n (%)	Overall (N=271) n (%)
Question 1: Do you agree to take part in this survey about Olumiant® (baricitinib)?					
Yes	66 (91.7)	43 (97.7)	87 (93.5)	50 (80.6)	246 (90.8)
No[a]	0	0	0	1 (1.6)	1 (0.4)
Discontinued	6 (8.3)	1 (2.3)	6 (6.5)	11 (17.7)	24 (8.9)
Question 2: Have you or any of your immediate family members ever worked directly for Eli Lilly and Company (Lilly) or its affiliates, United BioSource Corporation (UBC), the European Medicines Agency (EMA), or any National Competent Authority (NCA)?					
Yes[a]	2 (2.8)	1 (2.3)	2 (2.2)	1 (1.6)	6 (2.2)
No	63 (87.5)	42 (95.5)	84 (90.3)	49 (79.0)	238 (87.8)
Question not asked [b]	0	0	0	1 (1.6)	1 (0.4)
Discontinued	7 (9.7)	1 (2.3)	7 (7.5)	11 (17.7)	26 (9.6)
Question 3: Are you a rheumatologist currently treating patients with rheumatoid arthritis?					
Yes	63 (87.5)	41 (93.2)	83 (89.2)	49 (79.0)	236 (87.1)
No[a]	0	0	0	0	0
Question not asked [b]	2 (2.8)	1 (2.3)	2 (2.2)	2 (3.2)	7 (2.6)
Discontinued	7 (9.7)	2 (4.5)	8 (8.6)	11 (17.7)	28 (10.3)

[a] Ineligible to participate in the survey.
[b] Question not asked due to the skip pattern in the survey or previous question termination.
Note: Respondents are counted as discontinued if they did not answer all eligibility questions without being identified as ineligible in a previous question. Once respondents are counted as discontinued, they will count as discontinued in all subsequent eligibility questions.;

Table 2: Description of Eligible Healthcare Providers - Completed Surveys

Question	Germay (N=58) n (%)	Sweden (N=39) n (%)	United Kingdom (N=81) n (%)	France (N=48) n (%)	Overall (N=226) n (%)
Question 4: In total, how many years have you been treating patients with rheumatoid arthritis?					
Less than 5 years	5 (8.6)	5 (12.8)	9 (11.1)	7 (14.6)	26 (11.5)
5 - 10 years	8 (13.8)	13 (33.3)	30 (37.0)	16 (33.3)	67 (29.6)
11 - 15 years	14 (24.1)	6 (15.4)	26 (32.1)	6 (12.5)	52 (23.0)
More than 15 years	31 (53.4)	15 (38.5)	16 (19.8)	19 (39.6)	81 (35.8)
Question 5: Approximately, what proportion of your patients that you see have rheumatoid arthritis?					
0-25%	5 (8.6)	0	7 (8.6)	16 (33.3)	28 (12.4)
26-50%	40 (69.0)	17 (43.6)	47 (58.0)	27 (56.3)	131 (58.0)
51-75%	12 (20.7)	20 (51.3)	23 (28.4)	5 (10.4)	60 (26.5)
76-100%	1 (1.7)	2 (5.1)	4 (4.9)	0	7 (3.1)
Question 6: Have you prescribed Olumiant (baricitinib)?					
Yes	58 (100.0)	37 (94.9)	71 (87.7)	45 (93.8)	211 (93.4)
No	0	2 (5.1)	10 (12.3)	3 (6.3)	15 (6.6)
Question 7: Approximately, how many patients have you treated in the last six months with Olumiant (baricitinib)?					
None	0	0	0	0	0
1-5	20 (34.5)	27 (69.2)	31 (38.3)	29 (60.4)	107 (47.3)
6-10	20 (34.5)	7 (17.9)	16 (19.8)	14 (29.2)	57 (25.2)
More than 10	18 (31.0)	3 (7.7)	24 (29.6)	2 (4.2)	47 (20.8)
Question not asked[a]	0	2 (5.1)	10 (12.3)	3 (6.3)	15 (6.6)
Question 8: Which of the following groups best describes your age?					
Less than 40	7 (12.1)	10 (25.6)	27 (33.3)	23 (47.9)	67 (29.6)
40-59	41 (70.7)	23 (59.0)	50 (61.7)	20 (41.7)	134 (59.3)
60 or older	9 (15.5)	5 (12.8)	3 (3.7)	3 (6.3)	20 (8.8)
Prefer not to answer	1 (1.7)	1 (2.6)	1 (1.2)	2 (4.2)	5 (2.2)

[a] Question not asked due to the skip pattern in the survey or previous question termination.

Table 3: Responses to all Questions Related to the Understanding of the Important Safety Information - Completed Surveys

Question	Overall (N=226) n (%) [95% CI][b]
Question 9: Please answer True, False, or I don't know for each of the following statements.	
9a: CCI .	
True	2 (0.9)
False[a]	199 (88.1) [83.1-92.0]
I don't know	25 (11.1)
9b: CCI	
True[a]	197 (87.2) [82.1-91.2]
False	5 (2.2)
I don't know	24 (10.6)
Question 10: Please select one option. Which statement is correct regarding Olumiant (baricitinib)?	
CCI	5 (2.2)
	179 (79.2) [73.3-84.3]
I don't know.	42 (18.6)
Question 11: Please select one option. According to the information in the Healthcare Professional Educational Material for Olumiant (baricitinib).	
CCI	206 (91.2) [86.7-94.5]
	7 (3.1)
I don't know.	13 (5.8)
Question 12: Please select one option. What should you do if the patient develops Herpes Zoster infection?	
CCI	213 (94.2) [90.4-96.9]
	7 (3.1)
	4 (1.8)
I don't know.	2 (0.9)

Table 3: Responses to all Questions Related to the Understanding of the Important Safety Information - Completed Surveys

Question	Overall (N=226) n (%) [95% CI][b]
Question 13: Please select one option. What should you do if the patient develops an infection which does not respond to standard treatment?	
CCI	207 (91.6) [87.2-94.9]
	17 (7.5)
	0
I don't know.	2 (0.9)
Question 14: Please select one option. Which statement is correct regarding Olumiant (baricitinib)?	
CCI	210 (92.9) [88.8-95.9]
	15 (6.6)
	1 (0.4)
I don't know.	0
Question 15: Please answer True, False, or I don't know for each of the following statements regarding Olumiant (baricitinib).	
15a: CCI	
True[a]	207 (91.6) [87.2-94.9]
False	6 (2.7)
I don't know	13 (5.8)
15b: CCI	
True[a]	219 (96.9) [93.7-98.7]
False	4 (1.8)
I don't know	3 (1.3)
15c: CCI	
True	32 (14.2)

Table 3: Responses to all Questions Related to the Understanding of the Important Safety Information - Completed Surveys

Question	Overall (N=226) n (%) [95% CI][b]
False[a]	190 (84.1) [78.6-88.6]
I don't know	4 (1.8)
15d: CCI [redacted]	
True	16 (7.1)
False[a]	200 (88.5) [83.6-92.3]
I don't know	10 (4.4)

[a] Correct response.
[b] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.

Table 3.1: Responses to all Questions Related to the Understanding of the Important Safety Information by Country - Completed Surveys

Question	Country				
	Germany (N=58) n (%) [95% CI][b]	Sweden (N=39) n (%) [95% CI][b]	United Kingdom (N=81) n (%) [95% CI][b]	France (N=48) n (%) [95% CI][b]	Overall (N=226) n (%) [95% CI][b]
Question 9: Please answer True, False, or I don't know for each of the following statements.					
9a: CCI [redacted]					
True	1 (1.7)	0	1 (1.2)	0	2 (0.9)
False[a]	54 (93.1) [83.3-98.1]	36 (92.3) [79.1-98.4]	69 (85.2) [75.6-92.1]	40 (83.3) [69.8-92.5]	199 (88.1) [83.1-92.0]
I don't know	3 (5.2)	3 (7.7)	11 (13.6)	8 (16.7)	25 (11.1)
9b: CCI [redacted]					
True[a]	52 (89.7) [78.8-96.1]	35 (89.7) [75.8-97.1]	71 (87.7) [78.5-93.9]	39 (81.3) [67.4-91.1]	197 (87.2) [82.1-91.2]
False	5 (8.6)	0	0	0	5 (2.2)
I don't know	1 (1.7)	4 (10.3)	10 (12.3)	9 (18.8)	24 (10.6)
Question 10: Please select one option. Which statement is correct regarding Olumiant (baricitinib)?					
CCI [redacted]	1 (1.7)	2 (5.1)	0	2 (4.2)	5 (2.2)
CCI [redacted].[a]	51 (87.9) [76.7-95.0]	32 (82.1) [66.5-92.5]	58 (71.6) [60.5-81.1]	38 (79.2) [65.0-89.5]	179 (79.2) [73.3-84.3]
I don't know.	6 (10.3)	5 (12.8)	23 (28.4)	8 (16.7)	42 (18.6)

Table 3.1: Responses to all Questions Related to the Understanding of the Important Safety Information by Country - Completed Surveys

Question	Country				
	Germany (N=58) n (%) [95% CI][b]	Sweden (N=39) n (%) [95% CI][b]	United Kingdom (N=81) n (%) [95% CI][b]	France (N=48) n (%) [95% CI][b]	Overall (N=226) n (%) [95% CI][b]
Question 11: Please select one option. According to the information in the Healthcare Professional Educational Material for Olumiant (baricitinib).					
CCI [redacted][a]	50 (86.2) [74.6-93.9]	34 (87.2) [72.6-95.7]	76 (93.8) [86.2-98.0]	46 (95.8) [85.7-99.5]	206 (91.2) [86.7-94.5]
CCI [redacted]	4 (6.9)	2 (5.1)	1 (1.2)	0	7 (3.1)
I don't know.	4 (6.9)	3 (7.7)	4 (4.9)	2 (4.2)	13 (5.8)
Question 12: Please select one option. What should you do if the patient develops Herpes Zoster infection?					
CCI [redacted]	55 (94.8) [85.6-98.9]	37 (94.9) [82.7-99.4]	77 (95.1) [87.8-98.6]	44 (91.7) [80.0-97.7]	213 (94.2) [90.4-96.9]
	3 (5.2)	0	2 (2.5)	2 (4.2)	7 (3.1)
	0	1 (2.6)	1 (1.2)	2 (4.2)	4 (1.8)
I don't know.	0	1 (2.6)	1 (1.2)	0	2 (0.9)
Question 13: Please select one option. What should you do if the patient develops an infection which does not respond to standard treatment?					

Table 3.1: Responses to all Questions Related to the Understanding of the Important Safety Information by Country - Completed Surveys

Question	Country				
	Germany (N=58) n (%) [95% CI][b]	Sweden (N=39) n (%) [95% CI][b]	United Kingdom (N=81) n (%) [95% CI][b]	France (N=48) n (%) [95% CI][b]	Overall (N=226) n (%) [95% CI][b]
CCI [redacted]	48 (82.8) [70.6-91.4]	37 (94.9) [82.7-99.4]	80 (98.8) [93.3-100.0]	42 (87.5) [74.8-95.3]	207 (91.6) [87.2-94.9]
[redacted]	8 (13.8)	2 (5.1)	1 (1.2)	6 (12.5)	17 (7.5)
[redacted]	0	0	0	0	0
I don't know.	2 (3.4)	0	0	0	2 (0.9)
Question 14: Please select one option. Which statement is correct regarding Olumiant (baricitinib)?					
CCI [redacted]	55 (94.8) [85.6-98.9]	35 (89.7) [75.8-97.1]	76 (93.8) [86.2-98.0]	44 (91.7) [80.0-97.7]	210 (92.9) [88.8-95.9]
[redacted]	3 (5.2)	4 (10.3)	5 (6.2)	3 (6.3)	15 (6.6)
[redacted]	0	0	0	1 (2.1)	1 (0.4)
I don't know.	0	0	0	0	0
Question 15: Please answer True, False, or I don't know for each of the following statements regarding Olumiant (baricitinib).					

Table 3.1: Responses to all Questions Related to the Understanding of the Important Safety Information by Country - Completed Surveys

Question	Country				
	Germany (N=58) n (%) [95% CI][b]	Sweden (N=39) n (%) [95% CI][b]	United Kingdom (N=81) n (%) [95% CI][b]	France (N=48) n (%) [95% CI][b]	Overall (N=226) n (%) [95% CI][b]
15a: CCI					
True[a]	55 (94.8) [85.6-98.9]	35 (89.7) [75.8-97.1]	75 (92.6) [84.6-97.2]	42 (87.5) [74.8-95.3]	207 (91.6) [87.2-94.9]
False	1 (1.7)	0	1 (1.2)	4 (8.3)	6 (2.7)
I don't know	2 (3.4)	4 (10.3)	5 (6.2)	2 (4.2)	13 (5.8)
15b: CCI .					
True[a]	57 (98.3) [90.8-100.0]	37 (94.9) [82.7-99.4]	79 (97.5) [91.4-99.7]	46 (95.8) [85.7-99.5]	219 (96.9) [93.7-98.7]
False	1 (1.7)	1 (2.6)	2 (2.5)	0	4 (1.8)
I don't know	0	1 (2.6)	0	2 (4.2)	3 (1.3)
15c: CCI					
True	6 (10.3)	7 (17.9)	13 (16.0)	6 (12.5)	32 (14.2)
False[a]	52 (89.7) [78.8-96.1]	29 (74.4) [57.9-87.0]	68 (84.0) [74.1-91.2]	41 (85.4) [72.2-93.9]	190 (84.1) [78.6-88.6]
I don't know	0	3 (7.7)	0	1 (2.1)	4 (1.8)
15d: CCI					
True	5 (8.6)	2 (5.1)	6 (7.4)	3 (6.3)	16 (7.1)

Table 3.1: Responses to all Questions Related to the Understanding of the Important Safety Information by Country - Completed Surveys

Question	Country				
	Germany (N=58) n (%) [95% CI][b]	Sweden (N=39) n (%) [95% CI][b]	United Kingdom (N=81) n (%) [95% CI][b]	France (N=48) n (%) [95% CI][b]	Overall (N=226) n (%) [95% CI][b]
False[a]	51 (87.9) [76.7-95.0]	34 (87.2) [72.6-95.7]	72 (88.9) [80.0-94.8]	43 (89.6) [77.3-96.5]	200 (88.5) [83.6-92.3]
I don't know	2 (3.4)	3 (7.7)	3 (3.7)	2 (4.2)	10 (4.4)

[a] Correct response.
[b] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.

Table 3.2: Responses to all Questions Related to the Understanding of the Important Safety Information by Prescribing Status - Completed Surveys

Question	Prescribing Status		
	Active prescribers (N=211) n (%) [95% CI][b]	Potential prescribers (N=15) n (%) [95% CI][b]	Overall (N=226) n (%) [95% CI][b]
Question 9: Please answer True, False, or I don't know for each of the following statements.			
9a: CCI [redacted]			
True	2 (0.9)	0	2 (0.9)
False[a]	188 (89.1) [84.1-93.0]	11 (73.3) [44.9-92.2]	199 (88.1) [83.1-92.0]
I don't know	21 (10.0)	4 (26.7)	25 (11.1)
9b: CCI [redacted]			
True[a]	186 (88.2) [83.0-92.2]	11 (73.3) [44.9-92.2]	197 (87.2) [82.1-91.2]
False	5 (2.4)	0	5 (2.2)
I don't know	20 (9.5)	4 (26.7)	24 (10.6)
Question 10: Please select one option. Which statement is correct regarding Olumiant (baricitinib)?			
CCI [redacted]	4 (1.9)	1 (6.7)	5 (2.2)
[redacted]	172 (81.5) [75.6-86.5]	7 (46.7) [21.3-73.4]	179 (79.2) [73.3-84.3]
I don't know.	35 (16.6)	7 (46.7)	42 (18.6)
Question 11: Please select one option. According to the information in the Healthcare Professional Educational Material for Olumiant (baricitinib).			
CCI [redacted]	194 (91.9) [87.4-95.2]	12 (80.0) [51.9-95.7]	206 (91.2) [86.7-94.5]
[redacted]	6 (2.8)	1 (6.7)	7 (3.1)
I don't know.	11 (5.2)	2 (13.3)	13 (5.8)
Question 12: Please select one option. What should you do if the patient develops Herpes Zoster infection?			
CCI [redacted]	200 (94.8) [90.9-97.4]	13 (86.7) [59.5-98.3]	213 (94.2) [90.4-96.9]

Table 3.2: Responses to all Questions Related to the Understanding of the Important Safety Information by Prescribing Status - Completed Surveys

Question	Prescribing Status		
	Active prescribers (N=211) n (%) [95% CI][b]	Potential prescribers (N=15) n (%) [95% CI][b]	Overall (N=226) n (%) [95% CI][b]
CCI	6 (2.8)	1 (6.7)	7 (3.1)
	4 (1.9)	0	4 (1.8)
I don't know.	1 (0.5)	1 (6.7)	2 (0.9)
Question 13: Please select one option. What should you do if the patient develops an infection which does not respond to standard treatment?			
CCI	194 (91.9) [87.4-95.2]	13 (86.7) [59.5-98.3]	207 (91.6) [87.2-94.9]
	15 (7.1)	2 (13.3)	17 (7.5)
	0	0	0
I don't know.	2 (0.9)	0	2 (0.9)
Question 14: Please select one option. Which statement is correct regarding Olumiant (baricitinib)?			
CCI	195 (92.4) [88.0-95.6]	15 (100.0) [78.2-100.0]	210 (92.9) [88.8-95.9]
	15 (7.1)	0	15 (6.6)
	1 (0.5)	0	1 (0.4)
I don't know.	0	0	0
Question 15: Please answer True, False, or I don't know for each of the following statements regarding Olumiant (baricitinib).			
15a: CCI			
True[a]	193 (91.5) [86.9-94.9]	14 (93.3) [68.1-99.8]	207 (91.6) [87.2-94.9]
False	6 (2.8)	0	6 (2.7)

Table 3.2: Responses to all Questions Related to the Understanding of the Important Safety Information by Prescribing Status - Completed Surveys

Question	Prescribing Status		
	Active prescribers (N=211) n (%) [95% CI][b]	Potential prescribers (N=15) n (%) [95% CI][b]	Overall (N=226) n (%) [95% CI][b]
I don't know	12 (5.7)	1 (6.7)	13 (5.8)
15b: CCI [redacted]			
True[a]	204 (96.7) [93.3-98.7]	15 (100.0) [78.2-100.0]	219 (96.9) [93.7-98.7]
False	4 (1.9)	0	4 (1.8)
I don't know	3 (1.4)	0	3 (1.3)
15c: CCI [redacted]			
True	30 (14.2)	2 (13.3)	32 (14.2)
False[a]	177 (83.9) [78.2-88.6]	13 (86.7) [59.5-98.3]	190 (84.1) [78.6-88.6]
I don't know	4 (1.9)	0	4 (1.8)
15d: CCI [redacted]			
True	16 (7.6)	0	16 (7.1)
False[a]	185 (87.7) [82.5-91.8]	15 (100.0) [78.2-100.0]	200 (88.5) [83.6-92.3]
I don't know	10 (4.7)	0	10 (4.4)

[a] Correct response.
[b] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.

Table 3.3: Responses to all Questions Related to the Understanding of the Important Safety Information by Prescribing Frequency - Completed Surveys

Question	Prescribing Frequency			
	Potential prescribers (N=15) n (%) [95% CI][b]	Low prescribers (N=107) n (%) [95% CI][b]	High prescribers (N=104) n (%) [95% CI][b]	Overall (N=226) n (%) [95% CI][b]
Question 9: Please answer True, False, or I don't know for each of the following statements.				
9a: CCI [redacted]				
True	0	1 (0.9)	1 (1.0)	2 (0.9)
False[a]	11 (73.3) [44.9-92.2]	96 (89.7) [82.3-94.8]	92 (88.5) [80.7-93.9]	199 (88.1) [83.1-92.0]
I don't know	4 (26.7)	10 (9.3)	11 (10.6)	25 (11.1)
9b: CCI [redacted]				
True[a]	11 (73.3) [44.9-92.2]	94 (87.9) [80.1-93.4]	92 (88.5) [80.7-93.9]	197 (87.2) [82.1-91.2]
False	0	1 (0.9)	4 (3.8)	5 (2.2)
I don't know	4 (26.7)	12 (11.2)	8 (7.7)	24 (10.6)
Question 10: Please select one option. Which statement is correct regarding Olumiant (baricitinib)?				
CCI [redacted]	1 (6.7)	4 (3.7)	0	5 (2.2)
CCI [redacted]	7 (46.7) [21.3-73.4]	82 (76.6) [67.5-84.3]	90 (86.5) [78.4-92.4]	179 (79.2) [73.3-84.3]
I don't know.	7 (46.7)	21 (19.6)	14 (13.5)	42 (18.6)

Table 3.3: Responses to all Questions Related to the Understanding of the Important Safety Information by Prescribing Frequency - Completed Surveys

Question	Prescribing Frequency			
	Potential prescribers (N=15) n (%) [95% CI][b]	Low prescribers (N=107) n (%) [95% CI][b]	High prescribers (N=104) n (%) [95% CI][b]	Overall (N=226) n (%) [95% CI][b]
Question 11: Please select one option. According to the information in the Healthcare Professional Educational Material for Olumiant (baricitinib).				
CCI	12 (80.0) [51.9-95.7]	99 (92.5) [85.8-96.7]	95 (91.3) [84.2-96.0]	206 (91.2) [86.7-94.5]
	1 (6.7)	2 (1.9)	4 (3.8)	7 (3.1)
I don't know.	2 (13.3)	6 (5.6)	5 (4.8)	13 (5.8)
Question 12: Please select one option. What should you do if the patient develops Herpes Zoster infection?				
CCI	13 (86.7) [59.5-98.3]	104 (97.2) [92.0-99.4]	96 (92.3) [85.4-96.6]	213 (94.2) [90.4-96.9]
	1 (6.7)	2 (1.9)	4 (3.8)	7 (3.1)
	0	1 (0.9)	3 (2.9)	4 (1.8)
I don't know.	1 (6.7)	0	1 (1.0)	2 (0.9)
Question 13: Please select one option. What should you do if the patient develops an infection which does not respond to standard treatment?				

Table 3.3: Responses to all Questions Related to the Understanding of the Important Safety Information by Prescribing Frequency - Completed Surveys

Question	Prescribing Frequency			
	Potential prescribers (N=15) n (%) [95% CI][b]	Low prescribers (N=107) n (%) [95% CI][b]	High prescribers (N=104) n (%) [95% CI][b]	Overall (N=226) n (%) [95% CI][b]
CCI	13 (86.7) [59.5-98.3]	97 (90.7) [83.5-95.4]	97 (93.3) [86.6-97.3]	207 (91.6) [87.2-94.9]
	2 (13.3)	9 (8.4)	6 (5.8)	17 (7.5)
	0	0	0	0
I don't know.	0	1 (0.9)	1 (1.0)	2 (0.9)
Question 14: Please select one option. Which statement is correct regarding Olumiant (baricitinib)?				
CCI	15 (100.0) [78.2-100.0]	97 (90.7) [83.5-95.4]	98 (94.2) [87.9-97.9]	210 (92.9) [88.8-95.9]
	0	10 (9.3)	5 (4.8)	15 (6.6)
	0	0	1 (1.0)	1 (0.4)
I don't know.	0	0	0	0
Question 15: Please answer True, False, or I don't know for each of the following statements regarding Olumiant (baricitinib).				

Table 3.3: Responses to all Questions Related to the Understanding of the Important Safety Information by Prescribing Frequency - Completed Surveys

Question	Prescribing Frequency			
	Potential prescribers (N=15) n (%) [95% CI][b]	Low prescribers (N=107) n (%) [95% CI][b]	High prescribers (N=104) n (%) [95% CI][b]	Overall (N=226) n (%) [95% CI][b]
15a: CCI				
True[a]	14 (93.3) [68.1-99.8]	99 (92.5) [85.8-96.7]	94 (90.4) [83.0-95.3]	207 (91.6) [87.2-94.9]
False	0	3 (2.8)	3 (2.9)	6 (2.7)
I don't know	1 (6.7)	5 (4.7)	7 (6.7)	13 (5.8)
15b: CCI				
True[a]	15 (100.0) [78.2-100.0]	105 (98.1) [93.4-99.8]	99 (95.2) [89.1-98.4]	219 (96.9) [93.7-98.7]
False	0	0	4 (3.8)	4 (1.8)
I don't know	0	2 (1.9)	1 (1.0)	3 (1.3)
15c: CCI				
True	2 (13.3)	19 (17.8)	11 (10.6)	32 (14.2)
False[a]	13 (86.7) [59.5-98.3]	86 (80.4) [71.6-87.4]	91 (87.5) [79.6-93.2]	190 (84.1) [78.6-88.6]
I don't know	0	2 (1.9)	2 (1.9)	4 (1.8)
15d: CCI				
True	0	7 (6.5)	9 (8.7)	16 (7.1)

Table 3.3: Responses to all Questions Related to the Understanding of the Important Safety Information by Prescribing Frequency - Completed Surveys

Question	Prescribing Frequency			
	Potential prescribers (N=15) n (%) [95% CI][b]	Low prescribers (N=107) n (%) [95% CI][b]	High prescribers (N=104) n (%) [95% CI][b]	Overall (N=226) n (%) [95% CI][b]
False[a]	15 (100.0) [78.2-100.0]	94 (87.9) [80.1-93.4]	91 (87.5) [79.6-93.2]	200 (88.5) [83.6-92.3]
I don't know	0	6 (5.6)	4 (3.8)	10 (4.4)

[a] Correct response.
[b] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
Note: Low prescribers: <= 5 patients in the last 6 months; High prescribers: => 6 patients in the last 6 months.

Table 3.4: Responses to all Questions Related to the Understanding of the Important Safety Information by Experience in treating RA Patients - Completed Surveys

Question	Experience in treating RA Patients			
	High experience (N=22) n (%) [95% CI][b]	Medium experience (N=186) n (%) [95% CI][b]	Low experience (N=18) n (%) [95% CI][b]	Overall (N=226) n (%) [95% CI][b]
Question 9: Please answer True, False, or I don't know for each of the following statements.				
9a: CCI [redacted]				
True	0	2 (1.1)	0	2 (0.9)
False[a]	22 (100.0) [84.6-100.0]	161 (86.6) [80.8-91.1]	16 (88.9) [65.3-98.6]	199 (88.1) [83.1-92.0]
I don't know	0	23 (12.4)	2 (11.1)	25 (11.1)
9b: CCI [redacted]				
True[a]	20 (90.9) [70.8-98.9]	161 (86.6) [80.8-91.1]	16 (88.9) [65.3-98.6]	197 (87.2) [82.1-91.2]
False	1 (4.5)	4 (2.2)	0	5 (2.2)
I don't know	1 (4.5)	21 (11.3)	2 (11.1)	24 (10.6)
Question 10: Please select one option. Which statement is correct regarding Olumiant (baricitinib)?				
CCI [redacted]	0	4 (2.2)	1 (5.6)	5 (2.2)
[redacted]	18 (81.8) [59.7-94.8]	147 (79.0) [72.5-84.6]	14 (77.8) [52.4-93.6]	179 (79.2) [73.3-84.3]
I don't know.	4 (18.2)	35 (18.8)	3 (16.7)	42 (18.6)

Table 3.4: Responses to all Questions Related to the Understanding of the Important Safety Information by Experience in treating RA Patients - Completed Surveys

Question	Experience in treating RA Patients			
	High experience (N=22) n (%) [95% CI][b]	Medium experience (N=186) n (%) [95% CI][b]	Low experience (N=18) n (%) [95% CI][b]	Overall (N=226) n (%) [95% CI][b]
Question 11: Please select one option. According to the information in the Healthcare Professional Educational Material for Olumiant (baricitinib).				
CCI	19 (86.4) [65.1-97.1]	169 (90.9) [85.8-94.6]	18 (100.0) [81.5-100.0]	206 (91.2) [86.7-94.5]
	2 (9.1)	5 (2.7)	0	7 (3.1)
I don't know.	1 (4.5)	12 (6.5)	0	13 (5.8)
Question 12: Please select one option. What should you do if the patient develops Herpes Zoster infection?				
CCI	21 (95.5) [77.2-99.9]	175 (94.1) [89.7-97.0]	17 (94.4) [72.7-99.9]	213 (94.2) [90.4-96.9]
	1 (4.5)	5 (2.7)	1 (5.6)	7 (3.1)
	0	4 (2.2)	0	4 (1.8)
I don't know.	0	2 (1.1)	0	2 (0.9)
Question 13: Please select one option. What should you do if the patient develops an infection which does not respond to standard treatment?				

Table 3.4: Responses to all Questions Related to the Understanding of the Important Safety Information by Experience in treating RA Patients - Completed Surveys

Question	Experience in treating RA Patients			
	High experience (N=22) n (%) [95% CI][b]	Medium experience (N=186) n (%) [95% CI][b]	Low experience (N=18) n (%) [95% CI][b]	Overall (N=226) n (%) [95% CI][b]
CCI [redacted]	19 (86.4) [65.1-97.1]	174 (93.5) [89.0-96.6]	14 (77.8) [52.4-93.6]	207 (91.6) [87.2-94.9]
	2 (9.1)	11 (5.9)	4 (22.2)	17 (7.5)
	0	0	0	0
I don't know.	1 (4.5)	1 (0.5)	0	2 (0.9)
Question 14: Please select one option. Which statement is correct regarding Olumiant (baricitinib)?				
CCI [redacted]	19 (86.4) [65.1-97.1]	174 (93.5) [89.0-96.6]	17 (94.4) [72.7-99.9]	210 (92.9) [88.8-95.9]
	2 (9.1)	12 (6.5)	1 (5.6)	15 (6.6)
	1 (4.5)	0	0	1 (0.4)
I don't know.	0	0	0	0
Question 15: Please answer True, False, or I don't know for each of the following statements regarding Olumiant (baricitinib).				

Table 3.4: Responses to all Questions Related to the Understanding of the Important Safety Information by Experience in treating RA Patients - Completed Surveys

Question	Experience in treating RA Patients			
	High experience (N=22) n (%) [95% CI][b]	Medium experience (N=186) n (%) [95% CI][b]	Low experience (N=18) n (%) [95% CI][b]	Overall (N=226) n (%) [95% CI][b]
15a: CCI				
True[a]	20 (90.9) [70.8-98.9]	169 (90.9) [85.8-94.6]	18 (100.0) [81.5-100.0]	207 (91.6) [87.2-94.9]
False	1 (4.5)	5 (2.7)	0	6 (2.7)
I don't know	1 (4.5)	12 (6.5)	0	13 (5.8)
15b: CCI				
True[a]	20 (90.9) [70.8-98.9]	181 (97.3) [93.8-99.1]	18 (100.0) [81.5-100.0]	219 (96.9) [93.7-98.7]
False	2 (9.1)	2 (1.1)	0	4 (1.8)
I don't know	0	3 (1.6)	0	3 (1.3)
15c: CCI				
True	3 (13.6)	23 (12.4)	6 (33.3)	32 (14.2)
False[a]	19 (86.4) [65.1-97.1]	159 (85.5) [79.6-90.2]	12 (66.7) [41.0-86.7]	190 (84.1) [78.6-88.6]
I don't know	0	4 (2.2)	0	4 (1.8)
15d: CCI				
True	2 (9.1)	12 (6.5)	2 (11.1)	16 (7.1)

Table 3.4: Responses to all Questions Related to the Understanding of the Important Safety Information by Experience in treating RA Patients - Completed Surveys

Question	Experience in treating RA Patients			
	High experience (N=22) n (%) [95% CI][b]	Medium experience (N=186) n (%) [95% CI][b]	Low experience (N=18) n (%) [95% CI][b]	Overall (N=226) n (%) [95% CI][b]
False[a]	19 (86.4) [65.1-97.1]	165 (88.7) [83.3-92.9]	16 (88.9) [65.3-98.6]	200 (88.5) [83.6-92.3]
I don't know	1 (4.5)	9 (4.8)	0	10 (4.4)

[a] Correct response.
[b] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
Note: High experience will be defined as prescriber with >15 years experience and 51-75% or 76-100% RA patients. Low experience will be defined as prescribers with <5 years experience and 0-25% or 26 to 50% RA patients. All other prescribers will be counted as Medium experience including those with experience missing.

Table 4: Understanding the Key Risk Messages - Completed Surveys

	Rheumatologisits (N=226) n (%) [95% CI][e]
KRM#1 Pregnancy and breastfeeding (Q9, Q10)[a]	
Yes	164 (72.6) [66.3-78.3]
No	62 (27.4)
KRM#2 Lipid parameters (Q11)[b]	
Yes	206 (91.2) [86.7-94.5]
No	20 (8.8)
KRM#3 Management of infections (Q12, Q13, Q14)[c]	
Yes	179 (79.2) [73.3-84.3]
No	47 (20.8)
KRM#4 Reactivation of viral infections (Q15)[d]	
Yes	163 (72.1) [65.8-77.9]
No	63 (27.9)
Understanding all KRMs	
Yes	99 (43.8) [37.2-50.5]
No	127 (56.2)

[a] To be counted as understanding of KRM#1, both items of Q9 and Q10 must be answered correctly.
[b] To be counted as understanding of KRM#2, Q11 must be answered correctly.
[c] To be counted as understanding of KRM#3, Q12, Q13, and Q14 must be answered correctly.
[d] To be counted as understanding of KRM#4, all 4 items of Q15 must be answered correctly.
[e] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.

Table 4.1: Understanding the Key Risk Messages by Country - Completed Surveys

	Country				
	Germay (N=58) n (%) [95% CI][e]	**Sweden (N=39) n (%) [95% CI][e]**	**United Kingdom (N=81) n (%) [95% CI][e]**	**France (N=48) n (%) [95% CI][e]**	**Overall (N=226) n (%) [95% CI][e]**
KRM#1 Pregnancy and breastfeeding (Q9, Q10)[a]					
Yes	47 (81.0) [68.6-90.1]	30 (76.9) [60.7-88.9]	53 (65.4) [54.0-75.7]	34 (70.8) [55.9-83.0]	164 (72.6) [66.3-78.3]
No	11 (19.0)	9 (23.1)	28 (34.6)	14 (29.2)	62 (27.4)
KRM#2 Lipid parameters (Q11)[b]					
Yes	50 (86.2) [74.6-93.9]	34 (87.2) [72.6-95.7]	76 (93.8) [86.2-98.0]	46 (95.8) [85.7-99.5]	206 (91.2) [86.7-94.5]
No	8 (13.8)	5 (12.8)	5 (6.2)	2 (4.2)	20 (8.8)
KRM#3 Management of infections (Q12, Q13, Q14)[c]					
Yes	42 (72.4) [59.1-83.3]	32 (82.1) [66.5-92.5]	71 (87.7) [78.5-93.9]	34 (70.8) [55.9-83.0]	179 (79.2) [73.3-84.3]
No	16 (27.6)	7 (17.9)	10 (12.3)	14 (29.2)	47 (20.8)
KRM#4 Reactivation of viral infections (Q15)[d]					
Yes	45 (77.6) [64.7-87.5]	28 (71.8) [55.1-85.0]	56 (69.1) [57.9-78.9]	34 (70.8) [55.9-83.0]	163 (72.1) [65.8-77.9]
No	13 (22.4)	11 (28.2)	25 (30.9)	14 (29.2)	63 (27.9)
Understanding all KRMs					
Yes	27 (46.6) [33.3-60.1]	18 (46.2) [30.1-62.8]	38 (46.9) [35.7-58.3]	16 (33.3) [20.4-48.4]	99 (43.8) [37.2-50.5]
No	31 (53.4)	21 (53.8)	43 (53.1)	32 (66.7)	127 (56.2)

[a] To be counted as understanding of KRM#1, both items of Q9 and Q10 must be answered correctly.
[b] To be counted as understanding of KRM#2, Q11 must be answered correctly.
[c] To be counted as understanding of KRM#3, Q12, Q13, and Q14 must be answered correctly.
[d] To be counted as understanding of KRM#4, all 4 items of Q15 must be answered correctly.
[e] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.

Table 4.2: Understanding the Key Risk Messages by Prescribing Status - Completed Surveys

	Prescribing Status		
	Active Presciber (N=211) n (%) [95% CI][e]	**Potential Subscriber (N=15) n (%) [95% CI][e]**	**Overall (N=226) n (%) [95% CI][e]**
KRM#1 Pregnancy and breastfeeding (Q9, Q10)[a]			
Yes	157 (74.4) [68.0-80.2]	7 (46.7) [21.3-73.4]	164 (72.6) [66.3-78.3]
No	54 (25.6)	8 (53.3)	62 (27.4)
KRM#2 Lipid parameters (Q11)[b]			
Yes	194 (91.9) [87.4-95.2]	12 (80.0) [51.9-95.7]	206 (91.2) [86.7-94.5]
No	17 (8.1)	3 (20.0)	20 (8.8)
KRM#3 Management of infections (Q12, Q13, Q14)[c]			
Yes	168 (79.6) [73.5-84.8]	11 (73.3) [44.9-92.2]	179 (79.2) [73.3-84.3]
No	43 (20.4)	4 (26.7)	47 (20.8)
KRM#4 Reactivation of viral infections (Q15)[d]			
Yes	151 (71.6) [65.0-77.5]	12 (80.0) [51.9-95.7]	163 (72.1) [65.8-77.9]
No	60 (28.4)	3 (20.0)	63 (27.9)
Understanding all KRMs			
Yes	95 (45.0) [38.2-52.0]	4 (26.7) [7.8-55.1]	99 (43.8) [37.2-50.5]
No	116 (55.0)	11 (73.3)	127 (56.2)

[a] To be counted as understanding of KRM#1, both items of Q9 and Q10 must be answered correctly.
[b] To be counted as understanding of KRM#2, Q11 must be answered correctly.
[c] To be counted as understanding of KRM#3, Q12, Q13, and Q14 must be answered correctly.
[d] To be counted as understanding of KRM#4, all 4 items of Q15 must be answered correctly.
[e] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.

Table 4.3: Understanding the Key Risk Messages by Prescribing Frequency - Completed Surveys

	Prescribing Frequency			
	Potential Prescibers (N=15) n (%) [95% CI][e]	**Low Prescibers (N=107) n (%) [95% CI][e]**	**Heigh Prescribers (N=104) n (%) [95% CI][e]**	**Overall (N=226) n (%) [95% CI][e]**
KRM#1 Pregnancy and breastfeeding (Q9, Q10)[a]				
Yes	7 (46.7) [21.3-73.4]	75 (70.1) [60.5-78.6]	82 (78.8) [69.7-86.2]	164 (72.6) [66.3-78.3]
No	8 (53.3)	32 (29.9)	22 (21.2)	62 (27.4)
KRM#2 Lipid parameters (Q11)[b]				
Yes	12 (80.0) [51.9-95.7]	99 (92.5) [85.8-96.7]	95 (91.3) [84.2-96.0]	206 (91.2) [86.7-94.5]
No	3 (20.0)	8 (7.5)	9 (8.7)	20 (8.8)
KRM#3 Management of infections (Q12, Q13, Q14)[c]				
Yes	11 (73.3) [44.9-92.2]	85 (79.4) [70.5-86.6]	83 (79.8) [70.8-87.0]	179 (79.2) [73.3-84.3]
No	4 (26.7)	22 (20.6)	21 (20.2)	47 (20.8)
KRM#4 Reactivation of viral infections (Q15)[d]				
Yes	12 (80.0) [51.9-95.7]	77 (72.0) [62.5-80.2]	74 (71.2) [61.4-79.6]	163 (72.1) [65.8-77.9]
No	3 (20.0)	30 (28.0)	30 (28.8)	63 (27.9)
Understanding all KRMs				
Yes	4 (26.7) [7.8-55.1]	43 (40.2) [30.8-50.1]	52 (50.0) [40.0-60.0]	99 (43.8) [37.2-50.5]
No	11 (73.3)	64 (59.8)	52 (50.0)	127 (56.2)

[a] To be counted as understanding of KRM#1, both items of Q9 and Q10 must be answered correctly.
[b] To be counted as understanding of KRM#2, Q11 must be answered correctly.
[c] To be counted as understanding of KRM#3, Q12, Q13, and Q14 must be answered correctly.
[d] To be counted as understanding of KRM#4, all 4 items of Q15 must be answered correctly.
[e] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
Note: Low prescribers: <= 5 patients in the last 6 months; High prescribers: => 6 patienhts in the last 6 months.

Table 4.4: Understanding the Key Risk Messages by Experience in Treating RA Patients - Completed Surveys

	Experience in Treating RA Patients			
	High Experience (N=22) n (%) [95% CI][e]	**Medium Experience (N=186) n (%) [95% CI][e]**	**Low Experience (N=18) n (%) [95% CI][e]**	**Overall (N=226) n (%) [95% CI][e]**
KRM#1 Pregnancy and breastfeeding (Q9, Q10)[a]				
Yes	16 (72.7) [49.8-89.3]	135 (72.6) [65.6-78.9]	13 (72.2) [46.5-90.3]	164 (72.6) [66.3-78.3]
No	6 (27.3)	51 (27.4)	5 (27.8)	62 (27.4)
KRM#2 Lipid parameters (Q11)[b]				
Yes	19 (86.4) [65.1-97.1]	169 (90.9) [85.8-94.6]	18 (100.0) [81.5-100.0]	206 (91.2) [86.7-94.5]
No	3 (13.6)	17 (9.1)	0 (0.0)	20 (8.8)
KRM#3 Management of infections (Q12, Q13, Q14)[c]				
Yes	15 (68.2) [45.1-86.1]	152 (81.7) [75.4-87.0]	12 (66.7) [41.0-86.7]	179 (79.2) [73.3-84.3]
No	7 (31.8)	34 (18.3)	6 (33.3)	47 (20.8)
KRM#4 Reactivation of viral infections (Q15)[d]				
Yes	17 (77.3) [54.6-92.2]	135 (72.6) [65.6-78.9]	11 (61.1) [35.7-82.7]	163 (72.1) [65.8-77.9]
No	5 (22.7)	51 (27.4)	7 (38.9)	63 (27.9)
Understanding all KRMs				
Yes	8 (36.4) [17.2-59.3]	85 (45.7) [38.4-53.1]	6 (33.3) [13.3-59.0]	99 (43.8) [37.2-50.5]
No	14 (63.6)	101 (54.3)	12 (66.7)	127 (56.2)

[a] To be counted as understanding of KRM#1, both items of Q9 and Q10 must be answered correctly.
[b] To be counted as understanding of KRM#2, Q11 must be answered correctly.
[c] To be counted as understanding of KRM#3, Q12, Q13, and Q14 must be answered correctly.
[d] To be counted as understanding of KRM#4, all 4 items of Q15 must be answered correctly.
[e] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
Note: High experience will be defined as prescriber with >15 years experience and 51-75% or 76-100% RA patients. Low experience will be defined as prescribers with <5 years experience and 0-25% or 26 to 50% RA patients. All other prescribers will be counted as Medium experience, including those with experience missing.

Table 5: Responses to Questions about Healthcare Professional Educational Material for Olumiant (baricitinib) - Completed Surveys

Question	Overall (N=226) n (%)
Question 16: Prior to today, were you aware of the Healthcare Professional Educational Material for Olumiant (baricitinib)?	
Yes	149 (65.9)
No	77 (34.1)
Question 17: Did you receive a copy of the Healthcare Professional Educational Material for Olumiant (baricitinib)?[a]	
Yes	109 (73.2)
No	13 (8.7)
I don't remember	27 (18.1)
N/A (Answered 'No' to Question 16)	77
Question 18: Have you read the Healthcare Professional Educational Material for Olumiant (baricitinib)?[a]	
Yes	88 (80.7)
No	10 (9.2)
I don't remember	11 (10.1)
N/A (Answered 'No' to Question 16 or 'No' or 'I don't remember' to Question 17)	117

[a] Percentages are calculated based on the sample presented with this question because of the skip logic in the survey.

Table 6: Responses to Questions about Patient Alert Card for Olumiant (baricitinib) - Completed Surveys

Question	Overall (N=226) n (%)
Question 19: Prior to today, were you aware of the Patient Alert Card for Olumiant?	
Yes	152 (67.3)
No	74 (32.7)
Question 21: When prescribing Olumiant (baricitinib) for the first time is your patient provided with a Patient Alert Card?[a]	
Yes	97 (67.4)
No	19 (13.2)
I don't remember	28 (19.4)
N/A (Answered 'No' to Question 19 or 'No' to Question 6 (Have you prescribed Olumiant (baricitinib)?)	82

[a] Percentages are calculated based on the sample presented with this question because of the skip logic in the survey.

Table 6.1: Responses to Questions about Patient Alert Card for Olumiant (baricitinib) by Country - Completed Surveys

Question	Country				
	Germay (N=58) n (%)	Sweden (N=39) n (%)	United Kingdom (N=81) n (%)	France (N=48) n (%)	Overall (N=226) n (%)
Question 19: Prior to today, were you aware of the Patient Alert Card for Olumiant?					
Yes	43 (74.1)	28 (71.8)	50 (61.7)	31 (64.6)	152 (67.3)
No	15 (25.9)	11 (28.2)	31 (38.3)	17 (35.4)	74 (32.7)
Question 21: When prescribing Olumiant (baricitinib) for the first time is your patient provided with a Patient Alert Card?[a]					
Yes	32 (74.4)	20 (74.1)	28 (62.2)	17 (58.6)	97 (67.4)
No	5 (11.6)	2 (7.4)	1 (2.2)	11 (37.9)	19 (13.2)
I don't remember	6 (14.0)	5 (18.5)	16 (35.6)	1 (3.4)	28 (19.4)
N/A (Answered 'No' to Question 19 or 'No' to Question 6 (Have you prescribed Olumiant (baricitinib)?)	15	12	36	19	82

[a] Percentages are calculated based on the sample presented with this question because of the skip logic in the survey.

Table 6.2: Responses to Questions about Patient Alert Card for Olumiant (baricitinib) by Prescribing Status - Completed Surveys

Question	Prescribing Status		
	Active Presciber (N=211) n (%)	Potential Subscriber (N=15) n (%)	Overall (N=226) n (%)
Question 19: Prior to today, were you aware of the Patient Alert Card for Olumiant?			
Yes	144 (68.2)	8 (53.3)	152 (67.3)
No	67 (31.8)	7 (46.7)	74 (32.7)
Question 21: When prescribing Olumiant (baricitinib) for the first time is your patient provided with a Patient Alert Card?[a]			
Yes	97 (67.4)	0	97 (67.4)
No	19 (13.2)	0	19 (13.2)
I don't remember	28 (19.4)	0	28 (19.4)
N/A (Answered 'No' to Question 19 or 'No' to Question 6 (Have you prescribed Olumiant (baricitinib)?)	67	15	82

[a] Percentages are calculated based on the sample presented with this question because of the skip logic in the survey.

Table 6.3: Responses to Questions about Patient Alert Card for Olumiant (baricitinib) by Prescribing Frequency - Completed Surveys

Question	Prescribing Frequency			
	Potential Prescibers (N=15) n (%)	High Prescibers (N=107) n (%)	Low Prescribers (N=104) n (%)	Overall (N=226) n (%)
Question 19: Prior to today, were you aware of the Patient Alert Card for Olumiant?				
Yes	8 (53.3)	71 (66.4)	73 (70.2)	152 (67.3)
No	7 (46.7)	36 (33.6)	31 (29.8)	74 (32.7)
Question 21: When prescribing Olumiant (baricitinib) for the first time is your patient provided with a Patient Alert Card?[a]				
Yes	0	45 (63.4)	52 (71.2)	97 (67.4)
No	0	13 (18.3)	6 (8.2)	19 (13.2)
I don't remember	0	13 (18.3)	15 (20.5)	28 (19.4)
N/A (Answered 'No' to Question 19 or 'No' to Question 6 (Have you prescribed Olumiant (baricitinib)?)	15	36	31	82

[a] Percentages are calculated based on the sample presented with this question because of the skip logic in the survey.

Table 6.4: Responses to Questions about Patient Alert Card for Olumiant (baricitinib) by Prescriber Experience - Completed Surveys

Question	Prescriber Experience			
	High Experience (N=22) n (%)	Medium Experience (N=186) n (%)	Low Experience (N=18) n (%)	Overall (N=226) n (%)
Question 19: Prior to today, were you aware of the Patient Alert Card for Olumiant?				
Yes	16 (72.7)	122 (65.6)	14 (77.8)	152 (67.3)
No	6 (27.3)	64 (34.4)	4 (22.2)	74 (32.7)
Question 21: When prescribing Olumiant (baricitinib) for the first time is your patient provided with a Patient Alert Card? [a]				
Yes	10 (66.7)	81 (69.8)	6 (46.2)	97 (67.4)
No	0	15 (12.9)	4 (30.8)	19 (13.2)
I don't remember	5 (33.3)	20 (17.2)	3 (23.1)	28 (19.4)
N/A (Answered 'No' to Question 19 or 'No' to Question 6 (Have you prescribed Olumiant (baricitinib)?)	7	70	5	82

[a] Percentages are calculated based on the sample presented with this question because of the skip logic in the survey.

Table 7: Responses to Questions about the Communication of the Important Safety Information to patients prescribed baricitinib - Completed Surveys

Question	Overall (N=226) n (%)
Question 20: Do you or someone in your practice/hospital communicate the important safety information to your patients when prescribing Olumiant (baricitinib) for the first time? [a]	
Yes	200 (94.8)
No	7 (3.3)
I don't remember	4 (1.9)
N/A (Answered 'No' to Question 6 (Have you prescribed Olumiant (baricitinib)?)	15

[a] Percentages are calculated based on the sample presented with this question because of the skip logic in the survey.

Table 7.1: Responses to Questions about Communication of Important Safety Information by Country - Completed Surveys

Question	Country				
	Germay (N=58) n (%)	Sweden (N=39) n (%)	United Kingdom (N=81) n (%)	France (N=48) n (%)	Overall (N=226) n (%)
Question 20: Do you or someone in your practice/hospital communicate the important safety information to your patients when prescribing Olumiant (baricitinib) for the first time? [a]					
Yes	50 (86.2)	37 (100.0)	71 (100.0)	42 (93.3)	200 (94.8)
No	5 (8.6)	0	0	2 (4.4)	7 (3.3)
I don't remember	3 (5.2)	0	0	1 (2.2)	4 (1.9)
N/A (Answered 'No' to Question 6 (Have you prescribed Olumiant (baricitinib)?)	0	2	10	3	15

[a] Percentages are calculated based on the sample presented with this question because of the skip logic in the survey.

Table 7.2: Responses to Questions about Communication of Important Safety Information by Prescribing Status - Completed Surveys

Question	Prescribing Status		
	Active Presciber (N=211) n (%)	Potential Subscriber (N=15) n (%)	Overall (N=226) n (%)
Question 20: Do you or someone in your practice/hospital communicate the important safety information to your patients when prescribing Olumiant (baricitinib) for the first time? [a]			
Yes	200 (94.8)	0	200 (94.8)
No	7 (3.3)	0	7 (3.3)
I don't remember	4 (1.9)	0	4 (1.9)
N/A (Answered 'No' to Question 6 (Have you prescribed Olumiant (baricitinib)?)	0	15	15

[a] Percentages are calculated based on the sample presented with this question because of the skip logic in the survey.

Table 7.3: Responses to Questions about Communication of Important Safety Information by Prescribing Frequency - Completed Surveys

Question	Prescribing Frequency			
	Potential Prescibers (N=15) n (%)	High Prescibers (N=107) n (%)	Low Prescribers (N=104) n (%)	Overall (N=226) n (%)
Question 20: Do you or someone in your practice/hospital communicate the important safety information to your patients when prescribing Olumiant (baricitinib) for the first time? [a]				
Yes	0	102 (95.3)	98 (94.2)	200 (94.8)
No	0	2 (1.9)	5 (4.8)	7 (3.3)
I don't remember	0	3 (2.8)	1 (1.0)	4 (1.9)
N/A (Answered 'No' to Question 6 (Have you prescribed Olumiant (baricitinib)?)	15	0	0	15

[a] Percentages are calculated based on the sample presented with this question because of the skip logic in the survey.

Table 7.4: Responses to Questions about Communication of Important Safety Information by Prescriber Experience - Completed Surveys

Question	Prescriber Experience			
	High Experience (N=22) n (%)	Medium Experience (N=186) n (%)	Low Experience (N=18) n (%)	Overall (N=226) n (%)
Question 20: Do you or someone in your practice/hospital communicate the important safety information to your patients when prescribing Olumiant (baricitinib) for the first time? [a]				
Yes	21 (100.0)	164 (93.7)	15 (100.0)	200 (94.8)
No	0	7 (4.0)	0	7 (3.3)
I don't remember	0	4 (2.3)	0	4 (1.9)
N/A (Answered 'No' to Question 6 (Have you prescribed Olumiant (baricitinib)?)	1	11	3	15

[a] Percentages are calculated based on the sample presented with this question because of the skip logic in the survey.

Listing 1: Listing of Adverse Events and/or Product Complaints Reported by Modality

Adverse Event or Product Complaint?	Modality of Report	Verbatim Response
No data qualifies for this listing.		

Annex 2. Additional information

Not applicable.