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

REDACTED PROTOCOL

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
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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.

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Marketing Authorisation Holder

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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

Eli Lilly and Company Principal Investigator (Sponsor)

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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 1.1. (pages 30-43, inclusive) has been redacted.

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.