NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS Information

Title	Evaluation of the effectiveness of additional risk minimisation measures (aRMM) materials for Xeljanz® (tofacitinib) in Europe via a survey of healthcare professionals (HCPs): A non-interventional (NI) post-authorisation safety study (PASS)
Protocol number	A3921334
Protocol version identifier	3.0
Date	28 March 2022
EU Post Authorisation Study (PAS) register number	To be registered prior to the start of data collection
Active substance	Tofacitinib ATC (Anatomical Therapeutic Chemical) code: L04AA29
Medicinal product	Tofacitinib (Xeljanz®)
Product reference	EU/1/17/1178/001-014
Procedure number	EMEA/H/C/004214
Marketing Authorisation Holder (MAH)	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
Joint PASS	No
Research question and objectives	**Research Question:** Are the aRMM materials implemented across Europe effective in communicating the key risk messages associated with the use of Xeljanz to HCPs treating patients with rheumatoid arthritis (RA) and/or psoriatic arthritis (PsA) or ulcerative colitis (UC)?

	Objectives: To evaluate: • The aRMM program implementation (i.e., the HCPs' self-reported awareness [receipt]and utilisation of the aRMM materials and Xeljanz Prescriber Website); • The HCPs' knowledge of the key risk messages pertaining to special warnings and precautions associated with Xeljanz, as specified in the aRMM materials; and • The HCPs' self-reported adherence to the risk minimisation practices recommended in the aRMM materials.
Country(-ies) of study	France, Germany, the Netherlands, Poland, Romania, Spain, Sweden, and the United Kingdom
Author	***Pfizer:*** Juan (Joanne) Wu, ScD Associate Director Safety Surveillance Research, Pfizer, Inc. 235 East 42nd St Mail Stop 219/08/61 New York, NY 10017 United States ***Sub-contractor (IQVIA):*** Matthew Reynolds, PhD Vice President Real World Evidence, IQVIA 3110 Fairview Park Drive #400 Falls Church, VA 22042 Krystal Cantos, PhD, MS Associate Principal Epidemiology & Drug Safety, IQVIA 201 Broadway #2 Cambridge, MA 02139 United States Laura Walsh, MS Consultant

	Epidemiology & Drug Safety, IQVIA 201 Broadway #2 Cambridge, MA 02139 United States

Marketing Authorisation Holder(s)

Marketing Authorisation Holder(s)	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
MAH contact person	Maureen Agius Pfizer Ltd. Walton Oaks Dorking Road Tadworth Surrey KT20 7NS United Kingdom

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APPENDICES

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE(s)	Adverse event(s)
AEM	Adverse event monitoring
ALC	Absolute Lymphocyte Count
aRMM(s)	Additional risk minimisation measure(s)
ATC	Anatomical Therapeutic Chemical
BID	Bis in die (Latin: twice a day)
CI(s)	Confidence interval(s)
CHMP	Committee on Human Medicinal Products
CRF	Case report forms
DCT(s)	Data collection tool(s)
DILI	Drug-induced liver injury
DMARD(s)	Disease-modifying antirheumatic drug(s)
DVT	Deep Vein Thrombosis
EC	European Commission
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GEP	Good Epidemiological Practice
GERD/GORD	Gastroesophageal reflux disease
GI	Gastrointestinal
GVP	Good Pharmacovigilance Practices
HCP(s)	Healthcare professional(s)
Hgb	Haemoglobin
IEA	International Epidemiological Association
IEC	Independent ethics committee
ILD	Interstitial lung disease
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IQR(s)	Interquartile range(s)
MAH	Marketing Authorisation Holder
MERPHIN	Medical Radar Pharmaceutical Interviews
MR	Modified Release
MTX	Methotrexate
NI	Non-interventional
NIS	Non-interventional study
NMSC	Non-melanoma skin cancer
P	Proportion
PAS	Post-authorisation study
PASS	Post-authorisation safety study
PE	Pulmonary Embolism
PRAC	Pharmacovigilance Risk Assessment Committee

Abbreviation	Definition
PsA	Psoriatic arthritis
Q	Question
QC	Quality control
QD	Quaque die (Latin: once a day)
RA	Rheumatoid arthritis
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SC	Subcutaneous
SD(s)	Standard deviation(s)
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedures
TB	Tuberculosis
TNF	Tumour-necrosis factor
UC	Ulcerative colitis
UK	United Kingdom
US	United States
VTE	Venous thromboembolism
WHO	World Health Organization
YRR	Your Reporting Responsibility

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Sponsor

Name, degree(s)	Job Title	Affiliation	Address
Juan (Joanne) Wu	Associate Director, Epidemiologist, Safety Surveillance Research	Pfizer Inc.	235 East 42nd St Mail Stop 219/08/61 New York, NY 10017 United States Juan.wu3@pfizer.com

Subcontractor acting as contracted principal investigator:

Name, Degree(s)	Job Title	Affiliation	Address
Matthew Reynolds, PhD	Vice President	Real World Evidence	3110 Fairview Park Drive #400 Falls Church, VA 22042 United States matthew.reynolds@quintiles.com
Krystal Cantos, PhD, MS	Associate Principal	Epidemiology & Drug Safety, IQVIA	201 Broadway #2 Cambridge, MA 02139 United States Krystal.cantos@iqvia.com
Laura Walsh, MS	Consultant	Epidemiology & Drug Safety, IQVIA	201 Broadway #2 Cambridge, MA 02139 United States Laura.Walsh@iqvia.com
Anna Niedziolka	Project Manager, Fieldwork	Primary Intelligence, IQVIA	Ul. Domaniewska 48 02-672 Warsaw Poland Anna.Niedziolka@iqvia.com

3. ABSTRACT

Title: Evaluation of the effectiveness of additional risk minimisation measures (aRMMs) materials for Xeljanz® (tofacitinib) in Europe via a survey of healthcare professionals (HCPs): A non-interventional (NI) post-authorisation safety study (PASS).

Version: 3.0, 28 March 2022

Main Author: Krystal Cantos, PhD, MS, IQVIA, Epidemiology & Drug Safety

Rationale and Background: Xeljanz® (tofacitinib citrate) is an oral Janus kinase inhibitor approved by the European Commission for the treatment of adults with rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ulcerative colitis (UC). To minimise important potential and identified risks associated with the use of Xeljanz, the Marketing Authorisation Holder (MAH) implemented additional risk minimisation measures (aRMMs): an educational program intended to enhance the communication of the risks and risk minimisation practices to patients and healthcare professionals (HCPs). This protocol describes an HCP survey study to assess HCPs' awareness (receipt) and utilisation of the aRMM materials and Xeljanz Prescriber Website; knowledge of the key risk messages pertaining to the use of Xeljanz (including knowledge of the risk minimisation practices to prevent/minimise risks associated with Xeljanz); and self-reported adherence to the risk minimisation practices recommended in the aRMM materials.

Research Question and Objectives: The research question is, "Are the aRMM materials implemented across Europe effective in communicating the key risk messages associated with the use of Xeljanz to HCPs treating patients with RA and/or PsA or UC?". Specifically, the objectives of this study are to evaluate:

- The aRMM program implementation (i.e., the HCPs' self-reported awareness [receipt] and utilisation of the aRMM materials and Xeljanz Prescriber Website);
- The HCPs' knowledge of the key risk messages pertaining to special warnings and precautions associated with Xeljanz, as specified in the aRMM materials; and
- The HCPs' self-reported adherence to the risk minimisation practices recommended in the aRMM materials.

Study Design: This is a cross-sectional, non-interventional, multimodal survey study that will be conducted among HCPs who have prescribed Xeljanz for RA and/or PsA or UC in the 12 months preceding survey administration in 8 European countries (France, Germany, the Netherlands, Poland, Romania, Spain, Sweden, and the United Kingdom [UK]).

There will be 2 versions of the survey: one for rheumatologists and dermatologists (hereafter referred to as the "RA/PsA survey") and one for gastroenterologists (hereafter referred to as the "UC survey"). This is because there are survey questions that are specific to prescribing Xeljanz to patients with ulcerative colitis (e.g., related to initiation and maintenance dosing).

The anticipated start of data collection is 01 November 2021.

Population: The target study population will be specialist HCPs in Europe who are prescribers of Xeljanz for the treatment of PsA, RA, or UC (e.g., dermatologists, rheumatologists, and gastroenterologists), as these will be the HCPs who were targeted for the aRMM materials distribution by the MAH. All HCPs from the proprietary IQVIA OneKey database who meet the eligibility criteria will be invited to participate in the survey (i.e., the **Targeted HCPs**).

Variables:

- **HCP practice characteristics**: specialty, number of years in practice, experience prescribing Xeljanz within the past 12 months for RA and/or PsA or UC; self-reported most recent prescription for Xeljanz, self-reported approximate number of prescriptions of Xeljanz written in the past 12 months, self-reported approximate number of patients prescribed Xeljanz in the past 12 months, role in providing Xeljanz treatment, prior experience as a healthcare professional in a Xeljanz clinical trial.

- **aRMM program implementation**: HCPs' self-reported awareness (receipt) and utilisation of the aRMM materials and Xeljanz Prescriber Website.

- **Knowledge of the key risk messages pertaining to the use of Xeljanz** (including the risk minimisation practices to prevent/minimise risks associated with Xeljanz).

- **Self-reported adherence to the risk minimisation practices** recommended in aRMM materials (e.g., provision of patient counselling and the alert card to patients, patient screening, laboratory monitoring recommendations, and limitations of use).

- **Attitude toward the aRMM materials** (i.e., how useful do the HCPs find the various aRMM materials in their practices).

- **Source of HCPs' information on the safety of Xeljanz.**

- **Response rate, cooperation rate, refusal rate, and contact rate.**

Data Source: This study involves primary data collection. All data for analysis will be collected from HCPs directly via a multimodal survey instrument (i.e., a structured survey questionnaire implemented via Web portal or phone interview).

Study Size: Across the 8 survey countries, the MAH will aim for a sample size of 300 HCPs (i.e., completed surveys) for the RA/PsA survey and 300 HCPs for the UC survey, which would achieve an overall precision[1] for each survey of 5.7%. However, no sample size limit will be applied, and all completed surveys received during the 12-week data collection window will be included in the study analyses.

[1] Overall precision is measured as one half of the width of the 95% confidence interval for any given survey question, assuming a response proportion of 50% (maximal uncertainty).

Data Analysis: The data collected from the RA/PsA survey will be analysed separately from the data collected from the UC survey. For each survey (RA/PsA and UC), all primary analyses will be conducted using the *pooled* data from all countries, specialties (applies to the RA/PsA survey only), and indications (applies to the RA/PsA survey only), and will be descriptive in nature; no statistical comparisons within or between countries, specialties, and/or indications will be conducted. Only submitted and completed surveys by HCPs eligible to participate in the survey will be used in the analyses. The survey results will be weighted *overall* to reflect the true proportion of HCPs who prescribe Xeljanz in the countries and *within* each country, to reflect the true proportion of each HCP specialty authorised to prescribe Xeljanz in that country (applies to the RA/PsA survey only). Both unweighted and weighted results will be presented in the final study report.

Milestones: The data collection is anticipated to begin by 01 November 2021 and end by 18 April 2022. A final study report will be submitted to the Pharmacovigilance Risk Assessment Committee (PRAC) within 12 months after the end of data collection in the last survey country. The planned timeline is contingent upon the endorsement of the protocol amendment by the European Medicines Agency and local country Health Authorities and country Ethics Committees (as needed).

4. AMENDMENTS AND UPDATE

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1 (Version 2.0)	20 Jan 2021	4. Abstract	Changes were made to the Abstract to reflect the changes made in the body of the protocol.	Changes made to reflect the changes made in the body of the protocol.
		6. Milestones	The dates for the anticipated start of data collection, end of data collection and final study report submission were changed to the following dates: Statistical Analysis Plan (SAP) Finalization: 30 July 2021 Start of Data Collection: 31 May 2021. End of Data Collection: 31 August 2021 Final Study Report Submission: 31 August 2022 Wave II survey and interim report milestones were eliminated from the current protocol.	The date for start of data collection was changed due to the Agency's request to review the changes to the survey instrument post user testing; the marketing authorization holder (MAH) is submitting the final English version questionnaire. The translated version of the survey instrument will be user tested in the study countries in parallel with the Pharmacovigilance Risk Assessment Committee's (PRAC's) review of the latest English version; the steps will take place in parallel to keep the start of data collection delay to a minimum.
		7. Rationale and Background	Added a list of safety concerns which the aRMM program aims to mitigate and edited the objectives of the aRMM materials to reflect the objectives described in the Risk Management Plan.	The list of safety concerns was added for completion and the objectives edited to reflect how they are worded in the Risk Management Plan.
		9.1 Study Design	Changed **from**: "The anticipated start of data collection for France, Germany, the Netherlands, Poland, Sweden, and the UK will be January 2021	Data collection is postponed due to the Agency's request to review the changes to the survey instrument post optimization and user testing. The start of data collection was changed to a single date for all countries to

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			and the anticipated start of data collection for Romania and Spain will be April 2021." **To:** "The start of data collection for all study countries is 31 May 2021."	reflect data collection start dates listed in section 6, Milestones.
		9.2 Setting	Table 1 in section 9.2. was updated to reflect the actual dates of the additional risk minimization measures (aRMM) materials being available to all potential healthcare professionals (HCPs) as well as the window for data collection.	The changes to the fourth column were made to reflect the actual dates of the materials being available to all potential HCPs and the dates in the fifth column were changed to reflect the delay in the study start date caused by the request to resubmit the survey instrument that was modified according to the optimization and user testing feedback.
		9.3 Variables	Removed "Type of practice setting (i.e., office based, hospital based, or both);" from HCP practice characteristics.	The survey question that collected information about the setting in which HCP prescribed tofacitinib was deleted from the survey instrument in order to simplify the survey. The way that medicine is practiced during the current pandemic may have changed and the result of this question may be difficult to interpret.
		9.3 Variables	The variable: "Self-reported most recent prescription for Xeljanz for RA and/or PsA or UC;" was moved up ahead of the variable: "Self-reported approximate number of Xeljanz prescriptions written for RA and/or PsA or UC in the past 12 months";	This variable was moved up the list to reflect the change in order of the survey questions (Questions 1 and 2) in the survey instruments as indicated in Appendix 1 and Appendix 2.
		9.3 Variables	Changed **from**: "Prior experience as an investigator in a Xeljanz clinical trial." **To:** "Prior participation in a Pfizer-sponsored	Language changed to include tofacitinib rather than Xeljanz and to clarify what is meant by "investigator" in a clinical trial.

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			tofacitinib clinical trial as a healthcare professional."	
		9.3 Variables	The Note under "HCP Practice Characteristics" (p. 39) was edited **from:** "There are **3 questions** that ascertain information on the HCP's specialty and years of practice and **5 questions** that ascertain information on the HCP's experience prescribing Xeljanz." **To**: "There are **2 questions** that ascertain information on the HCP's specialty and years of practice and **7 questions in the RA/PsA survey and 6 questions in the UC survey** that ascertain information on the HCP's experience prescribing Xeljanz."	The Note was changed to reflect the changes made to the survey instruments as indicated in Appendix 1 and Appendix 2.
		9.3 Variables	Added "Awareness (receipt) of each of the aRMM materials *after February 2020;"* under aRMM program implementation.	The additional language was included to understand responses based on timing of receipt (ever and after February 2020).
		9.3 Variables	The Note under "aRMM program implementation" subsection (p. 39) was edited to reflect the updated numbers of questions. To the Note below aRMM program implementation: Changed the number of awareness and	The number of questions was recounted and updated, as appropriate. This additional language was included in the Note to clarify the difference between the number of questions in the surveys for Germany with regard to receipt and utilization of aRMM materials as compared to other countries in the study.

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			utilization questions from 10 to 14. Added "for all countries, except for Germany, which only has one aRMM HCP checklist rather than two".	
		9.3 Variables	Row added to table under subsection 5 (Effectiveness of the aRMM program in *each* of the following 4 domains) Row added column 1: Awareness (Receipt) *after February 2020* Row added column 2: ⩾80% of HCPs reporting that they received 4 out of the 4 (100%) aRMM materials in all countries, except for Germany ⩾80% of HCPs reporting that they received 3 out of the 3 (100%) aRMM materials in Germany Row added column 3: ⩾80% of HCPs reporting that they received 4 out of the 4 (100%) aRMM materials in all countries, except for Germany ⩾80% of HCPs reporting that they received 3 out of the 3	Changes made to reflect the additional questions included in the survey to understand the timing of the HCP receipt of the aRMM materials (ever and after February 2020).

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			(100%) aRMM materials in Germany	
		9.3 Variables	Added "except for Germany, which has 4 questions." Under subsection **6. Attitude toward the aRMM materials**	Language was added to reflect the different number of survey questions for Germany as compared to other countries in the study.
		9.3 Variables; subsection 8 Response Rate, eligibility rate and completion rate.	The formula for calculation of response rate, eligibility rate and completion rate was changed.	The formula for calculating the participation rates was changed because the "number of unreachable HCPs" were identified as a group that should not be included as part of the denominator in the response rate formula.
		9.3.1 Mapping of Select Variables to Survey Questions	In Table 2 revised counts of survey questions were made for all countries, except for Germany; differing counts for Germany were denoted aRMM materials and Xeljanz Prescriber Website awareness (receipt): 9 (7 for Germany) **TOTAL: 14 (12 for Germany)** In footnote b, the survey question was updated. Table 4 footnotes a and b were updated. The survey questions quoted were revised.	The number of questions for awareness and utilization were recounted and updated, as appropriate. Language was added to reflect the different number of survey questions for Germany with regard to receipt and utilization of aRMM materials as compared to other countries in the study. To be consistent with the revised survey instruments in Appendix 1 and Appendix 2. To be consistent with the revised survey instruments in Appendix 1 and Appendix 2.
		9.6.4 Data Collection Schedule	The approximate time the survey is expected to take was updated to 25 minutes.	The Changes were made to be consistent with the revised survey instruments in Appendix 1 and Appendix 2.

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			References to Q1-Q18 were deleted.	References to Q1-Q18 were deleted as it is not necessary to specify question # if all questions must be answered.
		9.7.1. General Statistical Consideration	References to "an investigator" were revised to: "a healthcare professional."	The Changes were made to be consistent with the revised survey instruments in Appendix 1 and Appendix 2.
		9.7.2 Primary Analysis: Study Objective 1-Awareness (Receipt) and Utilisation	Revised the per-question analysis **from:** Per question analysis: The number and proportion of HCPs self-reporting that they received and utilised each of the 4 aRMM materials will be reported. The number and proportion of HCPs self-reporting that they received information related to the Xeljanz Prescriber Website and that they utilised the website will also be reported. **To:** Per question analysis: The number and proportion of HCPs self-reporting that they received and utilised each of the 4 aRMM materials (3 in Germany) will be reported. If appropriate, the number and proportion of HCPs self-reporting that they received and utilised the aRMM materials will be reported by ever and after February 2020 or January 2020 in Poland (except for the website, which will be reported by "ever" only). The number and proportion	The change was made to account for potentially assessing ever receipt vs. receipt after February 2020.

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			of HCPs self-reporting that they received information related to the Xeljanz Prescriber Website and that they utilised the website will also be reported.	
		9.7.3. Primary Analysis: Study Objective 2 – Knowledge of Key Risk Messages	Added a category of "<13" and "<14" in the second row of the table.	The analysis category was added for completeness.
		9.7.4. Primary Analysis: Study Objective 3 – Adherence to the Risk Minimization Practices Recommended in the aRMM Materials.	Added a category of "<12" in the second row of the table.	The category "<12" was added for completion.
		9.7.5. Secondary Analysis: HCP Practice Characteristics	Revised the content **from:** HCPs' responses to the 8 questions (3 pre-survey and 5 survey) related to HCP practice characteristics will be presented descriptively using numbers and proportions. **To:** HCPs' responses to the questions (2 pre-survey and 7 in the RA/PsA survey and 6 in the UC survey) related to HCP practice characteristics will be presented descriptively using frequencies and proportions.	To be consistent with the revised survey instruments in Appendix 1 and Appendix 2.

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		9.7.6. Secondary Analysis: Attitude Towards the aRMM Materials	Revised the text **from:** The number and proportion of HCPs finding the aRMM materials "Extremely Useful," "Very Useful," "No opinion/Not sure," "Somewhat Useful," "Not Useful," or "Did not receive material/did not visit Prescriber Website" will be described for each aRMM material and the Xeljanz Prescriber Website. These categories may be collapsed, as needed, after reviewing the distribution of the data. **To:** For each aRMM material and the Xeljanz Prescriber Website, among the HCPs who self-reported receiving that aRMM material or who were aware of the Xeljanz Prescriber Website, the number and proportion of HCPs finding the aRMM materials or Xeljanz Prescriber Website "Very Useful," "Somewhat Useful," or "Not Useful" will be described These categories may be collapsed, as needed, after reviewing the distribution of the data.	To be consistent with the revised survey instruments in Appendix 1 and Appendix 2.
		9.8.1. Approaches for Validating the Questionnaires	The description of the translation method was changed **from:** back and forth method **to:** a **committee-based approach.**	To be consistent with the change in the approach to translation of the survey instruments in Appendix 1 and Appendix 2. To accurately reflect the organization that will translate the survey instruments.

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			The organization responsible for translation was changed **from:** IQVIA Primary Intelligence **to:** Research Support Services.	
		9.8.1.1. User Testing of the Survey Instrument	The organization responsible for testing the survey instrument was changed **from:** IQVIA **to:** Northwestern University or Research Support Services.	To accurately reflect the organization that will perform user testing.
		10.2 Participant Consent	The second paragraph was edited **from**: "The informed consent language incorporated within the survey and any HCP recruitment materials must be reviewed and approved by Pfizer …" **To:** "The country-specific informed consent language (including the study objectives and availability of honorarium) incorporated within the survey and any HCP recruitment materials must be reviewed and approved by Pfizer …).	The edits were made to this section to clarify that the objectives of the study as well as availability of honoraria will be communicated to the survey participant prior to them answering the survey questions.
		ANNEX 3. ADDITIONAL INFORMATION **Appendix 1. HCP Questionnaire for**	Throughout the survey instrument the **brand name "Xeljanz" was deleted** and replaced with the international nonproprietary name (**tofacitinib**) only.	The brand name Xeljanz was introduced once with the international nonproprietary name (tofacitinib) added in parenthesis. For simplicity and consistency, tofacitinib was then used throughout the survey without the brand name.

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		Rheumatoid Arthritis and/or Psoriatic Arthritis		
			Question S1 was simplified **from:** "Are you currently employed by the Xeljanz (tofacitinib citrate) marketing authorization holder (i.e. Pfizer)?" **To:** "Are you currently employed by Pfizer"?	The question was simplified to increase readability and clarity while keeping the intent of the question unchanged.
			Question S1: Screen Out message under response option "Yes" was simplified **from:** "Thank you for your interest in participating in this survey. Unfortunately, you cannot proceed with the survey." **To:** "Thank you for your interest. Unfortunately, you are not eligible to participate."	The "Screen Out" message under response option "Yes" was clarified. Stating that a respondent 'cannot proceed with the survey' was considered vague, more explicit text was therefore included.
			Introductory language was added at the beginning of the survey and throughout. "Thank you for your interest in this study. This survey should take about 25 minutes to complete and consists of 5 sections. It should be completed in one sitting. The first section includes questions about	The introductory language was added to orient respondents to how long the survey will take and to the types of questions that will be asked in the first section.

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			your professional background and practice".	
			Question D2 ("In which type of setting do you work the majority of your time?") was removed.	The question was removed as it was believed to not add value to the survey. Furthermore, it could have been confusing to respondents, as the way medicine is practiced has changed since the COVID-19 pandemic.
			Question D2 (former D3) was modified **from:** "For how many years have you been in practice? Select one." **To:** "After completing all specialist training, for how many years have you been in practice? Please select one."	A clarifying phrase "after completing all specialist training" was added to the question to promote clarity and obtain consistent responses from participants. HCPs provided input on ideal phrasing (e.g., specialist training vs. residency) during user testing. The word "please" was added to "select one" throughout the survey to improve the user experience and support completion.
			The formatting of the response options to question D2 (former D3) was changed. The response options now use words to specify the time periods rather than mathematical formulas. This was done throughout the survey when applicable.	The formatting of the response options were changed to increase readability. Asking respondents to interpret and apply mathematical formulas increases the difficulty of the task and could introduce error and/or slow down response times.
			Introductory language was added before question S2: "Thank you. The second section of questions asks about your experiences with Xeljanz (tofacitinib)."	The introductory language was added to orient respondents to the types of questions that will be asked in the next section of the survey. It also orients the respondent to their location within the survey (e.g., section two of five).
			The wording of **Question S2** was modified **from:** "Have you prescribed Xeljanz (tofacitinib) for	The changes (to question S2 and S3) were made to increase readability and clarity. Placing the timeframe (within past 12 months) first in the sentence helps to orient respondents to the time frame in question.

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			rheumatoid arthritis and/or psoriatic arthritis within the past 12 months? Select all responses that apply". **To:** "Within the past 12 months, have you prescribed tofacitinib for rheumatoid arthritis and/or psoriatic arthritis? **Please consider both new and repeat prescriptions.**" Additionally, the response options were simplified for this question to Yes/No only. **Another question (S3) was added** to ask about indication. Finally, the Screen out message was altered to be consistent with language from S1, **from:** "Thank you for your interest in participating in this survey. Unfortunately, you cannot proceed with the survey." **To:** "Thank you for your interest. Unfortunately, you are not eligible to participate."	Adding the clarification of both new and repeat prescriptions reduces differences in how the question is interpreted by different respondents; this is important for accurate measurement. As this question now requires a yes or no response, the direction to "select all responses that apply" is no longer applicable and was removed. Screen out text was altered to be consistent with prior text from S1.
			The former **Question 2** was moved up to **become Question 1** and the wording was changed **from:** "Please estimate when you most recently prescribed tofacitinib.	The order of the questions was changed to improve survey flow and support completion. The wording of the question was changed to increase readability. The second sentence was added to help orient the respondents to the

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			To: "When was the last time you prescribed tofacitinib? Please consider both new and repeat prescriptions The format of the response options was modified to remove mathematical formulas and clarify number ranges (e.g., Response option a) was modified from "<6 months" to "within the past 6 months" etc.).	type of prescriptions they should consider when answering the question. Mathematical formulas were removed and the presentation of number ranges simplified to support ease of interpretation and completion.
			Question 1 was moved to **become Question 2** and the wording was changed **from:** **"**Please estimate the number of prescriptions (not patients) for tofacitinib that you have written within the last 12 months for rheumatoid arthritis and/or psoriatic arthritis. Select one." **To:** "Within the last 12 months, how many **prescriptions** for tofacitinib have you have written for rheumatoid arthritis and/or psoriatic arthritis? Please think of **the total number of prescriptions** – both new and repeat – and not the number of patients. Please select one." The format of the response options was modified to remove mathematical formulas and clarify number	The order of the questions was changed to improve survey flow and support completion. The wording of the question was changed to increase readability. The second sentence was added to help orient the respondents to the type of prescriptions they should consider when answering the question. Mathematical formulas were removed and the presentation of number ranges simplified to support ease of interpretation and completion.

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			ranges (e.g., Response option a) was modified from "<10" to "fewer than 10", etc.).	
			The wording of **Question 3** was modified **from:** "Please estimate the number of patients that you have treated with tofacitinib for rheumatoid arthritis and/or psoriatic arthritis in the last 12 months. Select one." **To:** "Within the last 12 months, how many **patients** have you treated with tofacitinib for rheumatoid arthritis and/or psoriatic arthritis? Please select one." The number ranges and format of the number ranges in the response options was modified. The ranges were changed based on HCP user testing feedback. Response options were spelled out (vs. presented numerically; e.g., Response option a) was modified from "<10" to "fewer than 5")	The question wording was changed to increase readability. The word "patients" was bolded to highlight the distinguishing characteristic of the item for respondents' consideration and to differentiate it from "prescriptions" in the previous question. The ranges included as response options were changed based on HCP user testing feedback on how many patients are likely to be seen by a practice. As in prior questions, mathematical functions were removed and written out to increase ease of interpretation and completion.
			The wording of **Question 4** was modified **from:** "Which of the following statements would best describe your involvement for the majority of your patients in their	The question wording as well as the wording of the response options was changed to increase readability and provide greater clarity. Words like "initiation" and "maintenance" were bolded for emphasis. Run-on sentences were made into multiple, shorter sentences to enhance readability.

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			tofacitinib treatment? Select one." **To:** "Which of the following statements best describes your involvement in tofacitinib treatment for most of your patients? Please select one." The wording of the response options was also modified slightly and made into shorter sentences where possible. Bolding was also used to distinguish differences in the response options. The changes made are as follows: **From:** a. I'm only involved in the initiation of tofacitinib treatment and refer patients to another healthcare professionals (HCPs) for follow up and monitoring b. I'm involved both in initiation and maintenance of tofacitinib treatment c. I'm only involved in the maintenance and monitoring of patients initiated with tofacitinib by other HCPs **To:** a. I'm involved only in the **initiation** of tofacitinib treatment.	

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			I refer patients to another practice for follow up and monitoring. b. I'm involved in **both the initiation and maintenance** of tofacitinib treatment. c. I'm involved only in the **maintenance and monitoring** of patients who were prescribed tofacitinib by another HCP in another practice.	
			The wording of **Question 5** was modified **from:** "Have you ever served as an investigator for a tofacitinib trial? Select one." **To:** "Have you ever participated in a Pfizer-sponsored tofacitinib clinical trial as a healthcare provider? Please select one response." A response option "I'm not sure" was added. **The list of trials was deleted.**	The question wording was changed to increase readability. The response option "I am not sure" was added to allow for a full range of responses. The list of trials was deleted in response to HCP user testing feedback. The HCPs found the list of trials overwhelming and believed it was distracting the overall flow of the survey.
			Introductory language was added before Question 6: "Next, the third section of questions are designed to assess your understanding of the contraindications and risks of tofacitinib."	Introductory language was added to orient respondents to the types of questions that will be asked in this section.

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			The original Question 8 was moved up to become **Question 7**.	Question 8 was reorganized and moved up to improve the survey flow and to support completion.
			The wording of **Question 7** (previously Question 8) was modified **from:** "According to your knowledge of the risks associated with the use of tofacitinib, please select the best response (True, False, I Don't Know) for each of the following statements."	The question wording was changed to increase readability.
			To: "Please select the best response (True, False, I don't know) for each of the following statements about risks and use of tofacitinib.	
			Additionally, examples of "potent immunosuppressants" were added to **response option a).** These included: azathioprine, cyclosporine, 6-mercaptopurine, and tacrolimus.	Examples of "potent immunosuppressants" were added to the **response option a)** per HCP user testing feedback.
			The **response option f)** was rephrased **from:** "One factor which may increase the risk of herpes zoster is when the lymphocyte count (ALC) is lower than 1.0 cells x 10^9/L."	The **response option f)** was rephrased to increase clarity.
			To: "When taking tofacitinib, the risk of herpes zoster is increased when the lymphocyte count	The response option g) was rephrased to increase readability.

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			(ALC) is lower than 1.0 cells x 10^9/L." The response option g) was rephrased **from**: "Tofacitinib should only be considered in patients ages 65 years or greater if there is no suitable alternative" **To**: "Tofacitinib should only be considered in patients who are 65 years of age or older if there is no suitable alternative" The word "NOT" was capitalized in response option h) (Appendix 1 only) and venous thromboembolism was spelled out along with the acronym VTE.	The word "NOT" was capitalized in response option h) for emphasis. The acronym VTE was defined prior to use.
			Introductory language was added before Question 8: "For the fourth section of questions, please think about your own clinical practice."	The introductory language was added to orient respondents to the types of questions that will be asked in this section.
			The format of **Question 8** was changed **from**: "Please select all that apply" **to**: "Yes/No". **The abbreviation for gastroesophageal reflux disease was changed from "GERD" to "GORD".**	The format of Question 8 was modified as it is believed the change would allow collection of more meaningful data; the new format will force a response for each response option whereas the original format could allow for some response options to be skipped. The abbreviation for gastroesophageal reflux disease was changed from "GERD" to "GORD" per HCP user feedback to make it appropriate for the United Kingdom (UK).

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			The wording of Question 9 was modified from: "In your clinical practice which of the following tests do you perform to make a decision as to whether to initiate a patient on tofacitinib? (Yes/No)" **To:** "In your clinical practice, do you perform the following tests to make a decision about whether to **initiate** a patient on tofacitinib (Yes/No)?" The words **"screening" in response options a) and c) were changed to "screen".** **Haemoglobin "levels" was changed to "level."**	The question wording was changed to increase readability. **The words "screening" in response options a) and c) were changed to "screen"** to make the tense consistent with the other response options under this question and to increase readability. This tense discrepancy was noted during HCP user testing. Similarly, haemoglobin "levels" was changed to "level" for consistency and accuracy.
			In **Question 10,** the phrase **"treatment maintenance"** was bolded. Additionally, the following phrase was added in bold to the question: "**Assume in all scenarios that the patient** is receiving tofacitinib 5 mg twice daily." Capitalization of letters in the response options were changed for consistency.	The phrase **"treatment maintenance"** was bolded to emphasize which phase of treatment the question refers to. The phrase about which dose of tofacitinib a patient is receiving was added for clarity. Some of the original response options included this phrase, others did not, which may have been confusing to the respondent. The intention of adding the phrase to the question itself is to alleviate any uncertainty about what dose a patient is being treated with and to simplify the wording of the response options. How response options were capitalized was changed to be consistent with how responses were capitalized elsewhere in the survey. The sign "less than" was there previously but accidently got deleted but needed to be there

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			Under response option a) the phrase "less than" was added in front of 0.50 cells x 10^9/L Additionally the word "confirmed" was deleted from response options a), b), and e) in Appendix 1. The following phrase was added at the end of response options a), b), and e): "This is confirmed by repeat testing." In Appendix 2, the same changes were made to response options: a), b), c) and g). Haemoglobin "count" was changed to "haemoglobin level".	in order for the response option to be "I would discontinue treatment". The word "confirmed" was deleted from response options a), b), and e) per feedback from the HCPs, who found it confusing. Instead a sentence was added at the end of the response options ("This is confirmed by repeat testing") to emphasize the requirement that the laboratory values be confirmed by repeat testing before any action was taken. The change from "count" to "level" was done to ensure consistency throughout they survey.
			The response options to Question 11 were modified. **Response option a) was changed from:** "Distribute the patient alert card to patients." **To: "**Give the tofacitinib patient alert card to the patient." **Response option b) was changed from:** "Advise patients to refer to the patient alert card for a list of symptoms and changes in their medical status for which they should inform you immediately." **To:** "Advise the patient to inform you immediately if they	The response option wording was changed to increase readability and clarity.

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			experience any of the symptoms on the tofacitinib patient alert card." **Response option c) was changed from:** "Advise patients to carry the patient alert card with them, particularly when they visit a doctor's office and/or the emergency room." **To:** "Advise patients to carry the tofacitinib patient alert card with them, particularly when they visit a doctor, a hospital, or Accident and Emergency." **Response option d) was changed from:** "Discuss with patients or with their caregivers the signs and symptoms of venous thromboembolism (VTE)." **To:** "Discuss the signs and symptoms of venous thromboembolism (VTE) with the patient."	Additionally, the wording of the response option c) was changed wording more appropriate for the UK.
			The following introductory language was added before Question 12: "The final set of questions asks about sources of information on tofacitinib."	The introductory language was added to orient respondents to the types of questions that will be asked in this section.
			Question 12 was modified as follows.	The word "sources" was removed as it was considered duplicative in the sentence. The

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			From: "Which of the following sources would you say is your primary source of safety and prescribing information regarding Xeljanz (tofacitinib)? Select one. **To: "**Which of the following is your **primary source** of safety and prescribing information for tofacitinib? Please select one."	phrase "primary source" was bolded for emphasis.
			Questions 13.1 – 17.3 were split up to ask about receipt, timing of receipt*, utilization and usefulness of each aRMM material separately. The new question numbers pertaining to the different aRMM materials are: Questions about the **Prescriber Brochure for tofacitinib** (All Countries): Questions 13.1.a – 13.3. Questions about the **Prescriber Treatment Initiation checklist for tofacitinib** (All Countries Except Germany): Questions 14.1.a – 14.3. Questions about the **Prescriber Treatment Maintenance Checklist for tofacitinib** (All Countries Except	The questions about the tofacitinib aRMM materials were split up to help the respondent with recall and to consider each material individually. Each material title (**Prescriber brochure for tofacitinib**, etc.) was bolded to further distinguish differences between materials. The new questions ask about the receipt (including the timing of receipt), then utilisation and usefulness for each material before asking the same question about another material. This is believed to improve flow and readability.

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			Germany): Questions 15.1.a – 15.3. Questions about **Prescriber Treatment Checklist for tofacitinib** (Germany only): Questions 14.1.i.a. - 14.4.i. Questions about **tofacitinib patient alert cards** (All Countries): Questions 16.1a – 16.2. Questions about the **prescriber website for tofacitinib** (All Countries): Questions 17.1 – 17.3. *In addition to asking about the HCP's **ever** receipt of the aRMM materials, questions were added about the receipt of each materials **after February 2020 (or after January 2020 for Poland)** (Questions: 13.1b, 14.1b., 15.1b, 14.1.i.b, 16.1b). **The response options pertaining to usefulness** (current questions: 13.3, 14.3, 15.3, 14.4.i, 16.2, 17.3) were simplified **from:** "Not useful", "Somewhat useful", "No opinion/not sure", "Very useful", "Extremely useful", Did not receive material/did not visit Xeljanz Prescriber Website"	To distinguish between the HCP's ever receiving the aRMM materials vs. the receipt of the most recently updated version post Article 20 procedure, questions were added about the receipt of each material after February 2020. **The response options to the usefulness questions were changed** to simplify and allow better discernment between options. During HCP user testing it became clear that the "no opinion" option was not interpreted consistently; this could have led to measurement error.

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			To: "Very useful", "Somewhat useful", "Not useful"	
			Changes made to the Rheumatoid Arthritis and Psoriatic Arthritis survey were also made to the Ulcerative Colitis (UC) survey. Those changes are not described again.	The two surveys are nearly identical.
2 (Version 3.0)	28 March 2022	3. Abstract 5. Milestones 8.1 Study Design	The dates for the registration in the EU PASS register, SAP finalization, start of data collection, end of data collection and final study report submission were changed to the following dates: Registration in the EU PASS register: 29 September 2021 Statistical Analysis Plan (SAP) finalization: 28 February 2022 Start of Data Collection: 01 November 2021 End of Data Collection: 18 April 2022 Final Study Report Submission: 18 April 2023	Updating to match RMP, justification for milestone changes communicated to EMA in a regulatory response as part of Procedure EMEA/H/C/004214/IB/0042/G
		Table 1	Update to window for data collection for each country.	Updating to match RMP, justification for milestone changes communicated to EMA in a regulatory response as part of Procedure EMEA/H/C/004214/IB/0042/G.

5. MILESTONES

Milestone	Planned Date	Actual Dates
Registration in the EU PASS register	Prior to the start of data collection in the first survey country (29 September 2021)	
Statistical Analysis Plan (SAP) finalization	28 February 2022	
Start of data collection	01 November 2021[a]	
End of data collection	12 weeks after the start of data collection in the last survey country 18 April 2022[b]	
Final Study Report submitted to the PRAC[c]	Within 12 months after the end of data collection 18 April 2023	

Abbreviations: aRMM = additional risk minimisation measures; EU = European Union; PASS = post-authorisation safety study; PRAC = Pharmacovigilance Risk Assessment Committee; PsA = psoriatic arthritis; SAP = statistical analysis plan; UC = ulcerative colitis; UK = United Kingdom.

a. The start of data collection will be contingent upon PRAC's endorsement of the protocol amendment/ modified questionnaire, completion of user testing of the translated questionnaire in study countries, and local submissions of the final study protocol. There is a potential for variability in start dates (e.g., related to submissions/approvals from local Health Authorities, Ethics Committees, and other privacy and/or disclosure organizations). b. The survey will occur over a 12-week (3-month) period in each country. However, given potential variability in start dates the start and end dates of data collection may need to be adjusted accordingly. c. The final study report will contain the pooled results from all 8 survey countries. The date of the final study report submission will be dependent on the start of data collection for the last survey country. Survey initiation may be delayed due to submissions to local Health Authorities, Ethics Committees, and/or other competent authorities.

6. RATIONALE AND BACKGROUND

Xeljanz® (tofacitinib citrate) is an oral Janus kinase inhibitor approved by the European Commission (EC) in March 2017, as an immediate-release film-coated tablet (5 mg), taken twice a day (BID), for the treatment of adults with moderate-to-severe active rheumatoid arthritis (RA) who have had inadequate response or intolerance to one or more disease-modifying antirheumatic drugs (DMARDs).[1] The EC subsequently approved a prolonged-release film-coated tablet (11 mg), taken once a day (QD), in December 2019. RA is a chronic systemic autoimmune disease that affects approximately 6.2 million people in Europe.[2] It is characterized by inflammation, joint destruction, and progressive disability. Joint destruction is irreversible, resulting in significant long-term morbidity. Despite a number of treatment options available, many patients do not sustain remission.[3] In clinical trials, patients treated with 5 mg of Xeljanz BID, in combination with methotrexate (MTX), showed significantly reduced disease activity scores and improved physical functioning and general health status as compared to patients on placebo.[4] The approved dose of Xeljanz for the treatment of moderate-to-severe active RA is 5 mg BID or prolonged-release 11 mg QD (which should not be exceeded) in combination with MTX; it may also be given as monotherapy in the case of intolerance to MTX or when treatment with MTX is inappropriate.[5]

In June 2018, Xeljanz 5-mg tablet (immediate-release) was approved by the EC, in combination with MTX, for the treatment of active psoriatic arthritis (PsA) in adults with inadequate response or intolerance to a prior DMARD therapy. PsA is an inflammatory arthritis occurring in between 6-42% of patients with psoriasis.[6] In clinical trials, patients treated with 5 mg of Xeljanz BID, in combination with a non-biologic DMARD, achieved significantly improved clinical response and physical functioning over the 6- and 12-month study periods.[4] The approved dose of Xeljanz for the treatment of PsA is 5 mg BID, which should not be exceeded.[5]

In July 2018, Xeljanz 5-mg tablet and 10-mg tablet (immediate-release) was approved by the EC for the treatment of moderately-to-severely active ulcerative colitis (UC) in patients with an inadequate response, a loss of response, or an intolerance to conventional therapy or a biologic agent. UC is a bowel disease characterized by inflammation and ulcers in the colon and rectum. In clinical trials, patients treated with 5 or 10 mg of Xeljanz BID were more likely to achieve and maintain a clinical response and remission of their condition as compared to patients in the placebo group.[4] The approved doses of Xeljanz for the treatment of moderately-to-severely active UC are 10 mg BID for induction and 5 mg BID for maintenance. Some patients (patients who have failed to respond to alternative treatment options for UC such as tumour necrosis factor inhibitor [TNF inhibitor] treatment) who have a reduction in response to 5 mg BID maintenance treatment may benefit from an increase in maintenance dose to 10 mg BID; for these patients, the presence of known risk factors for venous thromboembolism (VTE) should be considered. Xeljanz 10 mg BID for maintenance treatment should be used for the shortest duration possible.[5]

To provide an appropriate tool designed to enhance the awareness and knowledge of HCPs and patients about important safety concerns (including: serious and other important infections, herpes zoster reactivation, decrease in neutrophil counts and neutropenia, decrease

in lymphocyte counts and lymphopenia, decrease in haemoglobin (Hgb) levels and anaemia, lipid elevations and hyperlipidaemia, non-melanoma skin cancer (NMSC), transaminase elevation and potential for DILI (drug-induced liver injury), venous thromboembolism (DVT/PE), malignancy, gastrointestinal (GI) Perforation, interstitial lung disease (ILD), increased immunosuppression when used in combination with biologics and immunosuppressants including B-lymphocyte depleting agents, increased risk of AEs when tofacitinib is administered in combination with Methotrexate (MTX) in RA or PsA, primary viral infection following live vaccination, increased exposure to tofacitinib when co-administered with CYP3A4 and CYP2C19 inhibitors, higher incidence and severity of AEs in the elderly (≥65 years) including infections, effects on pregnancy and the foetus, use in breastfeeding, effect on vaccination efficacy and the use of live/attenuated vaccines, use in RA patients with mild, moderate, or severe hepatic impairment. , the Marketing Authorisation Holder (MAH) implemented additional risk minimisation measure (aRMM) materials-i.e., an educational program intended to enhance the communication of the risks and risk minimisation practices to patients and healthcare professionals (HCPs). The program includes:

- A Xeljanz Prescriber Brochure;
- A Xeljanz Prescriber Treatment *Initiation* Checklist:[2] intended to remind HCPs of the risks associated with the use of Xeljanz and the recommended tests to administer *prior to* Xeljanz administration (**distributed in all countries, except for Germany**);
- A Xeljanz Prescriber Treatment *Maintenance* Checklist: intended to remind HCPs of the risks associated with the use of Xeljanz and the recommended tests to administer *during* treatment with Xeljanz (**distributed in all countries, *except* for Germany**);
- A Xeljanz Prescriber Treatment Initiation and Maintenance Checklist: intended to remind HCPs of the risks associated with the use of Xeljanz and the recommended tests to administer prior to Xeljanz administration and during treatment with Xeljanz (**distributed in Germany only**); and
- A Xeljanz Patient Alert Card: to be distributed to patients by HCPs.

The Xeljanz aRMMs are also available from a Xeljanz Prescriber Website, maintained by the MAH, or from National Health Authority website repositories. Good Pharmacovigilance Practices (GVP) module XVI suggests that national competent authorities make risk management tools available via their websites. In countries that have not opted for a national

[2] For simplicity, the Xeljanz Prescriber Treatment *Initiation* Checklist, the Xeljanz Prescriber Treatment *Maintenance* Checklist, and the Xeljanz Prescriber Treatment *Initiation and Maintenance* Checklist are termed *Xeljanz prescriber treatment checklists* in this protocol. This term is used when referring to 1 or more of the checklists. In all study countries, except Germany, 4 different aRMM materials were distributed (A Xeljanz Prescriber Brochure, A Xeljanz Prescriber Treatment *Initiation* Checklist, A Xeljanz Prescriber Treatment *Maintenance* Checklist, and a Xeljanz Patient Alert Card); In Germany the two checklists have been combined into one and thus in Germany 3 aRMM materials in total (a Xeljanz Prescriber Brochure, a Xeljanz Prescriber Treatment Initiation and Maintenance Checklist and a Xeljanz Patient Alert Card) were distributed.

website repository, a local website was implemented by the MAH, where possible, in alignment with local requirements. For simplicity, the Xeljanz Prescriber Website and the National Health Authority repositories are termed *Xeljanz Prescriber Website* in this protocol.

The distribution of the aRMM materials in the individual member states of the European Union (EU) began in April 2017 for the RA indication. Following that approval, the materials were updated to include the PsA indication (distribution beginning in June 2018) and the UC indications and distributed (distribution beginning in August 2018).

In May 2019, the EC requested a reassessment of the benefit-risk of Xeljanz pursuant to Article 20 of Regulation (EC) No 726/2004 due to a signal for increased risks of pulmonary embolism and mortality arising in an ongoing MAH-sponsored Phase 3b/4 safety study (A3921133) designed to evaluate the risk of malignancy and major adverse cardiac events in RA patients aged 50 years and older who had at least one cardiovascular risk factor. In November 2019, the Committee on Human Medicinal Products (CHMP) concluded, based on a recommendation from the Pharmacovigilance Risk Assessment Committee (PRAC), that patients treated with Xeljanz are at increased risk of VTE events, both for deep venous thrombosis as well as pulmonary embolism, especially in patients with risk factors for VTE. The PRAC further concluded that the risk of VTE events is dose-dependent. To minimise this risk, the PRAC recommended that warnings be added to the Summary of Product Characteristics (SmPC) regarding the increased risk of VTE observed in patients taking Xeljanz, especially for patients with known risk factors for VTE. The PRAC also recommended that treatment with Xeljanz be discontinued in patients with suspected VTE and that Xeljanz 10 mg BID for maintenance treatment is not recommended in patients with UC who have known VTE risk factors, unless there is no suitable alternative treatment available. Clarifications on the posology were also added particularly for UC patients in maintenance. PRAC also concluded that, based on the interim analyses of Study A3921133, there is a potential increased risk of mortality. This was partly driven by an increased risk of serious infections among patients aged 65 years and above. As such, Xeljanz should be considered among patients over 65 years of age only if no suitable alternative treatment is available. These conclusions and revisions to the SmPC, were approved by the EC on 31 January 2020.[5]

The aRMM materials were updated to reflect the findings from the CHMP's re-assessment of the benefit-risk of Xeljanz (hereafter referred to as the "current aRMM materials"); the projected current aRMM materials distribution date for each survey country can be found in Table 1.

Based on the content of the Xeljanz Prescriber Brochure and prescriber treatment checklists, the following key risk messages will be assessed:

- Key risk message 1: Use in special populations;
- Key risk message 2: Combination with biologics and/or other potent immunosuppressants;

- Key risk message 3: Important information on monitoring of laboratory parameters;
- Key risk message 4: Serious infections (including tuberculosis) and other important infections;
- Key risk message 5: Viral reactivation (including herpes zoster) and vaccination;
- Key risk message 6: Malignancies, lymphoproliferative disorder, and non-melanoma skin cancer;
- Key risk message 7: Gastrointestinal perforations;
- Key risk message 8: VTE risk; and
- Key risk message 9: Patient counselling.

The MAH plans to evaluate the effectiveness of the aRMM program per the GVP module XVI. This protocol describes how the effectiveness of the aRMM materials will be quantitatively evaluated among HCPs who prescribe Xeljanz to patients with RA, PsA, or UC.[3] Data from this study will be used to determine whether:

1. The aRMM materials have been implemented as intended;
2. The aRMM materials are effective in informing HCPs about the key risk messages pertaining to Xeljanz use; and
3. The HCPs self-report adhering to the risk minimisation practices recommended in the aRMM materials.

This non-interventional study (NIS) is designated as a post-authorisation safety study (PASS) and is a risk management plan Category 3 commitment to the European Medicines Agency (EMA).

7. RESEARCH QUESTION AND OBJECTIVES

The research question is, "Are the aRMM materials implemented across Europe effective in communicating the key risk messages associated with the use of Xeljanz to HCPs treating patients with RA and/or PsA or UC?".

Specifically, the objectives of this study are to evaluate:

- The aRMM program implementation (i.e., the HCPs' self-reported awareness [receipt] and utilisation of the aRMM materials and Xeljanz Prescriber Website);

[3] The term "HCP(s)" will be used throughout the protocol to refer to HCPs who prescribe Xeljanz for RA and/or PsA or UC.

- The HCPs' knowledge of the key risk messages pertaining to special warnings and precautions associated with Xeljanz, as specified in the aRMM materials; and

- The HCPs' self-reported adherence to the risk minimisation practices recommended in the aRMM materials.

8. RESEARCH METHODS

8.1. Study Design

This is a cross-sectional, non-interventional, multimodal survey study that will be conducted among HCPs who have prescribed Xeljanz for RA and/or PsA or UC in the 12 months preceding survey administration in 8 European countries (France, Germany, the Netherlands, Poland, Romania, Spain, Sweden, and the United Kingdom [UK]).

There will be 2 versions of the survey: one for rheumatologists and dermatologists (hereafter referred to as the "RA/PsA survey") and one for gastroenterologists (hereafter referred to as the "UC survey"). This is because there are survey questions that are specific to prescribing Xeljanz to patients with ulcerative colitis (e.g., related to initiation and maintenance dosing).

The survey study will be conducted in each country no earlier than 6 months after the distribution of the current aRMM materials or Xeljanz reimbursement for all indications to allow for sufficient time for HCPs to familiarize themselves with the materials and Xeljanz uptake (as applicable), respectively. The anticipated start of data collection for all study countries is 01 November 2021. Note that for some countries, the start of data collection may be delayed due to when the survey can feasibly begin (e.g., at least 6 months after the distribution of the current aRMM materials, local Health Authority approval, Ethics Committee approval, and competent authority approval, as needed).

8.2. Setting

Eight countries were selected for the survey: France, Germany, the Netherlands, Poland, Romania, Spain, Sweden, and the UK. Country selection was based on a combination of factors that make them the most operationally feasible European countries in which to implement the survey and most likely to yield a meaningfully large and representative sample of HCPs treating patients for RA, PsA, or UC. Those factors included:

- Highest numbers of potential Xeljanz prescribers (e.g., rheumatologists, dermatologists, and gastroenterologists);

- Highest projected number of patients to be treated with Xeljanz (data not shown as they are based on projections that are subject to change);

- Timing of Xeljanz reimbursement and aRMM materials distribution; and

- Geographic location (the selected countries represent Western, Northern, Southern, and Eastern Europe).

Table 1 shows the timetable for projected Xeljanz availability with full reimbursement, projected current aRMM materials distribution, and estimated windows for survey data collection.

Table 1. Provisional Dates for Xeljanz Availability with Full Reimbursement, aRMM Materials Distribution, and Estimated Start and End of Survey Data Collection in Selected European Countries

Country	Indication	Date Product *fully* Available on Market (i.e., with reimbursement)	Date Current aRMM Materials Available to All Potential HCPs	Window for Data Collection (i.e., start and end dates for data collection)[a]
Germany	RA	May 2017	20 March 2020	23 November 2021 – 01 March 2022
	PsA	June 2018		
	UC	July 2018		
UK	RA	January 2018	6 March 2020	01 November 2021 – 07 February 2022
	PsA	October 2018		
	UC	August 2018		
Netherlands	RA	May 2017	11 May 2020	01 November 2021 – 07 February 2022
	PsA	August 2018		
	UC	September 2018		
Sweden	RA	April 2017	5 March 2020	01 November 2021 – 07 February 2022
	PsA	October 2018		
	UC	October 2018		
Spain	RA	October 2017	30 November 2020	01 November 2021 – 07 February 2022
	PsA	August 2019		
	UC	August 2019		
France	RA	December 2017	29 April 2020	08 November 2021 – 15 February 2022
	PsA	July 2019		
	UC	July 2019		
Poland	RA	September 2019	05 February 2020	01 November 2021 – 07 February 2022
	PsA	Expected March 2020		
	UC	Expected March 2020		
Romania	RA	December 2019	26 August 2020	17 January 2022 – 25 April 2022 (tentative)
	PsA	Expected September 2020		
	UC	Expected September 2020		

Abbreviations: aRMM = additional risk minimisation measures; HCP = healthcare professional; PsA = psoriatic arthritis; RA = rheumatoid arthritis; UC = ulcerative colitis; UK = United Kingdom.

a. Every effort will be made to start and end the survey on the dates listed in this column. However, the exact start dates of data collection will be contingent upon at least 6 months passing from the date of distribution of the current aRMM materials, time of protocol endorsement by PRAC, and time required for submissions/approvals from local Health Authorities, Ethics Committees, and other privacy and/or

Table 1. Provisional Dates for Xeljanz Availability with Full Reimbursement, aRMM Materials Distribution, and Estimated Start and End of Survey Data Collection in Selected European Countries

Country	Indication	Date Product *fully* Available on Market (i.e., with reimbursement)	Date Current aRMM Materials Available to All Potential HCPs	Window for Data Collection (i.e., start and end dates for data collection)[a]

disclosure organizations, as needed. However, irrespective of the start date, the study window in which data collection will occur will be 12 weeks (3 months).

8.2.1. Selection Criteria for Targeted HCPs

The target study population will be specialist HCPs in Europe who are prescribers of Xeljanz for the treatment of RA, PsA, or UC (e.g., rheumatologists, dermatologists, and gastroenterologists), as these will be the HCPs who were targeted for the aRMM materials distribution by the MAH. All HCPs from the proprietary IQVIA OneKey database who meet the eligibility criteria will be invited to participate in the survey (i.e., the **Targeted HCPs**). A description of the IQVIA OneKey database can be found in Section 8.4 (Data Sources).

8.2.1.1. Inclusion Criteria

The following are the study inclusion criteria for the **Targeted HCPs**:

1. HCPs in the OneKey database who have "rheumatology," "dermatology," or "gastroenterology" listed as their primary, secondary, or tertiary specialty;

2. HCPs who have contact information available in the OneKey database (at least 1 of: email, mailing address, or phone number); and

3. HCPs who are located in the selected countries.

8.2.1.2. Exclusion Criteria

The following is the study exclusion criterion for the **Targeted HCPs**. HCPs are excluded if they meet the following criterion:

1. HCPs who participated in pilot testing of the Xeljanz PASS HCP survey (current study; Protocol Number: A3921334).

8.2.2. Inclusion and Exclusion Criteria for the Final Study Population

The **Final Study Population** will be used for all study analyses and will consist of those **Targeted HCPs** who submitted a completed survey. Inclusion/exclusion criteria for the **Final Study Population** are described below.

8.2.2.1. Inclusion Criteria

The following are the study inclusion criteria for the **Final Study Population**:

1. HCPs who are **Targeted HCPs**;[4]
2. HCPs who agree to participate in the survey voluntarily by answering "Yes" to Consent Question, "Do you agree to proceed with this survey?";
3. HCPs who have written at least 1 prescription for Xeljanz for patients with RA and/or PsA or UC in the 12 months preceding the survey administration; and
4. HCPs who submitted a completed survey (i.e., answered *all* survey questions).

8.2.2.2. Exclusion Criterion

The following is the study exclusion criterion for the **Final Study Population**:

1. HCPs who are current employees of Xeljanz's MAH (i.e., Pfizer).

8.3. Variables

The variables to be analysed will include:

1. **HCP practice characteristics.**
    - Specialty (i.e., In the RA/PsA Survey: rheumatology, dermatology or other and in the UC survey: gastroenterology, or other);
    - Number of years in practice;
    - Experience prescribing Xeljanz within the past 12 months for RA and/or PsA or UC;
        - This variable will be used as a proxy for indication. An HCP who has experience prescribing Xeljanz for multiple indications (of RA and PsA) will be classified in the indication that corresponds to the HCP's highest specialty designation in the OneKey database;
    - Self-reported most recent prescription for Xeljanz for RA and/or PsA or UC;
    - Self-reported approximate number of Xeljanz prescriptions written for RA and/or PsA or UC in the past 12 months;

[4] HCPs who respond to the survey but are not rheumatologists, dermatologists, or gastroenterologists (e.g., nurse practitioners, physician's assistants, physicians of other specialties) will be allowed to participate if they are prescribers of Xeljanz for patients diagnosed with RA and/or PsA or UC and meet the study inclusion/exclusion criteria.

- Self-reported approximate number of patients prescribed Xeljanz for RA and/or PsA or UC in the past 12 months;

- Role in providing Xeljanz treatment (i.e., only initiation, both initiation and maintenance, only maintenance); and

- Prior participation in a Pfizer-sponsored tofacitinib clinical trial as a healthcare professional.

Note: There are 2 questions that ascertain information on the HCP's specialty and years of practice and 7 questions in the RA/PsA survey and 6 questions in the UC survey that ascertain information on the HCP's experience prescribing Xeljanz (see survey instrument in Appendix 1 and Appendix 2 [HCP Questionnaire for RA/PsA and UC, respectively]).

2. **aRMM program implementation.**

- Awareness (receipt) of each of the aRMM materials *ever* (i.e., whether the respondents recalled receiving each of the following aRMM materials: the Xeljanz Prescriber Brochure, the Xeljanz prescriber treatment checklists, and the Xeljanz Patient Alert Card);

- Awareness (receipt) of each of the aRMM materials *after February 2020 (or after January 2020 for Poland)*;

- Utilisation of each of the aRMM materials (i.e., whether the respondents read the Xeljanz Prescriber Brochure, utilised the Xeljanz prescriber treatment checklists when prescribing Xeljanz), and distributed the Xeljanz Patient Alert Card to their patients); and

- Awareness and utilisation of the Xeljanz Prescriber Website (i.e., whether the respondents were aware of and visited the Xeljanz Prescriber Website).

Note: There are 14 questions for all countries, except for Germany, which only has one aRMM HCP checklist rather than two (see survey instrument in Appendix 1 and Appendix 2 [HCP Questionnaire for RA/PsA and UC, respectively]) that ascertain awareness [receipt] and utilisation of the aRMM materials and Xeljanz Prescriber Website, except for Germany, which has 12 questions. One of the utilisation questions is also counted as an adherence question (see Table 2).

3. **Knowledge of the key risk messages pertaining to the use of Xeljanz (including the risk minimisation practices to prevent/minimise risks associated with Xeljanz).**

- HCPs providing correct answers for each knowledge question, or each knowledge response option associated with a survey question (as applicable).

	RA/PsA survey	UC survey
• HCPs correctly answering **≥70% to <80%** of the knowledge questions	Correctly answering **13-14 out of 18** knowledge questions	Correctly answering **14-15 out of 20** knowledge questions
• HCPs correctly answering **≥80% to <90%** of the knowledge questions	Correctly answering >80 but <90% **15-16 out of 18** knowledge questions	Correctly answering **16-17 out of 20** knowledge questions
• HCPs correctly answering **≥90% to <100%** of the knowledge questions	Correctly answering **17 out of 18** knowledge questions	Correctly answering **18-19 out of 20** knowledge questions
• HCPs correctly answering **100%** of the knowledge questions	Correctly answering **18 out of 18 (100%)** of the knowledge questions	Correctly answering **20 out of 20 (100%)** of the knowledge questions

Note: For the RA/PsA survey, there are 18 questions that ascertain knowledge about the key risk messages (see Table 3). For the UC survey, there are 20 questions that ascertain knowledge about the key risk messages (see Table 4). Each key risk message and associated survey question(s) is described in more detail in Appendix 3 and Appendix 4 (Key Risk Messages for the RA/PsA survey and the UC survey, respectively).

4. **Self-reported adherence to the risk minimisation practices recommended in the aRMM materials (e.g., provision of patient counselling and the alert card to patients, patient screening, laboratory monitoring recommendations, and limitations of use).**

    - HCPs providing desirable responses for each adherence question, or each adherence response option associated with a survey question (as applicable).

	RA/PsA survey	UC survey
• HCPs providing desirable responses to **≥70% to <80%** of the adherence questions	Providing desirable responses to **12-13 out of 17** adherence questions	Providing desirable responses to **12-13 out of 17** adherence questions
• HCPs providing desirable responses to **≥80% to <90%** of the adherence questions	Providing desirable responses to **14-15 out of 17 (**adherence questions	Providing desirable responses to **14-15 out of 17** adherence questions
• HCPs providing desirable responses to **≥90% to <100%** of the adherence questions	Providing desirable responses to **16 out of 17** adherence questions	Providing desirable responses to **16 out of 17** adherence questions
• HCPs providing desirable responses to **100%** of the adherence questions	Providing desirable responses to **17 out of 17** adherence questions	Providing desirable responses to **17 out of 17** adherence questions

Note: There are 17 questions that ascertain adherence to the risk minimisation practices recommended in the aRMM materials in both the RA/PsA and UC surveys. One of these

questions is also counted as a utilisation question (see Table 3 [RA/PsA survey] and Table 4 [UC survey]).

5. Effectiveness of the aRMM program in *each* of the following 4 domains:

	RA/PsA survey	UC survey
• **Awareness (Receipt) *ever***	≥80% of HCPs reporting that they received 4 out of the 4 (100%) aRMM materials[5] in all countries, except for Germany[6] ≥80% of HCPs reporting that they received 3 out of the 3 (100%) aRMM materials[6] in Germany	≥80% of HCPs reporting that they received 4 out of the 4 (100%) aRMM materials[5] in all countries, except for Germany[6] ≥80% of HCPs reporting that they received 3 out of the 3 (100%) aRMM materials in Germany[6]
• **Awareness (Receipt) *after February 2020***	≥80% of HCPs reporting that they received 4 out of the 4 (100%) aRMM materials[5] in all countries, except for Germany ≥80% of HCPs reporting that they received 3 out of the 3 (100%) aRMM materials[6] in Germany	≥80% of HCPs reporting that they received 4 out of the 4 (100%) aRMM materials[5] in all countries, except for Germany ≥80% of HCPs reporting that they received 3 out of the 3 (100%) aRMM materials[6] in Germany
• **Knowledge**	≥80% of HCPs correctly answering ≥14 out of 18 (≥78% [or approximately 80%]) of the knowledge questions	≥80% of HCPs correctly answering ≥16 out of 20 (≥80%) of the knowledge questions
• **Adherence**	≥80% of HCPs providing desirable responses for ≥14 out of 17 (≥82% [or approximately 80%]) of the adherence questions	≥80% of HCPs providing desirable responses for ≥14 out of 17 (≥82% [or approximately 80%]) of the adherence questions

Note: The measures of effectiveness in each of the 4 domains listed above will be calculated variables.

[5] The 4 aRMM materials include: the Xeljanz Prescriber Brochure, the Xeljanz Prescriber Treatment Initiation Checklist, the Xeljanz Prescriber Treatment Maintenance Checklist, and the Xeljanz Patient Alert Card. As the Xeljanz Prescriber Website is a repository for the aRMM materials, rather than a tool in and of itself, awareness of the Xeljanz Prescriber Website will not be considered when evaluating the effectiveness of the entire aRMM program.

[6] The 3 aRMM materials include: the Xeljanz Prescriber Brochure, the Xeljanz Prescriber Treatment Initiation and Maintenance Checklist, and the Xeljanz Patient Alert Card. As the Xeljanz Prescriber Website is a repository for the aRMM materials, rather than a tool in and of itself, awareness of the Xeljanz Prescriber Website will not be considered when evaluating the effectiveness of the entire aRMM program.

6. **Attitude toward the aRMM materials** (i.e., how useful the HCPs find the various aRMM materials in their practice).

    - There are 5 survey questions (1 question for each of the aRMM materials plus 1 question for the Xeljanz Prescriber Website) that ascertain HCPs' attitudes towards the aRMM materials, except for Germany, which has 4 questions.

7. **Source of HCPs' information on the safety of Xeljanz.**

    - There is 1 survey question that asks HCPs to identify their primary source of safety and prescribing information regarding Xeljanz from a list of pre-populated choices.

    Response rate, eligibility rate, completion rate. The HCPs' participation in the survey study will be examined by calculating the following mutually exclusive categories of HCPs

    Survey administration statistics

    - The number of invitations issued (I);
    - The number of invitations returned as undeliverable (R)
    - The number of respondents screened for participation (S);
        - **Survey response rate** = S/(I-R);
    - The number of respondents eligible for participation (E);
        - **Eligibility rate** = E/S;
    - The number of eligible respondents who completed the survey (C);
        - **Completion rate** = C/E;

8.3.1. Mapping of Select Variables to Survey Questions

A cross-walk of the survey questions associated with each key risk message assessed in the RA/PsA and UC surveys are presented in Appendix 3 and Appendix 4 (Key Risk Messages for the RA/PsA survey and the UC survey, respectively).

The number of survey questions associated with HCPs' self-reported awareness (receipt) and utilisation of the aRMM materials and Xeljanz Prescriber Website for both the RA/PsA and UC surveys is listed in Table 2.

Table 2. Number of Survey Questions Associated with Awareness (Receipt) and Utilisation of the aRMM Materials for both the RA/PsA and UC Surveys

Concept	Total number of survey questions
aRMM materials and Xeljanz Prescriber Website awareness (receipt), *ever and after February 2020*	9 (7 for Germany)
aRMM materials and Xeljanz Prescriber Website utilisation	5[b]
TOTAL	**14 (12 for Germany)**

Abbreviations: aRMM = additional risk minimisation measures; PsA = psoriatic arthritis; RA = rheumatoid arthritis; UC = ulcerative colitis.

a. There are 4 aRMM materials in all countries, except for Germany: the Xeljanz Prescriber Brochure, the Xeljanz Prescriber Initiation Checklist, the Xeljanz Prescriber Maintenance Checklist, and the Xeljanz Patient Alert Card; there is also the Xeljanz Prescriber Website, a repository for the aRMM materials. In Germany, there are 3 aRMM materials: the Xeljanz Prescriber Brochure, the Xeljanz Prescriber Initiation and Maintenance Checklist, and the Xeljanz Patient Alert Card; there is also the Xeljanz Prescriber Website, a repository for the aRMM materials.

b. Survey question 11a. In your clinical practice, how frequently do you "give the patient alert card to the patient" is counted as both a utilisation and an adherence (Table 3 [RA/PsA survey] and Table 4 [UC survey]) question.

As shown in Table 3, each key risk message has at least 1 corresponding RA/PsA survey question. There is a total of 35 survey questions related to the key risk messages. Eighteen of these 35 questions are **knowledge questions** and 17 of the 35 are **adherence questions**. For survey questions consisting of several response options, each individual response option is counted as a separate question since they can be viewed as distinct sub-messages pertaining to the key risk messages.

Table 3. Key Risk Messages and Associated Number of RA/PsA Survey Questions, Stratified by Type of Question (i.e., Knowledge or Adherence)

#	Key Risk Message	Total Number of Survey Questions (counting each individual response option as a separate question)	Number of Knowledge Questions	Number of Adherence Questions
1	Use in special populations	4	4	0
2	Combination with biologics and/or other potent immunosuppressants	1	1	0
3	Lab monitoring	9	4	5
4	Serious infections	5	3	2

Table 3. Key Risk Messages and Associated Number of RA/PsA Survey Questions, Stratified by Type of Question (i.e., Knowledge or Adherence)

#	Key Risk Message	Total Number of Survey Questions (counting each individual response option as a separate question)	Number of Knowledge Questions	Number of Adherence Questions
5	Viral reactivation and vaccination	4	2	2
6	Malignancies	2	1	1
7	Gastrointestinal perforations	1	1	0
8	Venous thromboembolism	3	2	1
9	Patient counseling	4	0	4[a]
N/A	Other[b]	2	0	2[b]
	TOTAL	**35**	**18**	**17**

Abbreviations: N/A = not applicable; PsA = psoriatic arthritis; RA = rheumatoid arthritis.

a. Survey question 11a. In your clinical practice, how frequently do you "[d]istribute the patient alert card to patients" is counted as both an adherence and a utilisation (Table 2) question.

b. Survey questions 7a, "Does this patient have gastroesophageal reflux disease (GORD/GERD)?", and 7d, "Does this patient have a history of hyperthyroidism?", are wrong answer options that do not correspond to any of the key risk messages.

As shown in Table 4, each key risk message has at least 1 corresponding UC survey question. There is a total of 37 survey questions related to the key risk messages. Twenty of these 37 questions are **knowledge questions** and 17 of the 37 are **adherence questions**. For survey questions consisting of several response options, each individual response option is counted as a separate question since they can be viewed as distinct sub-messages pertaining to the key risk messages.

Table 4. Key Risk Messages and Associated Number of UC Survey Questions, Stratified by Type of Question (i.e., Knowledge or Adherence)

#	Key Risk Message	Total Number of Survey Questions (counting each individual response option as a separate question)	Number of Knowledge Questions	Number of Adherence Questions
1	Use in special populations	5	5	0
2	Combination with biologics and/or other potent immunosuppressants	1	1	0
3	Lab monitoring	10	5	5
4	Serious infections	5	3	2

Table 4. Key Risk Messages and Associated Number of UC Survey Questions, Stratified by Type of Question (i.e., Knowledge or Adherence)

#	Key Risk Message	Total Number of Survey Questions (counting each individual response option as a separate question)	Number of Knowledge Questions	Number of Adherence Questions
5	Viral reactivation and vaccination	4	2	2
6	Malignancies	2	1	1
7	Gastrointestinal perforations	1	1	0
8	Venous thromboembolism	3	2	1
9	Patient counseling	4	0	4[a]
N/A	Other[b]	2	0	2[b]
	TOTAL	**37**	**20**	**17**

Abbreviations: N/A = not applicable; UC = ulcerative colitis.

a. Survey question 11a. In your clinical practice, how frequently do you "give the patient alert card to the patient" is counted as both an adherence and a utilisation (Table 2) question.

b. Survey questions 8a, "Does this patient have gastroesophageal reflux disease (GORD/GERD) and 8d, "Does this patient have a history of hyperthyroidism?," are wrong answer options that do not correspond to any of the key risk messages.

8.4. Data Sources

This study involves primary data collection. All data for analysis will be collected from HCPs directly via a multimodal survey instrument (i.e., a structured survey questionnaire implemented via Web portal or phone interview; Appendix 1 and Appendix 2 [HCP Questionnaire for the RA/PsA survey and the UC survey, respectively]) that is written to follow the principles of health literacy and readability. The list of HCPs to be invited to participate in the survey will be derived from the proprietary OneKey database, a worldwide database, available in 73 countries, that contains more than 13.7 million HCPs. The OneKey database is continuously updated by phone operators who validate the database, adhering to International Standards Organization 9001 procedures.[7] Initially created for marketing purposes, it is used in research to recruit HCPs[8-10] and by international organisations to construct HCP census data.[11] Depending on the survey country and specialty, the proportion of HCPs in the OneKey database with contact information ranges from 23% (dermatologists in Germany) to 91% (rheumatologists in Sweden).

8.5. Study Size

This is a descriptive study and no comparative analyses will be conducted. Thus, the purpose of the sample size calculations provided below is to describe the precision of the estimated response proportions.

The following formula, based on the normal approximation to the binomial, was used to calculate the sample size:

$$n = \frac{P \cdot (1 - P) \cdot \left(Z_{1-\alpha/2}\right)^2}{e^2},$$

Where e is one-half the desired width of the confidence interval (CI), and $Z_{1-\alpha/2}$ is the standard normal Z-value corresponding to a cumulative probability of $1-\alpha/2$.

The proportions of interest (P) are the proportions of HCPs correctly answering or providing desirable responses to the survey questions related to the specific objectives above (or the expected proportion of HCPs meeting each of the outcomes of interest; see Section 8.3 [Variables]). As P is not known in advance, we considered it to be 50% (maximum uncertainty). Such an assumption yields the most conservative, i.e., the largest, sample size for a specified margin of error.

Table 5, below, provides sample sizes assuming a range of proportions and margins of error (i.e., one-half the width of the 95% CI around the estimate).

Table 5. Sample Sizes Assuming a Range of Proportions and Margins of Error

	Margin of error for the 95% CI		
	10%	**6%**	**5%**
Proportion (P)[a]	**N**	**N**	**N**
10% (and 90%)	35	97	139
30% (and 70%)	81	225	323
50%	97	267	384

Abbreviations: CI = confidence interval.

a. The proportions of interest (P) are the proportions of HCPs correctly answering or providing desirable responses to the survey questions related to the specific objectives above (or the expected proportion of HCPs meeting each of the outcomes of interest; see Section 8.3 [Variables]).

Across the 8 survey countries, the MAH will aim for a sample size of 300 HCPs (i.e., completed surveys) for the RA/PsA survey and 300 HCPs (completed surveys) for the UC survey, which would achieve an overall precision for each survey of 5.7%. However, no sample size limit will be applied, and all completed surveys received during the 12-week data collection window will be included in the study analyses.

The target sample size proposed is based on the above precision considerations, as well as on the operational feasibility of achieving it. OneKey feasibility counts for the study countries are provided in Appendix 5. While there are an estimated 47,000 total specialist HCPs (i.e., rheumatologists, dermatologists, gastroenterologists) across the survey countries, the anticipated number of HCPs expected to *participate* in the survey is limited by the following factors:

- Only a proportion of HCPs will meet the inclusion/exclusion criteria for **Targeted HCPs** (i.e., have contact information available in OneKey and not participate in pilot testing[7] of the survey; Section 8.2.1.1 [Inclusion Criteria] and Section 8.2.1.2 [Exclusion Criteria]); note that all **Targeted HCPs** will be invited to participate;

- An unknown proportion of specialist HCPs will be eligible to prescribe Xeljanz to their patients. For example, in Poland and Romania, specialist HCPs who treat RA, PsA or UC need an additional certification to be able to prescribe Xeljanz;

- Among HCPs eligible to prescribe Xeljanz, an unknown proportion are expected to *manage* patients who would be indicated for Xeljanz (particularly a concern among dermatologists, who treat many other conditions in addition to PsA);

- Of those who manage patients indicated for Xeljanz, an unknown proportion of those HCPs *will* have prescribed Xeljanz for RA, PsA, or UC in the prior 12 months (dependent on a number of factors, including Xeljanz market penetrance); and

- Among those remaining, a response rate of 1.5-10% (depending on the country) is expected for this type of survey, with response rates on the low end expected for countries in which an honorarium will not be provided (Germany, the Netherlands, Sweden, and the UK will not offer an honorarium).

8.6. Data Management

8.6.1. Case Report Forms (CRFs)/Data Collection Tools (DCTs)/Electronic Data Record

As used in this protocol, the term data collection tool (DCT) should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A completed DCT is required and should be completed for each included participant. The completed original DCTs are the sole property of Pfizer and will not be made available in any form to third parties, except for authorised representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. IQVIA (the study vendor) shall ensure that the DCTs are securely stored on the IQVIA internal server in encrypted electronic form and will be password protected to prevent access by unauthorised third parties.

[7] Three pilot tests per country are planned.

IQVIA has ultimate responsibility for the collection and reporting of all data entered on the DCTs, as required, and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The DCT serves as the source document. Any corrections to entries made in the DCTs will be dated, initialed, and explained (if necessary) and should not obscure the original entry.

Any applicable country-specific regulatory requirements will be identified before the start of data collection.

8.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, IQVIA agrees to keep all study-related records. The study records will be retained by IQVIA according to local regulations or as specified in the vendor contract, whichever is longer. IQVIA will ensure that the study records continue to be stored securely for as long as they are retained.

If IQVIA becomes unable, for any reason, to continue to retain study records for the required period, Pfizer will be prospectively notified. The study records will be transferred to a designee acceptable to Pfizer.

Study records will be kept for a minimum of 15 years after completion or discontinuation of the study, unless IQVIA and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Study records must be retained for longer than 15 years if required by applicable local regulations.

IQVIA must obtain Pfizer's written permission before disposing of any study records, even if the retention requirements have been met.

8.6.3. Data Management Systems and Storage

An electronic web-based survey system that can be accessed through the internet, Medical Radar Pharmaceutical Interviews (MERPHIN), will be used for data collection. MERPHIN simplifies information exchange and allows for online data quality control (QC). MERPHIN's administrative features can only be accessed with an Active Directory login and password. There is a separate content manager tool in the Survey Control System that determines different levels of user rights within MERPHIN. Data collected from the MERPHIN online survey tool is hosted on servers located in the IQVIA Global Data Center in the United States (US). The company network is not accessible from outside the company, unless through a defined remote data access procedure. Daily backups are performed to prevent any data loss or damage. The history of connections, data entry, and modifications are fully audit trailed. When the Web Survey is inactive, and the fieldwork phase has been closed, the QC team will export the data and save it as an Excel file on the restricted SharePoint site (i.e., document repository), where it will be accessible to authorised users only. The final Excel file will be transmitted to the statistician and will not include any identifying individual participant data.

Data saved on the SharePoint site is stored on servers located in the IQVIA Global Data Center in the US.

8.6.4. Data Collection Schedule

IQVIA Primary Intelligence will be responsible for conducting the survey. The data collection period will last 12 weeks for each survey country. To maximize the sample size, the survey window will remain open for 12 weeks even if the target sample size has already been reached.

Since Xeljanz will not have received full reimbursement at the same time in each of the survey countries, because approvals from local Health Authorities, Ethics Committees, and competent authorities (as needed) may also not be granted at the same time, and because the current aRMM materials will be distributed at different times in the survey countries, the survey field work may be conducted at different times in each survey country.

Prior to the survey, the HCPs will review a disclaimer about privacy information and then be asked if they wish to continue with the survey study. This question will serve the role of informed consent. Next, the HCP will answer a series of screening questions to assess their eligibility to take the survey. Depending on the answers provided to the screening questions, the HCP will either be terminated or allowed to continue with the survey study. If an HCP is determined to be *ineligible* to continue with the survey study, they will be immediately notified with a "thank you" message that survey participation has ended. If an HCP is determined to be *eligible*, they will be allowed to continue with survey participation.

After answering all the initial screening and demographic questions, the HCPs determined to be *eligible* to take the survey will enter the body of the survey.

The survey consists of closed-ended questions or statements with multiple response options (i.e., questions or statements asking the HCP to choose from a defined list of responses). The HCPs will not be able to go back to a question once the question has been answered and they will not be able to skip ahead. For survey questions where the response options are presented in a list, the response options will be randomised to minimise positional bias. Surveys can only be submitted once all the questions are answered. Each of the two surveys are expected to take approximately 25 minutes to complete. For surveys administered by phone, a time is arranged to suit the participant's schedule so that all questions can be answered during one phone call.

IQVIA Primary Intelligence will send out invitations to participate in the survey study to all **Targeted HCPs** (see Section 8.2.1.1 [Inclusion Criteria] and Section 8.2.1.2 [Exclusion Criteria] for more details). Invitations will be issued primarily by email, if available; by postal mail; or by phone, according to the country. After each contact attempt by IQVIA Primary Intelligence, the OneKey database will be cross-checked with any correspondence that had an invalid address or incorrect contact details, or that bounced back. For each **Targeted HCP**, the total number of contacts made by IQVIA Primary Intelligence will be recorded.

A **Targeted HCP** will be considered **contacted** if they:

- Expressed refusal to participate in the survey study (i.e., did not provide their consent; **"Refused HCPs"**);
- Partially completed the screening, demographic, or survey questions (**"Partial Complete HCPs"**);
- Were screened out of the study (i.e., were not eligible to participate in the survey study; **"Screened Out HCPs"**); or
- Submitted a completed survey ("**Completed Survey HCPs**").

A submitted and completed survey will be defined as a survey in which all of Questions (Q) of the survey were answered completely and submitted by the HCP. If an HCP completed only the screening questions or the demographic and screening questions, this information will not be used because it will not be considered a completed survey.

An HCP will be considered **unreachable** if he or she cannot be reached after at least 3 attempts by any means (i.e., email, postal mail, and/or phone) or were unreachable for other reasons (e.g., wrong workplace, retired, or temporarily unavailable). However, IQVIA maintains the flexibility to contact them more times if there is reason to believe that the additional contact will lead to participation.

Recruitment for each country will be stopped when all **Targeted HCPs** have been either considered **contacted** or deemed **unreachable** *or* after the data collection period ends, whichever occurs first.

To the extent possible, reasons for non-response will be collected. This will help ensure that missing data are reported with enough details to strengthen the results' validity, as recommended by the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[13,14]

8.6.5. Approaches for Increasing Response Rates

People are increasingly contacted to participate in research studies, telephone marketing, and mail-in marketing surveys that may resemble scientific surveys. Survey information that arrives in the post or by telephone may be assumed to be "spam," arriving together with unsolicited mail or calls from commercial sources, building additional barriers to participation when contacted.

Van Geest et al. conducted a systematic review of 66 published reports on efforts to improve response rates in surveys of physicians.[15] Two general strategies for enhancing response rates were explored: 1) incentive-based approaches, and 2) survey design-based approaches. Financial incentives, even small ones, were effective in improving HCP response rates while surveys with no monetary incentives had lower response rates. Effective survey

design-based approaches included the use of a short survey and surveys personalised and approved by professional associations.

Based on this evidence, to increase the response rate among HCPs, the following strategies will be applied to this survey:

- An honorarium will be offered to HCPs for their participation in the survey, where appropriate, according to local regulations. Initial feasibility assessments indicated that it will not be feasible to offer an honorarium in Germany, the Netherlands, Sweden, and the UK. However, an honorarium *may* be offered in France and Spain, and feasibility assessments regarding provision of honoraria are ongoing in Poland and Romania.

- A paragraph stating clearly that this survey is undertaken to comply with Article 21a.(b) of Directive 2001/83/EC to evaluate the effectiveness of the aRMM program for Xeljanz in the EU.

- A multimodal recruitment approach: all HCPs will be sent an email, a postal mailing, and/or be contacted by phone; and

- Multiple follow-ups: each HCP will be emailed or called at least 3 times before being considered "unreachable."

8.7. Data Analysis

8.7.1. General Statistical Consideration

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed, and maintained by the Sponsor. The SAP may modify the analyses outlined in this protocol; any major modifications of primary endpoint definitions or their analyses will be reflected in a protocol amendment.

The data collected from the RA/PsA survey will be analysed separately from the data collected from the UC survey. For each survey (RA/PsA and UC), all primary analyses will be conducted using the *pooled* data from all countries, specialties (applies to the RA/PsA survey only), and indications (applies to the RA/PsA survey only), and will be descriptive in nature; no statistical comparisons within or between countries, specialties, and/or indications will be conducted. Only submitted and completed surveys-i.e., all of Questions of the survey (Appendix 1 and Appendix 2 [HCP Questionnaire for the RA/PsA survey and the UC survey, respectively]) answered (taking into account skip patterns) by HCPs eligible to participate in the survey—will be used in the analyses.

Categorical variables will be presented using frequencies and proportions. For most outcomes, associated 95% CIs will also be calculated; 95% CIs will *not* be calculated for outcomes such as attitude towards the aRMM materials and Xeljanz Prescribe Website and source of HCPs' information on the safety of Xeljanz. Continuous variables will be presented using means, standard deviations (SDs), minimums, 25th percentiles, medians,

75th percentiles, and maximums. Depending on the sample size, stratification by country, number of patients treated with Xeljanz, experience prescribing Xeljanz (a proxy for indication), receipt and utilisation of the aRMM materials, and/or number of years in practice may be performed. The analysis may also be restricted to HCPs without prior experience as a healthcare professional in a Xeljanz clinical trial, if sample size is sufficient.

Since the relative weight of HCPs who prescribe Xeljanz for RA, PsA, or UC in each survey country will be different from a country's true relative weight of HCPs who prescribe Xeljanz for RA, PsA, or UC, extrapolation of the survey results to the overall target population (i.e., HCPs who prescribe Xeljanz for RA, PsA, or UC in Europe) would not be appropriate without adjustment. Thus, the survey results will be weighted *overall* to reflect the true proportion of HCPs who prescribe Xeljanz in the countries and *within* each country, to reflect the true proportion of each HCP specialty authorised to prescribe Xeljanz in that country (applies to the RA/PsA survey only). Both unweighted and weighted results will be presented in final study report. The details of the weighting schema will be presented in the SAP.

The statistical analysis will be conducted using the most recent version of SAS® (Statistical Analysis Software; SAS Institute, North Carolina, US) in use by IQVIA on Windows®.

8.7.2. Primary Analysis: Study Objective 1-Awareness (Receipt) and Utilisation

Per question analysis: The number and proportion of HCPs self-reporting that they received and utilised each of the 4 aRMM materials (3 in Germany) will be reported. If appropriate, the number and proportion of HCPs self-reporting that they received and utilised the aRMM materials will be reported by ever and after February 2020 or January 2020 in Poland (except for the website, which will be reported by "ever" only). The number and proportion of HCPs self-reporting that they received information related to the Xeljanz Prescriber Website and that they utilised the website will also be reported.

Overall: The self-reported number of aRMM materials received per HCP and the self-reported number of aRMM materials utilised per HCP will be summarized continuously using means, SDs, medians, ranges, and interquartile ranges (IQRs).

8.7.3. Primary Analysis: Study Objective 2—Knowledge of Key Risk Messages

	RA/PsA Survey	**UC Survey**
Per question analysis	The number and proportion of HCPs providing a correct answer for each of the **18 knowledge questions** will be reported.	The number and proportion of HCPs providing a correct answer for each of the **20 knowledge questions** will be reported.
Overall	The number and proportion of HCPs providing correct answers to <13, **13-14, 15-16, 17, and 18 out of the 18 knowledge questions** will be reported. The number of correct answers to the **18 knowledge questions** per HCP	The number and proportion of HCPs providing correct answers to <14, **14-15, 16-17, 18-19, and 20 out of the 20 knowledge questions** will be reported. The number of correct answers to the **20 knowledge questions** per

	RA/PsA Survey	UC Survey
	will also be summarized continuously using mean, SD, median, range, and IQR.	HCP will also be summarized continuously using mean, SD, median, range, and IQR.

8.7.4. Primary Analysis: Study Objective 3-Adherence to the Risk Minimisation Practices Recommended in the aRMM Materials

	RA/PsA survey	UC survey
Per question analysis	The number and proportion of HCPs providing a desirable response for each of the **17 adherence questions** will be reported.	The number and proportion of HCPs providing a desirable response for each of the **17 adherence questions** will be reported.
Overall	The number and proportion of HCPs providing desirable responses to <12, **12-13, 14-15, 16, and 17 out of the 17 adherence questions** will be reported. The number of desirable responses to the **17 adherence questions** per HCP will also be summarized continuously using mean, SD, median, range, and IQR.	The number and proportion of HCPs providing desirable responses to <12, **12-13, 14-15, 16, and 17 out of the 17 adherence questions** will be reported. The number of desirable responses to the **17 adherence questions** per HCP will also be summarized continuously using mean, SD, median, range, and IQR.

8.7.5. Secondary Analysis: HCP Practice Characteristics

HCPs' responses to the questions (2 pre-survey and 7 in the RA/PsA survey and 6 in the UC survey) related to HCP practice characteristics will be presented descriptively using frequencies and proportions.

8.7.6. Secondary Analysis: Attitude Towards the aRMM Materials

For each aRMM material and the Xeljanz Prescriber Website, among the HCPs who self-reported receiving the aRMM material or who were aware of the Xeljanz Prescriber Website, the number and proportion of HCPs finding the aRMM materials or Xeljanz Prescriber Website "Very Useful," "Somewhat Useful," or "Not Useful" will be described These categories may be collapsed, as needed, after reviewing the distribution of the data.

8.7.7. Secondary Analysis: Source of HCPs' Information on the Safety of Xeljanz

The number and proportion of HCPs selecting each pre-populated source of information as their primary source will be reported.

8.7.8. Secondary Analysis: Response Rate, Cooperation Rate, Refusal Rate, and Contact Rate

The number of **Targeted HCPs**, and, among them, the number and proportion of Unreachable HCPs, Contacted HCPs, Refused HCPs, Screened Out HCPs, Partial Complete HCPs, and Completed Survey HCPs will be reported. The Contact Rate, Response Rate, Cooperation Rate, and Refusal Rate will also be described.

8.8. Quality Control

QC will be conducted according to Pfizer's Non-Interventional Integrated Quality Control Plan and the standard operating procedures (SOPs) of IQVIA Primary Intelligence and IQVIA Real World Evidence Solutions.

All aspects of the study, from protocol development to the reporting of the results, will be conducted within the framework of the IQVIA Quality Management System.

A QC plan for the study will be developed and executed, which will include QC on the study methodology, SAP, programming, data management and analysis, study results, conclusions, and final study report. Furthermore:

- The study QC plan will establish ownership for the execution of the individual QC steps;
- The Principal in Charge of the study will ensure that individuals responsible for the execution of specific QC steps will have the knowledge, capability, and experience necessary to perform the assigned tasks; and
- The result of the execution of the individual steps of the QC plan will be documented, and will include the required corrective actions, if any. The execution of any required corrective action will also be documented.

The QC plan will be subjected to a final review and approval for sufficiency and completeness from the Principal in Charge of the study. IQVIA will have a qualified individual external to the writing team conduct QC reviews of all final deliverables, which will include the following:

- Confirming that the source of the data and/or results has been documented and that the reported data and/or results have been verified against the source;
- Checking the internal consistency of the results presented in the deliverable;
- Confirming that the conclusions are accurate, objective, balanced, and consistent with other published or released results; and
- Confirming that the format and content of the deliverable are aligned with applicable external requirements.

8.8.1. Approaches for Validating the Questionnaires

The survey questions will be programmed to ensure that they are asked in the appropriate sequence. Skip patterns will be clearly indicated. HCPs will not be able to go back to a question once the question has been answered and they will not be able to skip ahead. Response options presented in a list will be randomised to minimise positional bias. Programming will be reviewed by QC and simulated users (i.e., pilot testing) prior to survey implementation. Surveys will only be allowed to be submitted once all questions have been answered.

Survey items are presented in the following formats:

- Instructions prompting the HCP to indicate whether a series of statements are true or false, or if they do not know the answer (there are also questions that use "yes" or "no" or "I don't know" as potential response options); and

- Statements or questions asking the HCP to choose from a defined list of possible statements or answers.

The survey was developed jointly by the MAH and IQVIA based on the final approved aRMM materials[5] and is included in Appendix 1 and Appendix 2 (HCP Questionnaire for the RA/PsA survey and the UC survey, respectively). The survey instrument will be translated from English into the local language for each survey country using a committee-based approach; this method ensures accurate and comprehensive local versions of the survey by a team of translators. Translations will be performed by Research Support Services personnel or qualified vendors, if needed. All translations are performed by certified translators.

8.8.1.1. User Testing of the Survey Instrument

After translations have been completed and prior to fielding the survey, the survey instrument will be pilot-tested by Northwestern University or Research Support Services in each country using a sample of HCPs composed of a minimum of 2-3 specialists (a rheumatologist, dermatologist, and/or gastroenterologist) from each country. Pilot testing will occur in the predominant language of the country. This qualitative testing will assess comprehension among HCPs of the words, phrases, and response options used in the survey to ensure that the intended content of the questions is adequately conveyed. The feedback received from the pilot-testing will be incorporated into the final version of the survey instrument.

8.8.2. Approaches for Validating the Results

The QC for validating the results will be conducted as follows:

1. At the IQVIA Primary Intelligence management level (i.e., survey conduct), every effort will be undertaken to collect, complete, and valid data by:

    - Verification of the reliability and security of the web survey interface by a qualified webmaster for each country; and

- Monitoring the quality and definition of datasets by a qualified data manager.

2. Conducting real-time checks of the answers provided by the HCPs in the background of the web survey.

3. At the study database level (after merging datasets from each country), final data quality checks will be applied (beyond the data management process) including:

   - Distribution of each variable to count the number of missing values and estimate the associated relative percentage;

   - Estimation of the count and proportion of non-analysable surveys; and

   - Estimation of the count and proportion of non-submitted (i.e., partially completed) surveys.

Any changes in the study database will be tracked and documented. While data from the survey countries will be pooled into a final study database, the country-specific datasets will still be retained in a separate database. Once data are validated and quality checked, the database will be locked.

1. At the statistical analysis level, all data management and statistical analysis programming developed and used in the analysis will be documented. All programming versions generated will be dated, kept with accompanying documentation, and archived. The original study database will be stored according to IQVIA SOPs. A derived database will be created for new versions of the data to allow for recoding and computing of new variables (e.g., combination of modalities for categorical variables).

2. At the results level, a data quality review will be conducted to ensure data integrity. A final study report including all the results will be provided for review and discussion. The final study report will take into account the reviewers' comments.

3. The results validation will be conducted according to the SOPs of IQVIA Real World Evidence Solutions and IQVIA Primary Intelligence divisions.

8.8.3. Safeguards, Security, and Traceability of Contacts

Operators of a call centre specialised in health surveys will be assigned to the project and trained on the survey methodology prior to fieldwork. The postal mailings, email contacts, and phone calls will be traced using management software.[16]

Access to the web survey interface will be strictly limited to the invited HCPs, with the possibility to participate only once, which will be monitored using a traceability system. The same procedure will be followed if the invited HCPs take the survey over the phone.

8.9. Limitations of the Research Methods

8.9.1. Absence of Baseline

The Sponsor's ability to measure the extent to which HCPs' knowledge or behaviours can be attributed to the aRMM program will be limited. As the original aRMM materials were distributed at the time of initial marketing authorisation, no baseline measures of HCPs' knowledge or behaviour in the absence of the aRMM materials will be available. However, the knowledge and behaviour of the HCPs who self-reported having received and/or utilised the aRMM materials can be compared with the knowledge and behaviour of the HCPs who self-reported having *not* received and/or utilised the aRMM materials, provided that there is a sufficient number of respondents across both strata.

8.9.2. Limitation of Human Recall

The HCPs will be asked if they recall having received the aRMM materials. Because the MAH will have no way to verify true receipt of materials (original or current), it is possible that HCPs who report never receiving the materials will have, in fact, received them and vice versa.

8.9.3. Social Desirability

As in all surveys, this survey may promote a social desirability bias, which refers to the tendency of HCPs to give socially desirable/expected responses instead of choosing those reflecting their current knowledge or behaviour.[17] For example, HCPs can provide information gathered online instead of giving their own opinions, or declare a conforming prescribing practice when, in fact, they are not adherent to the aRMMs. Social desirability can affect the validity of survey research findings, but the use of pre-populated items (i.e., response options) in the survey could/tends to reduce this bias.[18]

8.9.4. Mode of Survey

HCPs will be offered the opportunity to complete the survey over the telephone, if preferred. However, the MAH does not expect that HCPs who complete the survey via telephone will have systematically better or worse recollection of the aRMM materials than HCPs who complete the survey online. Further, given the small number of surveys that are expected to be completed over the telephone, the MAH does not expect the impact of this bias to be large.

8.9.5. Generalisability

Generalising the results of a survey to the population of interest assumes that the HCPs who provided data are a representative sample of the population. In an attempt to assess this assumption, the distribution of select HCP characteristics (e.g., country, specialty, and any other available characteristics present in the OneKey database) will be compared between HCPs who responded and HCPs who did not respond to the survey study invitation. If survey non-response (i.e., failure to contact or elicit participation from eligible HCPs) creates non-response bias (because respondents differ from non-respondents), survey estimates of means, proportions, and other population parameters might be biased. Because information on important characteristics of non-respondents will be limited, our ability to assess

generalisability may be limited, especially if the response rate is low. Additionally, for the subgroup analyses, when the total number of HCPs from a particular subgroup (e.g., dermatologists) is less than 30, generalisability of study results to all HCPs of that subgroup in the target population (e.g., dermatologists in Europe) may not be possible.

8.9.6. Reaching the Minimum Target Sample Size

Reaching the minimum target sample size of 300 HCPs (i.e., completed surveys) for each survey (RA/PsA and UC) might not be feasible for a number of reasons. First, while the survey will not begin in each survey country until at least 6 months has passed between Xeljanz reimbursement and the start of data collection, it is possible that market penetrance may still be low at the start of data collection, especially for the survey countries where this interval is shorter (i.e., Romania for the PsA and UC indications). Low market penetrance means fewer HCPs with experience prescribing Xeljanz and thus a smaller base of HCPs eligible to participate in the survey.

Additionally, feasibility work suggests that offering an honorarium to participating HCPs is not feasible in Germany, the Netherlands, Sweden, and the UK. This may result in a lower HCP response rate for those countries. Indeed, a similar aRMM evaluation study conducted by the MAH in 10 European countries (9 of which had no honoraria) experienced a total response rate of only 1.7%.[12]

Finally, an unknown proportion of specialist HCPs are expected to (1) manage patients indicated for Xeljanz treatment on a regular basis and (2) have the necessary certification to prescribe Xeljanz. Because the OneKey database does not contain this information, the exact number of HCPs anticipated and/or certified to prescribe Xeljanz for patients with RA, PsA, and/or UC cannot be determined prior to the start of the study.

Despite these limitations, the MAH will make every effort to reach the minimum target sample size as described in Section 8.6.5 (Approaches for Increasing Response Rates). Regardless of whether the minimum target sample size is reached, all available results will be provided to the PRAC by the timelines proposed (barring administrative delays in protocol approval, local Health Authority and/or Ethics Committee approvals, other competent authorities, Xeljanz reimbursement dates, and/or timely distribution of the current aRMM materials).

8.10. Other Aspects

Strengths of the Research Methods:

- The survey includes general questions followed by specific ones to limit a learning process during the survey. As the HCPs may understand the correct answer or desirable response in subsequent questions, it will not be possible to go back in the survey to edit answers/responses for former questions; and

- The survey will be pilot-tested for its clarity. It will also be checked to determine whether there are any questions which would suggest a specific answer for any reason (e.g., social desirability).

9. PROTECTION OF HUMAN SUBJECTS

9.1. Study Participant Information

All parties will comply with all applicable laws, including laws regarding the implementation of organisational and technical measures to ensure protection of participant personal data. Such measures will include omitting participant names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

Participant personal data will be collected by IQVIA and stored on IQVIA's internal server in encrypted electronic form and will be password protected to ensure that only authorised study staff have access. IQVIA will implement appropriate technical and organisational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, IQVIA shall be responsible for determining whether a personal data breach has in fact occurred and, if so, provide breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled and aggregated for transfer to Pfizer and other authorised parties, any participant names will be removed and replaced by a single, specific, numerical code. All other identifiable data transferred to Pfizer or other authorised parties will be identified by this single, participant-specific code.

IQVIA will maintain a confidential list of respondents who participated in the study, linking each respondent's numerical code to his or her actual identity for 36 months. These identifiable data will not be transferred to Pfizer according to vendor contract.

9.2. Participant Consent

The informed consent language and any HCP recruitment materials must be in compliance with local regulatory requirements and legal requirements, including applicable privacy laws.

The country-specific informed consent language (including the study objective and availability of honorarium) incorporated within the survey and any HCP recruitment materials must be reviewed and approved by Pfizer, approved by the independent ethics committee (IEC), as locally required, before use, and made available for inspection.

The study vendor must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the participant's personal data. The study vendor further must ensure that each study participant is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

9.3. Participant Withdrawal

Participation in the survey is entirely voluntary and participants can withdraw from the survey at any time. Only completed and submitted surveys will be included in the analysis.

9.4. Independent Ethics Committee (IEC)

It is the responsibility of IQVIA to have prospective approval of the study protocol, protocol amendments, materials describing the consent process (e.g., statement regarding agreement to participate), and other relevant documents (e.g., recruitment advertisements), if applicable, from the IEC. All correspondence with the IEC should be retained by IQVIA. Copies of IEC approvals should be forwarded to Pfizer and stored in the trial master file.

9.5. 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 the generally accepted research practices described in the following documents:

- European Pharmaceutical Marketing Research Association Code of Conduct;[19]
- Module XVI of the EMA's *Guideline on good pharmacovigilance practices (GVP) – Risk minimisation measures: selection of tools and effectiveness indicators*;[20]
- *Good Pharmacoepidemiology Practices* issued by the International Society for Pharmacoepidemiology;[21]
- *Guidelines for Good Epidemiological Practice (GEP)* issued by the International Epidemiological Association (IEA);[22]
- *Good Practices for Outcomes Research* issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR);[22]
- *International Ethical Guidelines for Epidemiological Research* issued by the Council for International Organizations of Medical Sciences in collaboration with the World Health Organization (WHO);[23]
- EMA European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology*;[24] and
- The US Food and Drug Administration's Guidance for Industry: *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment.*[25]

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS REQUIREMENTS

This study does not involve data collection on individual patients by their treating HCPs and the DCT used in this study (i.e., the survey instrument) does not intend to identify product safety information.

The DCT for this study will be completed online via a secure website. The DCT does not provide a free text field where study participants (i.e., HCPs) could specify information that may constitute product safety information. Further, routine communication with study participants via email or phone with the study vendor staff (i.e., IQVIA) is not expected during the conduct of the study. However, it is possible that a study participant may volunteer product safety information to study vendor staff while in conversation about the DCT for any other reason (e.g., seeking information about the purpose of the study); this information must be reported as described below.

The following safety events must be reported on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form: serious and non-serious adverse events (AEs) when associated with the use of a Pfizer product, and scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure **(all reportable, regardless of whether associated with an AE)**, when associated with the use of a Pfizer product.

In the event that a study participant volunteers product safety information, study vendor staff at IQVIA must complete the NIS AEM Report Form and submit to Pfizer within 24 hours of becoming aware of the safety event. Included in the completion of the NIS AEM Report Form is the study participant's contact information; complete contact information should be obtained so that, once the NIS AEM Report Form is sent to Pfizer, the NIS AEM Report Form can be assessed and processed according to Pfizer's SOPs, including requests for follow-up with the study participant.

Study vendor staff at IQVIA who will serve to be available to study participants to address any query from participants about the study or conduct the survey over the phone must complete the following Pfizer training requirements:

- *"Your Reporting Responsibility (YRR) Training for Vendors*".

This training must be completed by study vendor staff at IQVIA prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. The study vendor will also provide copies of all signed training certificates to Pfizer.

Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant (i.e., HCP) is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the party responsible for collecting data from the participant will inform Pfizer immediately of any urgent safety measures taken by that party to protect the study participants against any immediate hazard and of any serious breaches of this NI study protocol that the party becomes aware of.

The study will be registered in the EU Post-Authorisation Study (EU PAS) Register by the MAH.

The final study report, which will contain the results from all 8 countries combined for the RA/PsA survey and the UC survey, will be written in English and submitted to EMA within 12 months of the end of data collection in the last survey study country.

12. REFERENCES

1. European Medicines Agency. Xeljanz. 2018; http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004214/human_med_001662.jsp. Accessed 13 September 2018.

2. World Health Organization. The Global Burden of Disease, 2004 Update. 2012; http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf. Accessed 8 January 2020.

3. Ma MH, Ibrahim F, Walker D, et al. Remission in early rheumatoid arthritis: predicting treatment response. *J Rheumatol.* 2012;39(3):470-475.

4. Pfizer. XELJANZ / XELJANZ XR (tofacitinib): Clinical Studies. https://www.pfizermedicalinformation.com/en-us/xeljanz/clinical-studies. Accessed 14 September 2018.

5. European Medicines Agency. Xeljanz : Summary of Product Characteristics: https://www.ema.europa.eu/en/documents/product-information/xeljanz-epar-product-information_en.pdfAccessed 14 January , 2021.

6. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. *Ann Rheum Dis.* 2005;64 Suppl 2:ii14-17.

7. IQVIA. OneKey Reference Data Set. https://www.iqvia.com/locations/united-states/commercial-operations/essential-information/onekey-reference-assets. Accessed 25 September 2018.

8. Halcox JP, Banegas JR, Roy C, et al. Prevalence and treatment of atherogenic dyslipidemia in the primary prevention of cardiovascular disease in Europe: EURIKA, a cross-sectional observational study. *BMC Cardiovascular Disorders.* 2017;17(1):160.

9. Valensi P, De Pouvourville G, Benard N, et al. Treatment maintenance duration of dual therapy with metformin and sitagliptin in type 2 diabetes: the ODYSSEE observational study. *Diabetes & Metabolism.* 2015;41(3):231-238.

10. Löfdahl C-G, Tilling B, Ekström T, Jörgensen L, Johansson G, Larsson K. COPD health care in Sweden–a study in primary and secondary care. *Respiratory Medicine.* 2010;104(3):404-411.

11. World Health Organization. Number of physicians, medical group of specialties (PP). 2018; https://gateway.euro.who.int/en/indicators/hfa_499-5261-number-of-physicians-medical-group-of-specialties-pp/. Accessed 25 September 2018.

12. Lem J, Younus M, Aram J, et al. Evaluating the Effectiveness of Additional Risk Minimisation Measures (aRMM) for Voriconazole in 10 European Countries. Paper presented at: International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ICPE); August 29, 2017.

13. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *International Journal of Surgery*. 2014;12(12):1495-1499.

14. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009;338:b2393.

15. VanGeest JB, Johnson TP, Welch VL. Methodologies for improving response rates in surveys of physicians: a systematic review. *Evaluation & the Health Professions*. 2007;30(4):303-321.

16. IQVIA data privacy obligations. https://www.iqvia.com/about-us/privacy.

17. Wyatt JC. When to use web-based surveys. In: BMJ Group BMA House, Tavistock Square, London, WC1H 9JR; 2000.

18. Nederhof AJ. Methods of coping with social desirability bias: A review. *European Journal of Social Psychology*. 1985;15(3):263-280.

19. European Pharmaceutical Marketing Research Association Code of Conduct. Code of Conduct 2018. https://www.ephmra.org/standards/code-of-conduct.

20. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP): Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 2). 2017; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/02/WC500162051.pdf. Accessed 19 September 2018.

21. Public Policy Committee International Society of Pharmacoepidemiology. Guidelines for good pharmacoepidemiology practice (GPP). *Pharmacoepidemiology and drug safety*. 2016;25(1):2-10.

22. International Epidemiological Association. Guidelines for Good Epidemiological Practice (GEP). 2010.

23. Council for International Organizations of Medical Sciences, World Health Organization. International Ethical Guidelines for Health-related Research Involving Humans. https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf. Accessed 19 September 2018.

24. European Medicines Agency (EMA) ENoCfPE. Guide on Methodological Standard in Pharmacoepidemiology. http://www.encepp.eu/standards_and_guidances.

25. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. 2005; https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071696.pdf. Accessed 19 September 2018.

13. LIST OF TABLES

14. LIST OF FIGURES

None.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title: Evaluation of the effectiveness of additional risk minimisation measures (aRMM) materials for Xeljanz® (tofacitinib) in Europe via a survey of healthcare professionals (HCPs): A non-interventional (NI) post-authorisation safety study (PASS)

Study reference number:
Protocol #: A3921334

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection.	☒	☐	☐	6
1.1.2 End of data collection.	☒	☐	☐	6
1.1.3 Study progress report(s).	☐	☐	☒	
1.1.4 Interim progress report(s).	☐	☐	☒	
1.1.5 Registration in the EU PAS register.	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
2.1.1 Why the study is conducted? (e.g., to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue).	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalised).	☒	☐	☐	9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design		Yes	No	N/A	Section Number
3.1	Is the study design described? (e.g., cohort, case-control, cross-sectional, new or alternative design).	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3	Does the protocol specify measures of occurrence? (e.g., incidence rate, absolute risk).	☐	☐	☒	
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).	☒	☐	☐	11

Comments:

Section 4: Source and study populations		Yes	No	N/A	Section Number
4.1	Is the source population described?	☒	☐	☐	9.2, 9.4
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period?	☒	☐	☐	6, 9.1
	4.2.2 Age and sex?	☐	☐	☒	
	4.2.3 Country of origin?	☒	☐	☐	9.1, 9.2
	4.2.4 Disease/indication?	☐	☐	☒	
	4.2.5 Duration of follow-up?	☐	☐	☒	
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria).	☒	☐	☐	9.2, 9.4

Comments:

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

This study is a survey of HCPs who have written at least one prescription for Xeljanz for patients diagnosed with RA and/or PsA or UC. There is no drug exposure in this study.

Section 6: Outcome definition and measurement		Yes	No	N/A	Section Number
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
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).	☐	☐	☒	
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	Section Number
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).	☒	☐	☐	9.9
	7.2.2. Information biases (e.g., misclassification of exposure and endpoints, time-related bias).	☒	☐	☐	9.9
7.3	Does the protocol address the validity of the study covariates?	☐	☐	☒	

Comments:

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

Comments:

Section 9: Data sources		Yes	No	N/A	Section Number
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview).	☐	☐	☒	
	9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics).	☒	☐	☐	9.3
	9.1.3 Covariates?	☒	☐	☐	9.3

Section 9: Data sources		Yes	No	N/A	Section Number
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g., date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber).	☐	☐	☒	
	9.2.2 Outcomes? (e.g., date of occurrence, multiple event, severity measures related to event).	☒	☐	☐	9.3
	9.2.3 Covariates? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle).	☒	☐	☐	9.3
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System).	☐	☐	☒	
	9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD)-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:

This study is a survey of HCPs who have written at least 1 prescription for Xeljanz for patients diagnosed with RA and/or PsA or UC. There is no drug exposure in this study.

Section 10: Analysis plan		Yes	No	N/A	Section Number
10.1	Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2	Are descriptive analyses included?	☒	☐	☐	9.7
10.3	Are stratified analyses included?	☒	☐	☐	9.7
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?	☒	☐	☐	9.5

Comments:

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP) which will be dated, filed, and maintained by the Sponsor.

Regarding stratified analysis, the protocol states the following: "Depending on the sample size, stratification by country, number of patients treated with Xeljanz, experience prescribing Xeljanz (a proxy for indication), receipt and utilisation of aRMM materials, and/or number of years in practice may be

performed. The analysis may also be restricted to HCPs without prior experience as an investigator in a Xeljanz clinical trial, if sample size is sufficient."

Section 11: Data management and quality control		**Yes**	**No**	**N/A**	**Section Number**
11.1	Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving).	☒	☐	☐	9.6
11.2	Are methods of quality assurance described?	☒	☐	☐	9.8
11.3	Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations		**Yes**	**No**	**N/A**	**Section Number**
12.1	Does the protocol discuss the impact on the study results of:				
12.1.1	Selection bias?	☒	☐	☐	9.9
12.1.2	Information bias?	☒	☐	☐	9.9
12.1.3	Residual/unmeasured confounding? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2	Does the protocol discuss study feasibility? (e.g., study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment).	☒	☐	☐	9.5

Comments:

Section 13: Ethical issues		Yes	No	N/A	Section Number
13.1	Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.4
13.2	Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3	Have data protection requirements been described?	☒	☐	☐	9.6, 10

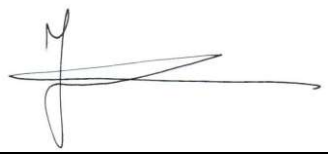
Comments:

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

Comments:

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

Comments:

Name of the main author of the protocol:	Joanna Lem	
Date: dd/Month/year	20 January 2021	
Signature:		

ANNEX 3. ADDITIONAL INFORMATION

Appendix 1. HCP Questionnaire for Rheumatoid Arthritis and/or Psoriatic Arthritis

[SCREENING QUESTION]

[QUESTION APPLIES TO ALL COUNTRIES]

Before starting the survey, we need to ensure that you are eligible for this survey by asking you the following question:

S1. Are you currently employed by Pfizer?

No ☐ *Continue*

Yes ☐ Thank you for your interest. Unfortunately, you are not eligible to participate. *Close* (*SCREEN OUT*)

(yes/no tick box)

If you have any questions, please contact: IQVIA Team at: *xxxxx [to be adapted to the country].*

Kind regards,

IQVIA Team

Start of Interview:

[QUESTIONS ABOUT HCP PRACTICE CHARACTERISTICS]

[QUESTION APPLIES TO ALL COUNTRIES]

Thank you for your interest in this study. This survey should take about 25 minutes to complete and consists of 5 sections. It should be completed in one sitting.

The first section includes questions about your professional background and practice.

D1. What is your main medical specialty? Please select one.

a	Rheumatologist	○
b	Dermatologist	○
c	Other	○

Data: Single punch.

[QUESTION APPLIES TO ALL COUNTRIES]

D2. After completing all specialist training, for how many years have you been in practice? Please select one.

a	Less than 1 year	○
b	1 year to less than 5 years	○
c	5 years to 10 years	○
d	More than 10 years	○

Data: Single punch.

[QUESTIONS ABOUT EXPERIENCE WITH XELJANZ (TOFACITNIB)]

Thank you. The second section of questions asks about your experiences with Xeljanz (tofacitinib).

[QUESTION APPLIES TO ALL COUNTRIES]

S2. Within the past 12 months, have you prescribed tofacitinib for rheumatoid arthritis and/or psoriatic arthritis? Please consider both new and repeat prescriptions.

a	No	☐	Thank you for your interest. Unfortunately, you are not eligible to participate. *Close (SCREEN OUT)*
b	Yes	☐	*Continue*

(yes/no tick box)

[QUESTION APPLIES TO ALL COUNTRIES]

S3. Please indicate the diagnosis for which you prescribed tofacitinib in the past 12 months. Please consider both new and repeat prescriptions. Select all responses that apply.

a	Rheumatoid arthritis	☐	*Continue*
b	Psoriatic arthritis	☐	*Continue*

Data: Multiple punch.

[QUESTION APPLIES TO ALL COUNTRIES]

Q1. When was the last time you prescribed tofacitinib? Please consider both new and repeat prescriptions.

a	Within the past 6 months	○
b	More than 6 months ago	○

Data: Single punch.

[QUESTION APPLIES TO ALL COUNTRIES]

Q2. Within the last 12 months, how many **prescriptions** for tofacitinib have you written for rheumatoid arthritis and/or psoriatic arthritis? Please think of **the total number of prescriptions** – both new and repeat – and not the number of patients. Please select one.

a	Fewer than 10 prescriptions	○
b	10 to 20 prescriptions	○
c	21 to 50 prescriptions	○
d	More than 50 prescriptions	○

Data: Single punch.

[QUESTION APPLIES TO ALL COUNTRIES]

Q3. Within the last 12 months, how many **patients** have you treated with tofacitinib for rheumatoid arthritis and/or psoriatic arthritis? Please select one.

a	Fewer than 5 patients	○
b	5 to 10 patients	○
c	11 to 20 patients	○
d	More than 20 patients	○

Data: Single punch.

[QUESTION APPLIES TO ALL COUNTRIES]

Q4. Which of the following statements best describes your involvement in tofacitinib treatment for most of your patients? Please select one.

a	I'm involved only in the **initiation** of tofacitinib treatment. I refer patients to another practice for follow-up and monitoring.	○
b	I'm involved in **both the initiation and maintenance** of tofacitinib treatment.	○

c	I'm involved only in the **maintenance and monitoring** of patients who were prescribed tofacitinib by another HCP.	○

Data: Single punch.

[QUESTION APPLIES TO ALL COUNTRIES]

Q5. Have you ever participated in a Pfizer-sponsored tofacitinib clinical trial as a healthcare provider? Please select one response.

a	Yes	○
b	No	○
c	I'm not sure	○

Data: Single punch.

[QUESTIONS ABOUT KNOWLEDGE OF KEY RISK MESSAGES FOR TOFACITINIB]

[QUESTION APPLIES TO ALL COUNTRIES]

Next, the third section of questions are designed to assess your understanding of the contraindications and risks of tofacitinib.

Q6. Please select the best response (True, False, I don't know) for each of the following statements about contraindications of tofacitinib.

		True	**False**	**I don't know**
a	Tofacitinib may be administered to patients with severe hepatic impairment.	○	•	○
b	Tofacitinib is contraindicated in patients who are pregnant or lactating.	•	○	○
c	Tofacitinib is contraindicated in patients with moderate renal impairment.	○	•	○
d	Tofacitinib is contraindicated in patients with active tuberculosis (TB) or other severe infections such as sepsis or opportunistic infections.	•	○	○

Data: Single punch per row.
Data: Answer options will be displayed in a random order for each survey participant.
Answer: Points a and c are wrong answers.

[QUESTION APPLIES TO ALL COUNTRIES]

Q7. Please select the best response (True, False, I don't know) for each of the following statements about the risks and use of tofacitinib.

		True	**False**	**I don't know**
a	Tofacitinib can be used in combination with biologic drugs or potent immunosuppressants, such as azathioprine, cyclosporine, 6-mercaptopurine, or tacrolimus.	○	•	○

b	The possibility exists for tofacitinib to affect host defenses against malignancies.	•	○	○
c	Live vaccines should not be given concurrently with tofacitinib.	•	○	○
d	Prior to administering tofacitinib, it is NOT necessary to check patients' laboratory parameters including lymphocytes, neutrophils, and haemoglobin.	○	•	○
e	Tofacitinib should be used with caution in patients who may be at increased risk for gastrointestinal perforation.	•	○	○
f	When taking tofacitinib, the risk of herpes zoster is increased when the lymphocyte count (ALC) is lower than 1.0 cells x 10^9/L.	•	○	○
g	Tofacitinib should only be considered in patients who are 65 years of age or older if there is no suitable alternative.	•	○	○
h	Tofacitinib 5 mg twice daily does NOT further increase the venous thromboembolism (VTE) risk in patients with existing VTE risk factors.	○	•	○

Data: Single punch per row.
Data: Answer options will be displayed in a random order for each survey participant.
Answer: Points a, d, and h are wrong answers.

[QUESTIONS ABOUT ADHERENCE TO KEY RISK MESSAGES FOR TOFACITINIB]

[QUESTION APPLIES TO ALL COUNTRIES]

For the fourth section of questions, please think about your own clinical practice.

Q8. In your clinical practice, **before starting** a patient on tofacitinib, which of the following do you check or ask?

		Yes	**No**
a	Does this patient have gastroesophageal reflux disease (GORD)?	○	•
b	Is the patient at an increased risk for skin cancer?	•	○
c	Are this patient's immunisations up to date?	•	○
d	Does this patient have a history of hyperthyroidism?	○	•
e	Is this patient at an increased risk for venous thromboembolism (VTE)?	•	○
f	If the patient is over 65 years of age, are there suitable alternative treatments to tofacitinib?	•	○

Data: Single punch per row.
Data: Answer options will be displayed in a random order for each survey participant.
Desired responses: b, c, e, f.

[QUESTIONS ABOUT ADHERENCE TO KEY RISK MESSAGES FOR TOFACITINIB]

[QUESTION APPLIES TO ALL COUNTRIES]

Q9. In your clinical practice, do you perform the following tests to make a decision about whether to **initiate** a patient on tofacitinib (Yes/No)?

		Yes	**No**
a	Screen for viral hepatitis	•	○
b	Perform a urinalysis	○	•
c	Screen for latent or active tuberculosis (TB)	•	○
d	Check lymphocyte count	•	○
e	Check absolute neutrophil count	•	○
f	Check haemoglobin level	•	○
g	Check blood glucose level	○	•

Data: Single punch per row.
Data: Answer options will be displayed in a random order for each survey participant.
Desired responses: a, c, d, e, f.

[QUESTIONS ABOUT KNOWLEDGE OF KEY RISK MESSAGES FOR TOFACITINIB]

[QUESTION APPLIES TO ALL COUNTRIES]

Q10. In your clinical practice, which actions would you take when faced with the following scenarios during tofacitinib **treatment maintenance**? **Assume in all scenarios that the patient is receiving tofacitinib 5 mg twice daily.**

Select the best response for each scenario: "I would discontinue tofacitinib," "I would interrupt dosing," "I would lower the dose," OR "I would take no action."

		I would discontinue tofacitinib	**I would interrupt dosing**	**I would lower the dose**	**I would take no action**
a	The patient's neutrophil count is less than 0.50 cells x 10^9/L. This is confirmed by repeat testing.	•	○	○	○
b	The patient's lymphocyte count is between 0.50-0.75 cells x 10^9/L. This is confirmed by repeat testing.	○	•	○	○
c	The patient develops a serious infection, an opportunistic infection or sepsis.	○	•	○	○
d	The patient develops severe hepatic impairment (Child Pugh C).	•	○	○	○
e	The patient's haemoglobin level is <8 g/dl. This is confirmed by repeat testing.	○	•	○	○
f	The patient has a suspected venous thromboembolism (VTE).	•	○	○	○

Data: Single punch per row.
Data: Answer options will be displayed in a random order for each survey participant.
Answer: The black circles indicate a desired response.

[QUESTIONS ABOUT ADHERENCE TO KEY RISK MESSAGES FOR TOFACITINIB]

[QUESTION APPLIES TO ALL COUNTRIES]

Q11. In your clinical practice, how frequently do you perform each of these activities when **initiating treatment** with tofacitinib? Please select the best response: "Always," "Sometimes," or "Never".

		Always	**Sometimes**	**Never**
a	Give the tofacitinib patient alert card to the patient.	•	•	○
b	Advise the patient to inform you immediately if they experience any of the symptoms on the tofacitinib patient alert card.	•	•	○
c	Advise patients to carry the tofacitinib patient alert card with them, particularly when they visit a doctor, a hospital, or Accident and Emergency.	•	•	○
d	Discuss the signs and symptoms of venous thromboembolism (VTE) with the patient.	•	•	○

Data: Multiple punch.
Answer: The black circles indicate a desired response.

[SOURCE OF HCPs' INFORMATION ON THE SAFETY OF TOFACITINIB]

[QUESTION APPLIES TO ALL COUNTRIES]

The final set of questions asks about sources of information on tofacitinib.

Q12. Which of the following is your **primary source** of safety and prescribing information for tofacitinib? Please select one.

a	Educational materials (documents designed for the patient and the physician, such as the tofacitinib prescriber brochure, the prescriber initiation and maintenance checklists, and the patient alert card)	○
b	Summary of Product Characteristics (Label)	○
c	National Health Authority website/National formulary website	○
d	Pharmaceutical company website	○
e	Do not know/recall the source	○
f	Other	○

Data: Single punch.
Data: Answer options will be displayed in a random order for each survey participant, with an exception for "Do not know" and "Other"– always keep these as the last two options.

[QUESTIONS ABOUT AWARENESS (RECEIPT) AND UTILISATION OF TOFACITINIB aRMM MATERIALS]

[QUESTION APPLIES TO ALL COUNTRIES]

Q13.1a. Have you ever received a **prescriber brochure for tofacitinib**? Please select one.

□ Yes

□ No

□ I don't remember

Data: Single punch.

[QUESTION APPLIES TO ALL COUNTRIES, EXCEPT POLAND]

Q13.1b. The **prescriber brochure for tofacitinib** was updated in 2020. Did you receive a prescriber brochure after February 2020? Please select one.

□ Yes

□ No

□ I don't remember

Data: Single punch.
Ask only if Yes in Q13.1a.

[QUESTION APPLIES TO POLAND ONLY]

Q13.1b. The **prescriber brochure for tofacitinib** was updated in 2020. Did you receive a prescriber brochure after January 2020? Please select one.

□ Yes

□ No

□ I don't remember

Data: Single punch.
Ask only if Yes in Q13.1a.

[QUESTION APPLIES TO ALL COUNTRIES]

Q13.2. Have you read the **prescriber brochure for tofacitinib**? Please select one.

□ Yes, all of it

□ Yes, some of it

□ No, I did not read it

□ I don't remember

Data: Single punch.

Ask only if Yes in Q13.1a.

[QUESTION APPLIES TO ALL COUNTRIES]

Q13.3. How useful or not useful do you find the **prescriber brochure for tofacitinib** in your clinical practice?

□ Very useful

□ Somewhat useful

□ Not useful

Data: Single punch.
Ask only if Yes in Q13.1a.

[QUESTION APPLIES TO ALL COUNTRIES EXCEPT GERMANY]

Q14.1a. Have you ever received the **prescriber treatment initiation checklist for tofacitinib**? Please select one.

□ Yes

□ No

□ I don't remember

Data: Single punch.

[QUESTION APPLIES TO ALL COUNTRIES EXCEPT GERMANY and POLAND]

Q14.1b. Did you receive the **prescriber treatment initiation checklist for tofacitinib** after February 2020? Please select one.

□ Yes

□ No

□ I don't remember

Data: Single punch.
Ask only if Yes in Q14.1a.

[QUESTION APPLIES TO POLAND ONLY]

Q14.1b. Did you receive the **prescriber treatment initiation checklist for tofacitinib** after January 2020? Please select one.

□ Yes

□ No

□ I don't remember

Data: Single punch.
Ask only if Yes in Q14.1a.

[QUESTION APPLIES TO ALL COUNTRIES EXCEPT GERMANY]

Q14.2. How often do you use the **prescriber treatment initiation checklist for tofacitinib** when writing a new prescription of tofacitinib for a patient? Please select one.

□ All of the time

□ Most of the time

□ Some of the time

□ Never

Data: Single punch.
Ask only if Yes in Q14.1a.

[QUESTION APPLIES TO ALL COUNTRIES EXCEPT GERMANY]

Q14.3. How useful or not useful do you find the **prescriber treatment initiation checklist for tofacitinib** in your clinical practice? Please select one.

□ Very useful

□ Somewhat useful

□ Not useful

Data: Single punch.
Ask only if Yes in Q14.1a.

[QUESTION APPLIES TO ALL COUNTRIES EXCEPT GERMANY]

Q15.1a. Have you ever received the **prescriber treatment maintenance checklist for tofacitinib**? Please select one.

□ Yes

□ No

□ I don't remember

Data: Single punch.

[QUESTION APPLIES TO ALL COUNTRIES EXCEPT GERMANY and POLAND]

Q15.1b. Did you receive the **prescriber treatment maintenance checklist for tofacitinib** after February 2020? Please select one.

□ Yes

□ No

□ I don't remember

Data: Single punch.
Ask only if Yes in Q15.1a.

[QUESTION APPLIES TO POLAND ONLY]

Q15.1b. Did you receive the **prescriber treatment maintenance checklist for tofacitinib** after January 2020? Please select one.

□ Yes

□ No

□ I don't remember

Data: Single punch.
Ask only if Yes in Q15.1a.

[QUESTION APPLIES TO ALL COUNTRIES, EXCEPT GERMANY]

Q15.2. How often do you use the **prescriber treatment maintenance checklist for tofacitinib** when writing a maintenance prescription of tofacitinib for a patient? Please select one.

□ All of the time

□ Most of the time

□ Some of the time

□ Never

Data: Single punch.
Ask only if Yes in Q15.1a.

[QUESTION APPLIES TO ALL COUNTRIES EXCEPT GERMANY]

Q15.3. How useful or not useful do you find the **prescriber treatment maintenance checklist for tofacitinib** in your clinical practice? Please select one.

□ Very useful

□ Somewhat useful

□ Not useful

Data: Single punch.
Ask only if Yes in Q15.1a.

[QUESTION APPLIES TO GERMANY ONLY]

Q14.1.i.a. Have you ever received the **prescriber treatment checklist for tofacitinib**? Please select one.

□ Yes

□ No

□ I don't remember

Data: Single punch.

[QUESTION APPLIES TO GERMANY ONLY]

Q14.1.i.b. Did you receive the **prescriber treatment checklist for tofacitinib** after February 2020? Please select one.

□ Yes

□ No

□ I don't remember

Data: Single punch.
Ask only if Yes in Q14.1.i.a.

[QUESTION APPLIES TO GERMANY ONLY]

Q14.2.i. How often do you use the **prescriber treatment checklist for tofacitinib** when writing **a new prescription** of tofacitinib for a patient? Please select one.

□ All of the time

□ Most of the time

□ Some of the time

□ Never

Data: Single punch.
Ask only if Yes in Q14.1.i.a.

[QUESTION APPLIES TO GERMANY ONLY]

Q14.3.i. How often do you use the **prescriber treatment checklist for tofacitinib** when writing a **maintenance prescription** of tofacitinib for a patient? Please select one.

□ All of the time

□ Most of the time

□ Some of the time

□ Never

Data: Single punch.
Ask only if Yes in Q14.1.i.a.

[QUESTION APPLIES TO GERMANY ONLY]

Q14.4.i. How useful or not useful do you find the **prescriber treatment checklist for tofacitinib** in your clinical practice? Please select one.

□ Very useful

□ Somewhat useful

□ Not useful

Data: Single punch.
Ask only if Yes in Q14.1.i.a.

[QUESTION APPLIES TO ALL COUNTRIES]

Q16.1a. Have you ever received a supply of **tofacitinib patient alert cards**? This is a card which is designed to be given to patients. Please select one.

□ Yes

□ No

□ I don't remember

Data: Single punch.

[QUESTION APPLIES TO ALL COUNTRIES. EXCEPT FOR POLAND]

Q16.1b. Did you receive a supply of **tofacitinib patient alert cards** after February 2020? Please select one.

□ Yes

□ No

□ I don't remember

Data: Single punch.
Ask only if Yes in Q16.1a.

[QUESTION APPLIES TO POLAND ONLY]

Q16.1b. Did you receive a supply of **tofacitinib patient alert cards** after January 2020? Please select one.

□ Yes

□ No

□ I don't remember

Data: Single punch.
Ask only if Yes in Q16.1a.

[QUESTION APPLIES TO ALL COUNTRIES]

Q16.2. How useful or not useful did you find the **tofacitinib patient alert card** in your clinical practice?

□ Very useful

□ Somewhat useful

□ Not useful

Data: Single punch.
Ask only if Yes in Q16.1a.

[QUESTION APPLIES TO ALL COUNTRIES]

Q17.1 Are you aware of a **prescriber website for tofacitinib** where you can obtain prescribing information and where you can view and/or download the tofacitinib prescriber brochure, prescriber treatment checklists, and patient alert card? Please select one.

□ Yes

□ No

Data: Single punch.

[QUESTION APPLIES TO ALL COUNTRIES]

Q17.2. Have you ever visited the **prescriber website for tofacitinib**? Please select one.

□ Yes

□ No

□ I don't remember

Data: Single punch.
Ask only if Yes in Q17.1

[QUESTION APPLIES TO ALL COUNTRIES]

Q17.3. How useful or not useful do you find the **prescriber website for tofacitinib** in your clinical practice? Please select one.

□ Very useful

□ Somewhat useful

□ Not useful

Data: Single punch.
Ask only if Yes in Q17.2.

Thank you for your participation in this survey

IQVIA Team

Appendix 2. HCP Questionnaire for Ulcerative Colitis

[SCREENING QUESTION]

[QUESTION APPLIES TO ALL COUNTRIES]

Before starting the survey, we need to ensure that you are eligible for this survey by asking you the following question:

S1. Are you currently employed by Pfizer?

No ☐ *Continue*

Yes ☐ Thank you for your interest. Unfortunately, you are not eligible to participate. *Close (SCREEN OUT)*.

(yes/no tick box)

If you have any questions, please contact: IQVIA Team at: *xxxxx [to be adapted to the country]*.

Kind regards,

IQVIA Team

Start of Interview:

[QUESTIONS ABOUT HCP PRACTICE CHARACTERISTICS]

[QUESTION APPLIES TO ALL COUNTRIES]

Thank you for your interest in this study. This survey should take about 25 minutes to complete and consists of 5 sections. It should be completed in one sitting.

The first section includes questions about your professional background and practice.

D1. What is your main medical specialty? Please select one.

a	Gastroenterologist	○
b	Other	○

Data: Single punch.

[QUESTION APPLIES TO ALL COUNTRIES]

D2. After completing all specialist training, for how many years have you been in practice? Please select one.

a	Less than 1 year	○
b	1 year to less than 5 years	○
c	5 years to 10 years	○
d	More than 10 years	○

Data: Single punch.

[QUESTIONS ABOUT EXPERIENCE WITH XELJANZ (TOFACITINIB)]

Thank you. The second section of questions asks about your experiences with Xeljanz (tofacitinib).

[QUESTION APPLIES TO ALL COUNTRIES]

S2. Within the past 12 months, have you prescribed tofacitinib for ulcerative colitis? Please consider both new and repeat prescriptions.

a	No	☐	Thank you for your interest. Unfortunately, you are not eligible to participate. *Close (SCREEN OUT)*
b	Yes	☐	*Continue*

(yes/no tick box)

[QUESTION APPLIES TO ALL COUNTRIES]

Q1. When was the last time you prescribed tofacitinib? Please consider both new and repeat prescriptions. Please select one response.

a	Within the past 6 months	○
b	More than 6 months ago	○

Data: Single punch.

[QUESTION APPLIES TO ALL COUNTRIES]

Q2. Within the last 12 months, how many **prescriptions** for tofacitinib have you written for ulcerative colitis? Please think of **the total number of prescriptions** – both new and repeat – and not the number of patients. Please select one.

a	Fewer than 10 prescriptions	○
b	10 to 20 prescriptions	○
c	21 to 50 prescriptions	○
d	More than 50 prescriptions	○

Data: Single punch.

[QUESTION APPLIES TO ALL COUNTRIES]

Q3. Within the last 12 months, how many **patients** have you treated with tofacitinib for ulcerative colitis? Please select one.

a	Fewer than 5 patients	○
b	5 to 10 patients	○
c	11 to 20 patients	○
d	More than 20 patients	○

Data: Single punch.

[QUESTION APPLIES TO ALL COUNTRIES]

Q4. Which of the following statements best describes your involvement in tofacitinib treatment for most of your patients? Please select one.

a	I'm involved only in the **initiation** of tofacitinib treatment. I refer patients to another practice for follow up and monitoring.	○
b	I'm involved in **both the initiation and maintenance** of tofacitinib treatment.	○
c	I'm involved only in the **maintenance and monitoring** of patients who were prescribed tofacitinib by another HCP.	○

Data: Single punch.

[QUESTION APPLIES TO ALL COUNTRIES]

Q5. Have you ever participated in a Pfizer-sponsored tofacitinib clinical trial as a healthcare provider? Please select one response.

a	Yes	○
b	No	○
c	I'm not sure	

Data: Single punch.

[QUESTIONS ABOUT KNOWLEDGE OF KEY RISK MESSAGES FOR TOFACITINIB]

[QUESTION APPLIES TO ALL COUNTRIES]

Next, the third section of questions are designed to assess your understanding of the contraindications and risks of tofacitinib.

Q6. Please select the best response (True, False, I don't know) for each of the following statements about contraindications of tofacitinib.

		True	**False**	**I don't know**
a	Tofacitinib may be administered to patients with severe hepatic impairment.	○	•	○
b	Tofacitinib is contraindicated in patients who are pregnant or lactating.	•	○	○
c	Tofacitinib is contraindicated in patients with moderate renal impairment.	○	•	○
d	Tofacitinib is contraindicated in patients with active tuberculosis (TB) or other severe infections such as sepsis or opportunistic infections.	•	○	○

Data: Single punch per row.
Data: Answer options will be displayed in a random order for each survey participant.
Answer: Points a and c are wrong answers.

[QUESTIONS ABOUT KNOWLEDGE OF KEY RISK MESSAGES FOR TOFACITINIB]

[QUESTION APPLIES TO ALL COUNTRIES]

Q7. Please select the best response (True, False, I don't know) for each of the following statements about risks and use of tofacitinib.

		True	False	I don't know
a	Tofacitinib can be used in combination with biologic drugs or potent immunosuppressants, such as azathioprine, cyclosporine, 6-mercaptopurine, or tacrolimus.	○	•	○
b	The possibility exists for tofacitinib to affect host defenses against malignancies.	•	○	○
c	Live vaccines should not be given concurrently with tofacitinib.	•	○	○
d	Prior to administering tofacitinib, it is NOT necessary to check patients' laboratory parameters including lymphocytes, neutrophils, and haemoglobin.	○	•	○
e	Tofacitinib should be used with caution in patients who may be at increased risk for gastrointestinal perforation.	•	○	○
f	When taking tofacitinib, the risk of herpes zoster is increased when the lymphocyte count (ALC) is lower than 1.0 cells x 109/L.	•	○	○
g	Tofacitinib should only be considered in patients who are 65 years of age or older if there is no suitable alternative.	•	○	○
h	Assuming there are other treatment options, tofacitinib 10 mg twice daily can be used in patients with venous thromboembolism (VTE) risk factors.	○	•	○

Data: Single punch per row.
Data: Answer options will be displayed in a random order for each survey participant.
Answer: Points a, d, and h are wrong answers.

[QUESTIONS ABOUT ADHERENCE TO KEY RISK MESSAGES FOR TOFACITINIB]

[QUESTION APPLIES TO ALL COUNTRIES]

For the fourth set of questions, please think about your own clinical practice.

Q8. In your clinical practice, **before starting** a patient on tofacitinib, which of the following do you check or ask?

		Yes	**No**
a	Does this patient have gastroesophageal reflux disease (GORD)?	○	•
b	Is the patient at an increased risk for skin cancer?	•	○
c	Are this patient's immunisations up to date?	•	○
d	Does this patient have a history of hyperthyroidism?	○	•
e	Is this patient at an increased risk for venous thromboembolism (VTE)?	•	○
f	If the patient is over 65 years of age, are there suitable alternative treatments to tofacitinib?	•	○

Data: Single punch per row. Data: Answer options will be displayed in a random order for each survey participant.
Desired responses: b, c, e, f.

[QUESTIONS ABOUT ADHERENCE TO KEY RISK MESSAGES FOR TOFACITINIB]

[QUESTION APPLIES TO ALL COUNTRIES]

Q9. In your clinical practice, do you perform the following tests to make a decision about whether to **initiate** a patient on tofacitinib (Yes/No)?

		Yes	**No**
a	Screen for viral hepatitis	•	○
b	Perform a urinalysis	○	•
c	Screen for latent or active tuberculosis (TB)	•	○
d	Check lymphocyte count	•	○
e	Check absolute neutrophil count	•	○
f	Check haemoglobin level	•	○
g	Check blood glucose level	○	•

Data: Single punch per row.
Data: Answer options will be displayed in a random order for each survey participant.
Desired responses: a, c, d, e, f.

[QUESTIONS ABOUT KNOWLEDGE OF KEY RISK MESSAGES FOR TOFACITINIB]

[*QUESTION APPLIES TO ALL COUNTRIES]*

Q10. In your clinical practice, which actions would you take when faced with the following scenarios during tofacitinib **treatment maintenance**? **Assume in all scenarios that the patient is receiving tofacitinib 5 mg twice daily unless otherwise noted.**

Select the best response for each scenario: "I would discontinue tofacitinib," "I would interrupt dosing," "I would lower the dose," OR "I would take no action."

		I would discontinue tofacitinib	I would interrupt dosing	I would lower the dose	I would take no action
a	The patient's neutrophil count is less than 0.50 cells x 109/L. This is confirmed by repeat testing.	•	○	○	○
b	The patient's lymphocyte count is between 0.50-0.75 cells x 109/L. This is confirmed by repeat testing.	○	•	○	○
c	The patient's lymphocyte count is between 0.50-0.75 cells x 109/L. This is confirmed by repeat testing. The **patient is receiving tofacitinib 10 mg twice daily for ulcerative colitis**.	○	○	•	○
d	The patient develops a serious	○	•	○	○

		I would discontinue tofacitinib	I would interrupt dosing	I would lower the dose	I would take no action
	infection, an opportunistic infection or sepsis.				
e	The patient develops severe renal impairment (creatinine clearance <30 mL/min) and is taking **tofacitinib 10 mg twice daily for ulcerative colitis**.	○	○	•	○
f	The patient develops severe hepatic impairment (Child Pugh C).	•	○	○	○
g	The patient's haemoglobin level is <8 g/dl. This is confirmed by repeat testing.	○	•	○	○
h	The patient has a suspected venous thromboembolism (VTE).	•	○	○	○

Data: Multiple punch.
Data: Answer options will be displayed in a random order for each survey participant.
Answer: The black circles indicate a desired response.

[QUESTIONS ABOUT ADHERENCE TO KEY RISK MESSAGES FOR TOFACITINIB]

[QUESTION APPLIES TO ALL COUNTRIES]

Q11. In your clinical practice, how frequently do you perform each of these activities when **initiating treatment** with tofacitinib? Please select the best response: "Always," "Sometimes," or "Never".

		Always	**Sometimes**	**Never**
a	Give the tofacitinib patient alert card to the patient.	•	•	○
b	Advise the patient to inform you immediately if they experience any of the symptoms on the tofacitinib patient alert card.	•	•	○
c	Advise patients to carry the tofacitinib patient alert card with them, particularly when they visit a doctor, a hospital, or Accident and Emergency.	•	•	○
d	Discuss the signs and symptoms of venous thromboembolism (VTE) with the patient.	•	•	○

Data: Multiple punch.
Answer: The black circles indicate a desired response.

[SOURCE OF HCPs' INFORMATION ON THE SAFETY OF TOFACITINIB]

[QUESTION APPLIES TO ALL COUNTRIES, EXCEPT FOR GERMANY]

The final set of questions asks about sources of information on tofacitinib.

Q12. Which of the following is your **primary source** of safety and prescribing information for tofacitinib? Please select one.

a	Educational materials (documents designed for the patient and the physician, such as the tofacitinib prescriber brochure, the prescriber initiation and maintenance checklists, and the patient alert card)	○
b	Summary of Product Characteristics (Label)	○
c	National Health Authority website/National formulary website	○
d	Pharmaceutical company website	○
e	Do not know/recall the source	○
f	Other	○

Data: Single punch.
Data: Answer options will be displayed in a random order for each survey participant, with an exception for "Do not know" and "Other"– always keep these as the last two options.

[QUESTIONS ABOUT AWARENESS (RECEIPT) AND UTILISATION OF TOFACITINIB aRMM MATERIALS]

[QUESTION APPLIES TO ALL COUNTRIES]

Q13.1a. Have you ever received a **prescriber brochure for tofacitinib**? Please select one.

□ Yes

□ No

□ I don't remember

Data: Single punch.

[QUESTION APPLIES TO ALL COUNTRIES EXCEPT POLAND]

Q13.1b. The **prescriber brochure for tofacitinib** was updated in 2020. Did you receive a prescriber brochure after February 2020? Please select one.

□ Yes

□ No

□ I don't remember

Data: Single punch.
Ask only if Yes in Q13.1a.

[QUESTION APPLIES TO POLAND ONLY]

Q13.1b. The **prescriber brochure for tofacitinib** was updated in 2020. Did you receive a prescriber brochure after January 2020? Please select one.

□ Yes

□ No

□ I don't remember

Data: Single punch.
Ask only if Yes in Q13.1a.

[QUESTION APPLIES TO ALL COUNTRIES]

Q13.2. Have you read **the prescriber brochure for tofacitinib**? Please select one.

□ Yes, all of it

□ Yes, some of it

□ No, I did not read it

□ I don't remember

Data: Single punch.

Ask only if Yes in Q13.1a.

[QUESTION APPLIES TO ALL COUNTRIES]

Q13.3. How useful or not useful do you find the **prescriber brochure for tofacitinib** in your clinical practice?

□ Very useful

□ Somewhat useful

□ Not useful

Data: Single punch.
Ask only if Yes in Q13.1a.

[QUESTION APPLIES TO ALL COUNTRIES EXCEPT GERMANY]

Q14.1a. Have you ever received the **prescriber treatment initiation checklist for tofacitinib**? Please select one.

□ Yes

□ No

□ I don't remember

Data: Single punch.

[QUESTION APPLIES TO ALL COUNTRIES EXCEPT GERMANY AND POLAND]

Q14.1b. Did you receive the **prescriber treatment initiation checklist for tofacitinib** after February 2020? Please select one.

□ Yes

□ No

□ I don't remember

Data: Single punch.
Ask only if Yes in Q14.1a.

[QUESTION APPLIES TO POLAND ONLY]

Q14.1b. Did you receive the **prescriber treatment initiation checklist for tofacitinib** after January 2020? Please select one.

□ Yes

□ No

□ I don't remember

Data: Single punch.
Ask only if Yes in Q14.1a.

[QUESTION APPLIES TO ALL COUNTRIES EXCEPT GERMANY]

Q14.2. How often do you use the **prescriber treatment initiation checklist for tofacitinib** when writing a new prescription of tofacitinib for a patient? Please select one.

□ All of the time

□ Most of the time

□ Some of the time

□ Never

Data: Single punch.
Ask only if Yes in Q14.1a.

[QUESTION APPLIES TO ALL COUNTRIES EXCEPT GERMANY]

Q14.3. How useful or not useful do you find the **prescriber treatment initiation checklist for tofacitinib** in your clinical practice? Please select one.

□ Very useful

□ Somewhat useful

□ Not useful

Data: Single punch.
Ask only if Yes in Q14.1a.

[QUESTION APPLIES TO ALL COUNTRIES EXCEPT GERMANY]

Q15.1a. Have you ever received the **prescriber treatment maintenance checklist for tofacitinib**? Please select one.

□ Yes

□ No

□ I don't remember

Data: Single punch.

[QUESTION APPLIES TO ALL COUNTRIES EXCEPT GERMANY AND POLAND]

Q15.1b. Did you receive the **prescriber treatment maintenance checklist for tofacitinib** after February 2020? Please select one.

□ Yes

□ No

□ I don't remember

Data: Single punch.
Ask only if Yes in Q15.1a.

[QUESTION APPLIES TO POLAND ONLY]

Q15.1b. Did you receive the **prescriber treatment maintenance checklist for tofacitinib** after January 2020? Please select one.

□ Yes

□ No

□ I don't remember

Data: Single punch.
Ask only if Yes in Q15.1a.

[QUESTION APPLIES TO ALL COUNTRIES EXCEPT GERMANY]

Q15.2. How often do you use the **prescriber treatment maintenance checklist for tofacitinib** when writing a maintenance prescription of tofacitinib for a patient? Please select one.

□ All of the time

□ Most of the time

□ Some of the time

□ Never

Data: Single punch.
Ask only if Yes in Q15.1a.

[QUESTION APPLIES TO ALL COUNTRIES EXCEPT GERMANY]

Q15.3. How useful or not useful do you find the **prescriber treatment maintenance checklist for tofacitinib** in your clinical practice? Please select one.

□ Very useful

□ Somewhat useful

□ Not useful

Data: Single punch.
Ask only if Yes in Q15.1a.

[QUESTION APPLIES TO GERMANY ONLY]

Q14.1.i.a. Have you ever received the **prescriber treatment checklist for tofacitinib**? Please select one.

□ Yes

□ No

□ I don't remember

Data: Single punch.

[QUESTION APPLIES TO GERMANY ONLY]

Q14.1.i.b. Did you receive the **prescriber treatment checklist for tofacitinib** after February 2020? Please select one.

□ Yes

□ No

□ I don't remember

Data: Single punch.
Ask only if Yes in Q14.1.i.a.

QUESTION APPLIES TO GERMANY ONLY]

Q14.2.i. How often do you use the **prescriber treatment checklist for tofacitinib** when writing a new prescription of tofacitinib for a patient? Please select one.

□ All of the time

□ Most of the time

□ Some of the time

□ Never

Data: Single punch.
Ask only if Yes in Q14.1.i.a.

QUESTION APPLIES TO GERMANY ONLY]

Q14.3.i. How often do you use the **prescriber treatment checklist for tofacitinib** when writing a maintenance prescription of tofacitinib for a patient? Please select one.

□ All of the time

□ Most of the time

□ Some of the time

□ Never

Data: Single punch.
Ask only if Yes in Q14.1.i.a.

QUESTION APPLIES TO GERMANY ONLY]

Q14.4.i. How useful or not useful do you find the **prescriber treatment checklist for tofacitinib** in your clinical practice? Please select one.

□ Very useful

□ Somewhat useful

□ Not useful

Data: Single punch.
Ask only if Yes in Q14.1.i.a.

[QUESTION APPLIES TO ALL COUNTRIES]

Q16.1a. Have you ever received a supply of **tofacitinib patient alert cards**? This is a card which is designed to be given to patients. Please select one.

□ Yes

□ No

□ I don't remember

Data: Single punch.
Deliberately skipping a question number in Germany.

[QUESTION APPLIES TO ALL COUNTRIES EXCEPT POLAND]

Q16.1b. Did you receive a supply of **tofacitinib patient alert cards** after February 2020? Please select one.

□ Yes

□ No

□ I don't remember

Data: Single punch.
Ask only if Yes in Q16.1a.

[QUESTION APPLIES TO POLAND ONLY]

Q16.1b. Did you receive a supply of **tofacitinib patient alert cards** after January 2020? Please select one.

□ Yes

□ No

□ I don't remember

Data: Single punch.
Ask only if Yes in Q16.1a.

[QUESTION APPLIES TO ALL COUNTRIES]

Q16.2. How useful or not useful did you find the **tofacitinib patient alert card** in your clinical practice?

□ Very useful

□ Somewhat useful

□ Not useful

Data: Single punch.
Ask only if Yes in Q16.1a.

[QUESTION APPLIES TO ALL COUNTRIES]

Q17.1 Are you aware of a **prescriber website for tofacitinib** where you can obtain prescribing information and where you can view and/or download the tofacitinib prescriber brochure, prescriber treatment checklists, and patient alert card? Please select one.

□ Yes

□ No

Data: Single punch.

[QUESTION APPLIES TO ALL COUNTRIES]

Q17.2. Have you ever visited the **prescriber website for tofacitinib**? Please select one.

□ Yes

□ No

□ I don't remember

Data: Single punch.
Ask only if Yes in Q17.1.

[QUESTION APPLIES TO ALL COUNTRIES]

Q17.3. How useful or not useful do you find the **prescriber website for tofacitinib** in your clinical practice? Please select one.

□ Very useful

□ Somewhat useful

□ Not useful

Data: Single punch.
Ask only if Yes in Q17.2.

Thank you for your participation in this survey

IQVIA Team

Appendix 3. Key Risk Messages and Other Questions About Awareness (Receipt), Utilisation, Practice Characteristics-Crosswalk of Survey Questions to Study Outcomes (Rheumatoid Arthritis and/or Psoriatic Arthritis)

The listed key risk messages were extracted from the Xeljanz Prescriber Brochure. Messages in bold have a corresponding survey question(s). All questions that correspond to key risk messages 1-9 apply to all countries as they are written (i.e., the questions are not worded differently per country). Remaining questions apply to all countries, unless otherwise noted.

Key Risk Message 1: Use in special populations

Patients with renal impairment:

1. No dose adjustment is required in patients with mild (creatinine clearance 50-80 mL/min) or moderate renal impairment (creatinine clearance 30-49 mL/min).

2. **In patients with severe renal impairment (creatinine clearance <30 mL/min), XELJANZ dose should be reduced to 5 mg once daily when the indicated dose in the presence of normal renal function is 5 mg twice daily or 11 mg prolonged-release once daily (RA). XELJANZ dose should be reduced to 5 mg twice daily when the indicated dose in the presence of normal renal function is 10 mg twice daily in patients with UC. Patients with severe renal impairment should remain on a reduced dose even after haemodialysis.**

Patients with hepatic impairment:

3. No dose adjustment is required in patients with mild hepatic impairment (Child Pugh A).

4. In patients with moderate hepatic impairment (Child Pugh B), XELJANZ dose should be reduced to 5 mg once daily when the indicated dose in the presence of normal hepatic function is 5 mg twice daily or 11 mg prolonged-release once daily (RA). XELJANZ dose should be reduced to 5 mg twice daily when the indicated dose in the presence of normal hepatic function is 10 mg twice daily in patients with UC.

5. **XELJANZ is contraindicated in patients with severe hepatic impairment (Child Pugh C).**

Pregnancy and Lactation:

6. Use of XELJANZ during pregnancy is contraindicated.

7. Use of XELJANZ during breastfeeding is contraindicated.

Question No.	Question	Desired Response	Question Category

Q6. Please select the best response (True, False, I don't know) for each of the following statements about contraindications of tofacitinib.			
Q6a	Tofacitinib may be administered to patients with severe hepatic impairment.	False	Knowledge of Key Risk Message
Q6b	Tofacitinib is contraindicated in patients who are pregnant or lactating.	True	Knowledge of Key Risk Message
Q6c	Tofacitinib is contraindicated in patients with moderate renal impairment.	False	Knowledge of Key Risk Message
Q10. In your clinical practice, which actions would you take when faced with the following scenarios during tofacitinib **treatment maintenance**? **Assume in all scenarios that the patient is receiving tofacitinib 5 mg twice daily.** Select the best response for each scenario: "I would discontinue tofacitinib," "I would interrupt dosing," "I would lower the dose," OR "I would take no action."			
Q10d	The patient develops severe hepatic impairment (Child Pugh C).	"I would discontinue tofacitinib"	Knowledge of Key Risk Message
<u>Key Risk Message 2: Combination with biologics and/or other potent immunosuppressants</u> XELJANZ has not been studied and its **use should be avoided in combination with biologics** such as TNF antagonists, IL-1R antagonists, IL-6R antagonists, anti-CD20 monoclonal antibodies, IL-17 antagonists, IL-12/IL-23 antagonists, anti-integrins, and selective co-stimulation modulators **and potent immunosuppressants** such as azathioprine, 6-mercaptopurine, cyclosporine and tacrolimus because of the possibility of increased immunosuppression and increased risk of infection.			
Question No.	Question	Desired Response	Question Category
Q7. Please select the best response (True, False, I don't know) for each of the following statements about the risks and use of tofacitinib.			

Q7a	Tofacitinib can be used in combination with biologic drugs or potent immunosuppressants, such as azathioprine, cyclosporine, 6-mercaptopurine, or tacrolimus	False	Knowledge of Key Risk Message
Key Risk Message 3: Important information on monitoring of laboratory parameters **It is important to check patients' laboratory parameters including lymphocytes, neutrophils, haemoglobin, lipids, and hepatic enzymes. Initiating treatment is not recommended in patients with:** **1. Low absolute lymphocyte count (<0.75 cells x 10^9/L).** **2. Low absolute neutrophil count (<1.0 cells x 10^9/L).** 3. Low haemoglobin (<9 g/dl).			
Question No.	Question	Desired Response	Question Category
Q7. Please select the best response (True, False, I don't know) for each of the following statements about the risks and use of tofacitinib.			
Q7d	Prior to administering tofacitinib, it is NOT necessary to check patients' laboratory parameters including lymphocytes, neutrophils, and haemoglobin.	False	Knowledge of Key Risk Message
Q9. In your clinical practice, do you perform the following tests to make a decision about whether to **initiate** a patient on tofacitinib (Yes/No)?			
Q9b	Perform a urinalysis	No	Adherence to Key Risk Message
Q9d	Check lymphocyte count	Yes	Adherence to Key Risk Message
Q9e	Check absolute neutrophil count	Yes	Adherence to Key Risk Message

Q9f	Check haemoglobin level	Yes	Adherence to Key Risk Message
Q9g	Check blood glucose level	No	Adherence to Key Risk Message
Q10. In your clinical practice, which actions would you take when faced with the following scenarios during tofacitinib **treatment maintenance**? **Assume in all scenarios that the patient is receiving tofacitinib 5 mg twice daily.** Select the best response for each scenario: "I would discontinue tofacitinib," "I would interrupt dosing," "I would lower the dose," OR "I would take no action."			
Q10a	The patient's neutrophil count is less than 0.50 cells x 10^9/L. This is confirmed by repeat testing.	"I would discontinue tofacitinib"	Knowledge of Key Risk Message
Q10b	The patient's lymphocyte count is between 0.50-0.75 cells x 10^9/L This is confirmed by repeat testing.	"I would interrupt dosing"	Knowledge of Key Risk Message
Q10e	The patient's haemoglobin level is <8 g/dl. This is confirmed by repeat testing.	"I would interrupt dosing"	Knowledge of Key Risk Message

Key Risk Message 4: Serious infections (including tuberculosis) and other important infections

XELJANZ should not be initiated in patients with active infections, including localised infections.

The risks and benefits of treatment should be considered prior to initiating tofacitinib in patients:

- **with recurrent infections;**
- **with a history of a serious or an opportunistic infection;**
- **who have resided or travelled in areas of endemic mycoses;**
- **who have underlying conditions that may predispose them to infection; and/or**
- **who are over 65 years of age.**

As there is a higher incidence of infections in the elderly and in the diabetic populations in general, caution should be used when treating the elderly and patients with diabetes. In patients over 65 years of age, tofacitinib should only be considered if no suitable alternative treatment is available.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with XELJANZ. Treatment must be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with XELJANZ should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient, appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

- Evaluate and test the patient for latent or active TB infection. Patients with latent TB should be treated with standard antimycobacterial therapy before administering XELJANZ.

Question No.	Question	Desired Response	Question Category
Q6. Please select the best response (True, False, I don't know) for each of the following statements about contradictions of tofacitinib.			
Q6d	Tofacitinib is contraindicated in patients with active tuberculosis (TB) or other severe infections such as sepsis or opportunistic infections.	True	Knowledge of Key Risk Message

Q8. In your clinical practice, **before starting** a patient on tofacitinib, which of the following do you check or ask?			
Q8f	If the patient is over 65 years of age, are there suitable alternative treatments to tofacitinib?	(selected Yes)	Adherence to Key Risk Message
Q7. Please select the best response (True, False, I don't know) for each of the following statements about the risks and use of tofacitinib.			
Q7g	Tofacitinib should only be considered in patients who are 65 years of age or older if there is no suitable alternative.	True	Knowledge of Key Risk Message
Q9. In your clinical practice, do you perform the following tests to make a decision about whether to **initiate** a patient on tofacitinib (Yes/No)?			
Q9c	Screen for latent or active tuberculosis (TB).	Yes	Adherence to Key Risk Message
Q10. In your clinical practice, which actions would you take when faced with the following scenarios during tofacitinib **treatment maintenance**? **Assume in all scenarios that the patient is receiving tofacitinib 5 mg twice daily.** Select the best response for each scenario: "I would discontinue tofacitinib," "I would interrupt dosing," "I would lower the dose," OR "I would take no action."			
Q10c	The patient develops a serious infection, an opportunistic infection or sepsis.	"I would interrupt dosing"	Knowledge of Key Risk Message

Key Risk Message 5: Viral reactivation (including herpes zoster) and vaccination

Viral reactivation and cases of herpes virus reactivation (e.g., herpes zoster) were observed in clinical studies with XELJANZ. In patients treated with XELJANZ, the risk of herpes zoster appears to be increased in:

1. Japanese and Korean patients;

2. **Patients with an absolute lymphocyte count (ALC) lower than 1.0 cells x 10^9/L;**

3. Patients with long standing rheumatoid arthritis who have previously received two or more prior biological DMARDs; and

4. Patients with UC treated with 10 mg twice daily.

Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with XELJANZ.

Prior to initiating XELJANZ it is recommended that all **patients be brought up to date with all immunisations in agreement with current immunisation guidelines.**

It is recommended that **live vaccines not be given concurrently with XELJANZ**. The decision to use live vaccines prior to XELJANZ treatment should take into account the pre-existing immunosuppression of a given patient.

Question No.	Question	Desired Response	Question Category
Q8. In your clinical practice, **before starting** a patient on tofacitinib, which of the following do you check or ask?			
Q8c	Are this patient's immunisations up to date?	(selected Yes)	Adherence to Key Risk Message
Q7. Please select the best response (True, False, I don't know) for each of the following statements about the risks and use of tofacitinib.			
Q7c	Live vaccines should not be given concurrently with tofacitinib.	True	Knowledge of Key Risk Message
Q7f	When taking tofacitinib, the risk of herpes zoster is increased when the lymphocyte count (ALC) is lower than 1.0 cells x 109/L.	True	Knowledge of Key risk Message

Q9. In your clinical practice, do you perform the following tests to make a decision about whether to **initiate** a patient on tofacitinib (Yes/No)?			
Q9a	Screen for viral hepatitis	Yes	Adherence to Key Risk Message

Key Risk Message 6: Malignancies and lymphoproliferative disorder and non-melanoma skin cancer

The risks and benefits of XELJANZ treatment should be considered prior to initiating therapy in patients with current or a history of malignancy other than a successfully treated non-melanoma skin cancer or when considering continuing XELJANZ in patients who develop a malignancy. **The possibility exists for XELJANZ to affect host defenses against malignancies.**

Non-melanoma skin cancers have been reported in patients treated with XELJANZ. The risk of non-melanoma skin cancers may be higher in patients treated with XELJANZ 10 mg twice daily than in patients treated with 5 mg twice daily. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Question No.	Question	Desired Response	Question Category
Q8. In your clinical practice, **before starting** a patient on tofacitinib, which of the following do you check or ask?			
Q8b	Is the patient at an increased risk for skin cancer?	(selected Yes)	Adherence to Key Risk Message
Q7. Please select the best response (True, False, I don't know) for each of the following statements about the risks and use of tofacitinib.			
Q7b	The possibility exists for tofacitinib to affect host defenses against malignancies.	True	Knowledge of Key Risk Message

Key Risk Message 7: Gastrointestinal perforations

Events of gastrointestinal perforation have been reported in clinical trials although the role of Janus-kinase inhibition in these events is not known.

XELJANZ should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis and patients with concomitant use of corticosteroids and/or nonsteroidal anti-inflammatory medicinal products). Patients presenting with new onset abdominal signs and symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

Question No.	Question	Desired Response	Question Category
Q7. Please select the best response (True, False, I don't know) for each of the following statements about the risks and use of tofacitinib.			
Q7e	Tofacitinib should be used with caution in patients who may be at increased risk for gastrointestinal perforation.	True	Knowledge of Key Risk Message

Key Risk Message 8: Venous thromboembolism (VTE) risk

Serious VTE events including pulmonary embolism (PE), some of which were fatal, and deep vein thrombosis (DVT) have been observed in patients taking tofacitinib. A dose dependent increased risk for VTE was observed in clinical study with tofacitinib, compared to Tumour Necrosis Factor (TNF) inhibitors.

1. Prior to initiation of treatment, prescribers should assess patients for risk factors of VTE. Tofacitinib should be used with caution in patients with known risk factors for VTE, regardless of indication and dosage.
2. Prescribers should discuss the signs and symptoms of VTE with their patients.
3. Prescribers should promptly evaluate patients with signs and symptoms of VTE and discontinue tofacitinib in patients with suspected VTE, regardless of dose or indication.
4. The following recommended doses in RA/PsA should not be exceeded: 5 mg tablets BID (RA/PsA) or 11 mg prolonged release tablets QD (RA).

Question No.	Question	Desired Response	Question Category
Q8. In your clinical practice, **before starting** a patient on tofacitinib, which of the following do you check or ask?			
Q8e	Is this patient at an increased risk for venous thromboembolism (VTE)?	(selected Yes)	Adherence to Key Risk Messages
Q7. Please select the best response (True, False, I don't know) for each of the following statements about the risks and use of tofacitinib.			
Q7h	Tofacitinib 5 mg twice daily does NOT further increase the venous thromboembolism (VTE) risk in patients with existing VTE risk factors.	False	Knowledge of Key Risk Message
Q10. In your clinical practice, which actions would you take when faced with the following scenarios during tofacitinib **treatment maintenance**? **Assume in all scenarios that the patient is receiving tofacitinib 5 mg twice daily.** Select the best response for each scenario: "I would discontinue tofacitinib," "I would interrupt dosing," "I would lower the dose," OR "I would take no action."			

Q10f	The patient has a suspected venous thromboembolism (VTE).	"I would discontinue tofacitinib"	Knowledge of Key Risk Message

Key Risk Message 9: Patient counseling

It is important for prescribers to discuss the risks associated with use of XELJANZ with their patients, and in applicable instances, with their caregivers.

It is important for physicians to:

1. **Provide the patient alert card to each patient who is prescribed with XELJANZ;**
2. **Remind patients to use the patient alert card;**
3. Discuss the risks with each patient and ensure patient understanding of the treatment potential risks; and
4. **Ensure patients carry the patient alert card with them, particularly when they visit a doctor's office and/or the emergency room.**

Question No.	Question	Desired Response	Question Category
[QUESTION APPLIES TO ALL COUNTRIES]			
Q11. In your clinical practice, how frequently do you perform each of these activities when **initiating treatment** with tofacitinib? Please select the best response: "Always," "Sometimes," or "Never."			
Q11a	Give the tofacitinib patient alert card to the patient.	"Always" or "Sometimes"	Adherence to Key Risk Message
Q11b	Advise the patient to inform you immediately if they experience any of the symptoms on the tofacitinib patient alert card.	"Always" or "Sometimes"	Adherence to Key Risk Message
Q11c	Advise patients to carry the tofacitinib patient alert card with them, particularly when they a visit a doctor, a hospital, or Accident and Emergency.	"Always" or "Sometimes"	Adherence to Key Risk Message

Q11d	Discuss the signs and symptoms of venous thromboembolism (VTE) with the patient.	"Always" or "Sometimes"	Adherence to Key Risk Message

[QUESTIONS APPLY TO ALL COUNTRIES] **Wrong Answer Options Not Associated with a Key Risk Message**			
Q8. In your clinical practice, **before starting** a patient on tofacitinib, which of the following do you check or ask?			
Q8a	Does this patient have gastroesophageal reflux disease (GORD)?	(selected No)	Adherence to Key Risk Messages
Q8d	Does this patient have a history of hyperthyroidism?	(selected No)	Adherence to Key Risk Messages

Other questions:

[QUESTION APPLIES TO ALL COUNTRIES] **Consent Question**			
Question No.	Question	Desired Response	Question Category
N/A	Do you agree to proceed with this survey?	Yes	Consent

This question is contained in the invitation and consent form.

[*QUESTIONS APPLY TO ALL COUNTRIES]* **Screening Questions**			
Question No.	Question	Desired Response	Question Category

S1.	Are you currently employed by Pfizer?	No	Screening
S2.	Within the past 12 months have you prescribed tofacitinib for rheumatoid arthritis and/or psoriatic arthritis? Please consider both new and repeat prescriptions.	Yes	Screening
S3.	Please indicate the diagnosis for which you prescribed tofacitinib in the past 12 months. Please consider both new and repeat prescriptions. Select all responses that apply.	Rheumatoid arthritis and/or Psoriatic arthritis	Screening

[QUESTIONS APPLY TO ALL COUNTRIES] **HCP Practice Characteristics**			
Question No.	Question	Desired Response	Question Category
D1.	What is your main medical specialty? Please select one.	N/A	HCP Practice Characteristics
D2.	After completing all specialist training, for how many years have you been in practice? Please select one.	N/A	HCP Practice Characteristics
Q1	When was the last time you prescribed tofacitinib? Please consider both new and repeat prescriptions.	N/A	HCP Practice Characteristics

Q2.	Within the last 12 months, how many **prescriptions** for tofacitinib have you written for rheumatoid arthritis and/or psoriatic arthritis? Please think of **the total number of prescriptions** – both new and repeat – and not the number of patients. Please select one.	N/A	HCP Practice Characteristics
Q3.	Within the last 12 months, how many **patients** have you treated with tofacitinib for rheumatoid arthritis and/or psoriatic arthritis? Please select one.	N/A	HCP Practice Characteristics
Q4.	Which of the following statements best describes your involvement in tofacitinib treatment for most of your patients? Please select one.	N/A	HCP Practice Characteristics
Q5.	Have you ever participated in a Pfizer-sponsored tofacitinib clinical trial as a healthcare provider? Please select one response.	N/A	HCP Practice Characteristics

Awareness (Receipt), Utilisation of and Attitude towards the Xeljanz aRMM Materials				
Question No.	Question	Desired Response	Question Category	Applicable Survey Countries
				All countries
Q13.1a.	Have you ever received a **prescriber brochure for tofacitinib**? Please select one.	Yes	Awareness (Receipt)	
Q13.1b.	The **prescriber brochure for tofacitinib** was updated in 2020. Did you receive a prescriber brochure after February *[January for Poland]* 2020? Please select one.	Yes	Awareness (Receipt)	
Q13.2	Have you read the **prescriber brochure for tofacitinib**? Please select one.	Yes, all of it OR Yes, some of it	Utilisation	
Q13.3	How useful or not useful do you find the **prescriber brochure for tofacitinib** in your clinical practice?	"Very useful" or "Somewhat useful"	Attitude towards the aRMM Materials	

Q14.1a	Have you ever received the **prescriber treatment initiation checklist for tofacitinib**? Please select one.	Yes	Awareness (Receipt)	All Countries Except Germany
Q14.1b.	Did you receive the **prescriber treatment initiation checklist** for tofacitinib after February 2020 *[January 2020 for Poland]* Please select one.	Yes	Awareness (Receipt)	
Q14.2	How often do you use the **prescriber treatment initiation checklist for tofacitinib** when writing a new prescription of tofacitinib for a patient? Please select one.	All of the time Most of the time Some of the time Never	Utilisation	
Q. 14.3	How useful or not useful do you find the **prescriber treatment initiation checklist for tofacitinib** in your clinical practice? Please select one.	Very useful Somewhat useful Not useful	Utilisation	

Q15.1a	Have you ever received the **prescriber treatment maintenance checklist for tofacitinib**? Please select one.	Yes	Awareness (Receipt)	All countries, except Germany
Q15.1b.	Did you receive the **prescriber treatment maintenance checklist for tofacitinib** after February 2020 [*January 2020 for Poland]?* Please select one.	Yes	Awareness (Receipt)	All countries, except Germany
Q15.2.	How often do you use the **prescriber treatment maintenance checklist for tofacitinib** when writing a maintenance prescription of tofacitinib for a patient? Please select one.	All of the time Most of the time Some of the time Never	Utilisation.	

Q15.3	How useful or not useful do you find **the prescriber treatment maintenance checklist for tofacitinib** in your clinical practice? Please select one.	Very useful Somewhat useful Not useful	Attitude towards the aRMM Materials	
Q14.1.i.a	Have you ever received the **prescriber treatment checklist for tofacitinib**? Please select one.	Yes	Awareness (Receipt)	Germany only
Q14.1.i.b	Did you receive the **prescriber treatment checklist for tofacitinib** after February 2020? Please select one.	Yes	Awareness (Receipt)	
Q14.2.i	How often do you use the **prescriber treatment checklist for tofacitinib** when writing **a new prescription** of tofacitinib for a patient? Please select one.	All of the time Most of the time Some of the time Never	Utilisation	

Q14.3.i.	How often do you use the **prescriber treatment checklist for tofacitinib** when writing a **maintenance prescription** of tofacitinib for a patient? Please select one.	"All of the time", "Most of the time" or "Some of the time"	Utilisation	
Q14.4.i.	How useful or not useful do you find the **prescriber treatment checklist for tofacitinib** in your clinical practice? Please select one.	Very useful Somewhat useful Not useful	Utilisation	
Q14.5.i.	How useful or not useful do you find the **prescriber treatment checklist for tofacitinib** in your clinical practice? Please select one.	"Very useful" or "Somewhat useful"	Attitude towards the aRMM Materials	
Q16.1a.	Have you ever received a supply of **tofacitinib patient alert cards**? This is a card which is designed to be given to patients. Please select one.	Yes	Awareness (Receipt)	All Countries

Q16.1b	Did you receive a supply of **tofacitinib patient alert cards** after February 2020 [*January 2020 for Poland]*? Please select one.	Yes	Awareness (Receipt)	
Q16.2.	How useful or not useful did you find the **tofacitinib patient alert card** in your clinical practice?	Very useful Somewhat useful Not useful	Utilisation	
Q17.1	Are you aware of a **prescriber website for tofacitinib** where you can obtain prescribing information and where you can view and/or download the tofacitinib prescriber brochure, prescriber treatment checklists, and patient alert card? Please select one.	Yes	Awareness	
Q17.2	Have you ever visited the **prescriber website for tofacitinib**? Please select one	Yes	Utilisation	

Q17.3	How useful or not useful do you find the **prescriber website for tofacitinib** in your clinical practice? Please select one.	"Very useful" or "Somewhat useful"	Attitude towards the aRMM Materials	

[QUESTION APPLIES TO ALL COUNTRIES]

Source of HCPs' Information on the Safety of Xeljanz

Question No.	Question	Desired Response	Question Category
Q12.	Which of the following is your **primary source** of safety and prescribing information for tofacitinib? Please select one.	N/A	Source of HCPs' Information on the Safety of Xeljanz

Appendix 4. Key Risk Messages and Other Questions About Awareness (Receipt), Utilisation, Practice Characteristics-Crosswalk of Survey Questions to Study Outcomes (Ulcerative Colitis)

The listed key risk messages were extracted from the Xeljanz Prescriber Brochure. Messages in bold have a corresponding survey question(s). All questions that correspond to key risk messages 1-9 apply to all countries as they are written (i.e., the questions are not worded differently per country). Remaining questions apply to all countries, unless otherwise noted.

Key Risk Message 1: Use in special populations

Patients with renal impairment:

1. No dose adjustment is required in patients with mild (creatinine clearance 50-80 mL/min) or moderate renal impairment (creatinine clearance 30-49 mL/min).

2. **In patients with severe renal impairment (creatinine clearance <30 mL/min), XELJANZ dose should be reduced to 5 mg once daily when the indicated dose in the presence of normal renal function is 5 mg twice daily. XELJANZ dose should be reduced to 5 mg twice daily when the indicated dose in the presence of normal renal function is 10 mg twice daily in patients with UC. Patients with severe renal impairment should remain on a reduced dose even after haemodialysis.**

Patients with hepatic impairment:

3. No dose adjustment is required in patients with mild hepatic impairment (Child Pugh A).

4. In patients with moderate hepatic impairment (Child Pugh B), XELJANZ dose should be reduced to 5 mg once daily when the indicated dose in the presence of normal hepatic function is 5 mg twice daily. XELJANZ dose should be reduced to 5 mg twice daily when the indicated dose in the presence of normal hepatic function is 10 mg twice daily in patients with UC.

5. **XELJANZ is contraindicated in patients with severe hepatic impairment (Child Pugh C).**

Pregnancy and Lactation:

6. Use of XELJANZ during pregnancy is contraindicated.

7. Use of XELJANZ during breastfeeding is contraindicated.

Question No.	Question	Desired Response	Question Category

Q6. Please select the best response (True, False, I don't know) for each of the following statements about contraindications of tofacitinib.			
Q6a	Tofacitinib may be administered to patients with severe hepatic impairment.	False	Knowledge of Key Risk Message
Q6b	Tofacitinib is contraindicated in patients who are pregnant or lactating.	True	Knowledge of Key Risk Message
Q6c	Tofacitinib is contraindicated in patients with moderate renal impairment.	False	Knowledge of Key Risk Message
Q10. In your clinical practice, which actions would you take when faced with the following scenarios during tofacitinib **treatment maintenance**? **Assume in all scenarios that the patient is receiving tofacitinib 5 mg twice daily unless otherwise noted.** Select the best response for each scenario: "I would discontinue tofacitinib," "I would interrupt dosing," "I would lower the dose," OR "I would take no action."			
Q10e	The patient develops severe renal impairment (creatinine clearance <30 mL/min) and is taking **tofacitinib 10 mg twice daily for ulcerative colitis**.	"I would lower the dose"	Knowledge of Key Risk Message
Q10f	The patient develops severe hepatic impairment (Child Pugh C).	"I would discontinue tofacitinib"	Knowledge of Key Risk Message
Key Risk Message 2: Combination with biologics and/or other potent immunosuppressants XELJANZ has not been studied and its **use should be avoided in combination with biologics** such as TNF antagonists, IL-1R antagonists, IL-6R antagonists, anti-CD20 monoclonal antibodies, IL-17 antagonists, IL-12/IL-23 antagonists, anti-integrins, and selective co-stimulation modulators **and potent immunosuppressants** such as azathioprine, 6-mercaptopurine, cyclosporine and tacrolimus because of the possibility of increased immunosuppression and increased risk of infection.			
Question No.	Question	Desired Response	Question Category

Q7. Please select the best response (True, False, I don't know) for each of the following statements about risks and use of tofacitinib.			
Q7a	Tofacitinib can be used in combination with biologic drugs or potent immunosuppressants, such as azathioprine, cyclosporine, 6-mercaptopurine, or tacrolimus.	False	Knowledge of Key Risk Message
Key Risk Message 3: Important information on monitoring of laboratory parameters **It is important to check patients' laboratory parameters including lymphocytes, neutrophils, haemoglobin, lipids, and hepatic enzymes. Initiating treatment is not recommended in patients with:** **1. Low absolute lymphocyte count (<0.75 cells x 10^9/L);** **2. Low absolute neutrophil count (<1.0 cells x 10^9/L);** 3. Low haemoglobin (<9 g/dl).			
Question No.	Question	Desired Response	Question Category
Q7. Please select the best response (True, False, I don't know) for each of the following statements about risks and use of tofacitinib.			
Q7d	Prior to administering tofacitinib, it is NOT necessary to check patients' laboratory parameters including lymphocytes, neutrophils, and haemoglobin.	False	Knowledge of Key Risk Message
Q9. In your clinical practice, do you perform the following tests to make a decision about whether to **initiate** a patient on tofacitinib (Yes/No)?			
Q9b	Perform a urinalysis	No	Adherence to Key Risk Message
Q9d	Check lymphocyte count	Yes	Adherence to Key Risk Message

Q9e	Check absolute neutrophil count	Yes	Adherence to Key Risk Message
Q9f	Check haemoglobin level	Yes	Adherence to Key Risk Message
Q9g	Check blood glucose level	No	Adherence to Key Risk Message
Q10. In your clinical practice, which actions would you take when faced with the following scenarios during tofacitinib **treatment maintenance**? **Assume in all scenarios that the patient is receiving tofacitinib 5 mg twice daily unless otherwise noted.** Select the best response for each scenario: "I would discontinue tofacitinib," "I would interrupt dosing," "I would lower the dose," OR "I would take no action."			
Q10a	The patient's neutrophil count is less than 0.50 cells x 10^9/L. This is confirmed by repeat testing.	"I would discontinue tofacitinib"	Knowledge of Key Risk Message
Q10b	The patient's lymphocyte count is between 0.50-0.75 cells x 10^9/L. This is confirmed by repeat testing.	"I would interrupt dosing"	Knowledge of Key Risk Message
Q10c	The patient's lymphocyte count is between 0.50-0.75 cells x 10^9/L. This is confirmed by repeat testing. **The patient is receiving tofacitinib 10 mg twice daily for ulcerative colitis.**	"I would lower the dose"	Knowledge of Key Risk Message
Q10g	The patient's haemoglobin level is <8 g/dl. This is confirmed by repeat testing	"I would interrupt dosing"	Knowledge of Key Risk Message

Key Risk Message 4: Serious infections (including tuberculosis) and other important infections

XELJANZ should not be initiated in patients with active infections, including localised infections.

The risks and benefits of treatment should be considered prior to initiating tofacitinib in patients:

- with recurrent infections;
- with a history of a serious or an opportunistic infection;
- who have resided or travelled in areas of endemic mycoses;
- who have underlying conditions that may predispose them to infection; and/or
- who are over 65 years of age.

As there is a higher incidence of infections in the elderly and in the diabetic populations in general, caution should be used when treating the elderly and patients with diabetes. In patients over 65 years of age tofacitinib should only be considered if no suitable alternative treatment is available.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with XELJANZ. Treatment must be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with XELJANZ should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient, appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

- Evaluate and test the patient for latent or active TB infection. Patients with latent TB should be treated with standard antimycobacterial therapy before administering XELJANZ.

Question No.	Question	Desired Response	Question Category
Q6. Please select the best response (True, False, I don't know) for each of the following statements about contradictions of tofacitinib.			
Q6d	Tofacitinib is contraindicated in patients with active tuberculosis (TB) or other severe infections such as sepsis or opportunistic infections.	True	Knowledge of Key Risk Message

Q8. In your clinical practice, **before starting** a patient on tofacitinib, which of the following do you check?			
Q8f	If the patient is over 65 years of age, are there suitable alternative treatments to tofacitinib?	Yes	Adherence to Key Risk Message
Q7. Please select the best response (True, False, I don't know) for each of the following statements about risks and use of tofacitinib.			
Q7g	Tofacitinib should only be considered in patients who are 65 years of age or older if there is no suitable alternative.	True	Knowledge of Key Risk Message
Q9. In your clinical practice, do you perform the following tests to make a decision about whether to **initiate** a patient on tofacitinib (Yes/No)?			
Q9c	Screen for latent or active tuberculosis (TB).	Yes	Adherence to Key Risk Message
Q10. In your clinical practice, which actions would you take when faced with the following scenarios during tofacitinib **treatment maintenance**? **Assume in all scenarios that the patient is receiving tofacitinib 5 mg twice daily unless otherwise noted.** Select the best response for each scenario: "I would discontinue tofacitinib," "I would interrupt dosing," "I would lower the dose," OR "I would take no action."			
Q10d	The patient develops a serious infection, an opportunistic infection or sepsis.	"I would interrupt dosing"	Knowledge of Key Risk Message

Key Risk Message 5: Viral reactivation (including herpes zoster) and vaccination

Viral reactivation and cases of herpes virus reactivation (e.g., herpes zoster) were observed in clinical studies with XELJANZ. In patients treated with XELJANZ, the risk of herpes zoster appears to be increased in:

1. Japanese and Korean patients;
2. **Patients with an absolute lymphocyte count (ALC) lower than 1.0 cells x 10^9/L;**
3. Patients with long standing rheumatoid arthritis who have previously received two or more prior biological DMARDs; and
4. Patients with UC treated with 10 mg twice daily.

Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with XELJANZ.

Prior to initiating XELJANZ it is recommended that all **patients be brought up to date with all immunisations in agreement with current immunisation guidelines.**

It is recommended that **live vaccines not be given concurrently with XELJANZ**. The decision to use live vaccines prior to XELJANZ treatment should take into account the pre-existing immunosuppression of a given patient.

Question No.	Question	Desired Response	Question Category
Q8. In your clinical practice, **before starting** a patient on tofacitinib, which of the following do you check or ask?			
Q8c	Are this patient's immunisations up to date?	Yes	Adherence to Key Risk Message
Q7. Please select the best response (True, False, I don't know) for each of the following statements about risks and use of tofacitinib.			
Q7c	Live vaccines should not be given concurrently with tofacitinib.	True	Knowledge of Key Risk Message
Q7f	When taking tofacitinib, the risk of herpes zoster is increased when the lymphocyte count (ALC) is lower than 1.0 cells x 109/L.	True	Knowledge of Key risk Message

Q9. In your clinical practice, do you perform the following tests to make a decision about whether to **initiate** a patient on tofacitinib (Yes/No)?			
Q9a	Screen for viral hepatitis	Yes	Adherence to Key Risk Message
Key Risk Message 6: Malignancies and lymphoproliferative disorder and non-melanoma skin cancer The risks and benefits of XELJANZ treatment should be considered prior to initiating therapy in patients with current or a history of malignancy other than a successfully treated non-melanoma skin cancer or when considering continuing XELJANZ in patients who develop a malignancy. **The possibility exists for XELJANZ to affect host defenses against malignancies.** Non-melanoma skin cancers have been reported in patients treated with XELJANZ. The risk of non-melanoma skin cancers may be higher in patients treated with XELJANZ 10 mg twice daily than in patients treated with 5 mg twice daily. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.			
Question No.	Question	Desired Response	Question Category
Q8. In your clinical practice, **before starting** a patient on tofacitinib, which of the following do you check or ask?			
Q8b	Is the patient at an increased risk for skin cancer?	Yes	Adherence to Key Risk Message
Q7. Please select the best response (True, False, I don't know) for each of the following statements about risks and use of tofacitinib. .			
Q7b	The possibility exists for tofacitinib to affect host defenses against malignancies.	True	Knowledge of Key Risk message

Key Risk Message 7: Gastrointestinal perforations

Events of gastrointestinal perforation have been reported in clinical trials although the role of Janus-kinase inhibition in these events is not known.

XELJANZ should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis and patients with concomitant use of corticosteroids and/or nonsteroidal anti-inflammatory medicinal products). Patients presenting with new onset abdominal signs and symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

Question No.	Question	Desired Response	Question Category
Q7. Please select the best response (True, False, I don't know) for each of the following statements about risks and use of tofacitinib. .			
Q7e	Tofacitinib should be used with caution in patients who may be at increased risk for gastrointestinal perforation.	True	Knowledge of Key Risk Message

Key Risk Message 8: Venous thromboembolism (VTE) risk

Serious VTE events including pulmonary embolism (PE), some of which were fatal, and deep vein thrombosis (DVT) have been observed in patients taking tofacitinib. A dose dependent increased risk for VTE was observed in clinical study with tofacitinib, compared to Tumour Necrosis Factor (TNF) inhibitors.

1. Prior to initiation of treatment, prescribers should assess patients for risk factors of VTE. **Tofacitinib should be used with caution in patients with known risk factors for VTE, regardless of indication and dosage.**
2. Prescribers should discuss the signs and symptoms of VTE with their patients.
3. Prescribers should promptly evaluate patients with signs and symptoms of VTE and **discontinue tofacitinib in patients with suspected VTE, regardless of dose or indication.**
4. Tofacitinib 10 mg film-coated tablets twice daily for maintenance treatment is not recommended in patients with UC who have known venous thromboembolism (VTE) risk factors, unless there is no suitable alternative treatment available.
5. **For patients with UC who are not at increased risk for VTE, tofacitinib 10 mg orally twice daily may be considered** if the patient experiences a decrease in response on tofacitinib 5 mg twice daily and failed to respond to alternative treatment options for ulcerative colitis such as TNF inhibitor treatment. Tofacitinib 10 mg twice daily for maintenance treatment should be used for the shortest duration possible. The lowest effective dose needed to maintain response should be used.

Question No.	Question	Desired Response	Question Category
Q8. In your clinical practice, **before starting** a patient on tofacitinib, which of the following do you check or ask?			
Q8e	Is this patient at an increased risk for venous thromboembolism (VTE)?	(selected Yes)	Adherence to Key Risk Messages
Q7. Please select the best response (True, False, I don't know) for each of the following statements about risks and use of tofacitinib.			
Q7h	Assuming there are other treatment options, tofacitinib 10 mg twice daily can be used in patients with venous thromboembolism (VTE) risk factors.	False	Knowledge of Key Risk Message

Q10. In your clinical practice, which actions would you take when faced with the following scenarios during tofacitinib **treatment maintenance**? **Assume in all scenarios that the patient is receiving tofacitinib 5 mg twice daily unless otherwise noted.** Select the best response for each scenario: "I would discontinue tofacitinib," "I would interrupt dosing," "I would lower the dose," OR "I would take no action."

Q10h	The patient has a suspected venous thromboembolism (VTE).	"I would discontinue tofacitinib"	Knowledge of Key Risk Message

Key Risk Message 9: Patient counseling

It is important for prescribers to discuss the risks associated with use of XELJANZ with their patients, and in applicable instances, with their caregivers.

It is important for physicians to:

1. **Provide the patient alert card to each patient who is prescribed with XELJANZ;**
2. **Remind patients to use the patient alert card;**
3. Discuss the risks with each patient and ensure patient understanding of the treatment potential risks; and
4. **Ensure patients carry the patient alert card with them, particularly when they visit a doctor's office and/or the emergency room.**

Question No.	Question	Desired Response	Question Category

[QUESTION APPLIES TO ALL COUNTRIES]

Q11. In your clinical practice, how frequently do you perform each of these activities when **initiating treatment** with tofacitinib? Please select the best response: "Always," "Sometimes," or "Never."

Q11a	Give the tofacitinib patient alert card to the patient.	"Always" or "Sometimes"	Adherence to Key Risk Message
Q11b	Advise the patient to inform you immediately if they experience any of the symptoms on the tofacitinib patient alert card.	"Always" or "Sometimes"	Adherence to Key Risk Message

Q11c	Advise patients to carry the tofacitinib patient alert card with them, particularly when they visit a doctor, a hospital, or Accident and Emergency.	"Always" or "Sometimes"	Adherence to Key Risk Message
Q11d	Discuss the signs and symptoms of venous thromboembolism (VTE) with the patient.	"Always" or "Sometimes"	Adherence to Key Risk Message

[QUESTION APPLIES TO ALL COUNTRIES] **Wrong Answer Options Not Associated with a Key Risk Message**			
Q8. In your clinical practice, **before starting** a patient on tofacitinib, which of the following do you check or ask?			
Q8a	Does this patient have gastroesophageal reflux disease (GORD)?	No	Adherence to Key Risk Messages
Q8d	Does this patient have a history of hyperthyroidism?	No	Adherence to Key Risk Messages

Other questions:

[QUESTION APPLIES TO ALL COUNTRIES] **Consent Question**			
Question No.	Question	Desired Response	Question Category
N/A	Do you agree to proceed with this survey?	Yes	Consent

This question is contained in the invitation and consent form.

[QUESTIONS APPLY TO ALL COUNTRIES] **Screening Questions**			
Question No.	Question	Desired Response	Question Category
S1.	Are you currently employed by Pfizer?	No	Screening
S2.	Within the past 12 months, have you prescribed tofacitinib for ulcerative colitis? Please consider both new and repeat prescriptions.	Yes	Screening

[QUESTIONS APPLY TO ALL COUNTRIES] **HCP Practice Characteristics**			
Question No.	Question	Desired Response	Question Category
D1.	What is your main medical specialty? Select one.	N/A	HCP Practice Characteristics
D2.	After completing all specialist training, for how many years have you been in practice? Please select one.	N/A	HCP Practice Characteristics
Q1.	When was the last time you prescribed tofacitinib? Please consider both new and repeat prescriptions. Please select one response.	N/A	HCP Practice Characteristics

[QUESTIONS APPLY TO ALL COUNTRIES] **HCP Practice Characteristics**			
Q2.	Within the last 12 months, how many **prescriptions** for tofacitinib have you written for ulcerative colitis? Please think of **the total number of prescriptions** – both new and repeat – and not the number of patients. Please select one.	N/A	HCP Practice Characteristics
Q3.	Within the last 12 months, how many **patients** have you treated with tofacitinib for ulcerative colitis? Please select one.	N/A	HCP Practice Characteristics
Q4.	Which of the following statements best describes your involvement in tofacitinib treatment for most of your patients? Please select one.	N/A	HCP Practice Characteristics
Q5.	Have you ever participated in a Pfizer-sponsored tofacitinib clinical trial as a healthcare provider? Please select one response.	N/A	HCP Practice Characteristics

Awareness (Receipt), Utilisation of and Attitude towards the Xeljanz aRMM Materials				
Question No.	Question	Desired Response	Question Category	Applicable Survey Countries
				All countries
Q13.1a.	Have you ever received a **prescriber brochure for tofacitinib**? Please select one.	Yes	Awareness (Receipt)	
Q13.1b.	The **prescriber brochure for tofacitinib** was updated in 2020. Did you receive a prescriber brochure after February 2020 [*January 2020 for Poland]*? Please select one.	Yes	Awareness (Receipt)	
Q13.2	Have you read **the prescriber brochure for tofacitinib**? Select one.	"Yes, all of it" OR "Yes, some of it"	Utilisation	

Q13.3	How useful or not useful do you find the **prescriber brochure for tofacitinib** in your clinical practice?	"Very useful" or "Somewhat useful"	Attitude towards the aRMM Materials	
				All Countries Except Germany
Q14.1.a	Have you ever received the **prescriber treatment initiation checklist for tofacitinib**? Please select one.	Yes	Awareness (Receipt)	
Q14.1b.	Did you receive the **prescriber treatment initiation checklist for tofacitinib** after February 2020 [*January 2020 for Poland]*? Please select one.	Yes	Awareness (Receipt)	

Q.14.2	How often do you use the **prescriber treatment initiation checklist for tofacitinib** when writing a new prescription of tofacitinib for a patient? Please select one.	"All of the time", "Most of the time" or "Some of the time"	Utilization	
Q14.3	How useful or not useful do you find **the prescriber treatment initiation checklist for tofacitinib** in your clinical practice? Please select one.	"Very useful" or "Somewhat useful"	Attitude towards the aRMM Materials	
Q15.1.a	Have you ever received the **prescriber treatment maintenance checklist for tofacitinib**? Please select one.	Yes	Awareness (Receipt)	All countries, except Germany

Q15.1.b.	Did you receive the **prescriber treatment maintenance checklist for tofacitinib** after February 2020 [*January 2020 for Poland]*? Please select one.	Yes	Awareness (Receipt)	All countries, except Germany
Q15.2	How often do you use the **prescriber treatment maintenance checklist for tofacitinib** when writing a maintenance prescription of tofacitinib for a patient? Please select one.	"All of the time", "Most of the time" or "Some of the time".	Utilization	
Q15.3	How useful or not useful do you find **the prescriber treatment maintenance checklist for tofacitinib** in your clinical practice? Please select one.	"Very useful" or "Somewhat useful"	Attitude towards the aRMM Materials	

Q14.1.i.a	Have you ever received the **prescriber treatment checklist for tofacitinib**? Please select one.	Yes	Awareness (Receipt)	Germany only
Q14.1.i.b	Did you receive the **prescriber treatment checklist for tofacitinib** after February 2020? Please select one.	Yes	Awareness (Receipt)	
Q14.2.i.	How often do you use the **prescriber treatment checklist for tofacitinib** when writing a new prescription of tofacitinib for a patient? Please select one.	"All of the time", "Most of the time" or "Some of the time"	Utilization	
Q14.3.i.	How often do you use the **prescriber treatment checklist for tofacitinib** when writing a maintenance prescription of tofacitinib for a patient? Please select one.	"All of the time", "Most of the time" or "Some of the time"	Utilization	

Q14.4.i.	How useful or not useful do you find the **prescriber treatment checklist for tofacitinib** in your clinical practice? Please select one.	"Very useful" or "Somewhat useful"	Attitude towards the aRMM Materials	
Q16.1a.	Have you ever received a supply of **tofacitinib patient alert cards**? This is a card which is designed to be given to patients. Please select one.	Yes	Awareness (Receipt)	All Countries
Q16.1b	Did you receive a supply of **tofacitinib patient alert cards** after February 2020 [*January 2020 for Poland]*? Please select one.	Yes	Awareness (Receipt)	
Q16.2	How useful or not useful did you find the **tofacitinib patient alert card** in your clinical practice?	"Very useful" or "Somewhat useful"	Attitude towards the aRMM Materials	

A17.1	Are you aware of a **prescriber website for tofacitinib** where you can obtain prescribing information and where you can view and/or download the tofacitinib prescriber brochure, prescriber treatment checklists, and patient alert card? Please select one.	Yes	Awareness	
Q17.2	Have you ever visited the **prescriber website for tofacitinib**? Please select one	Yes	Utilization	
A17.3	How useful or not useful do you find the **prescriber website for tofacitinib** in your clinical practice? Please select one.	"Very useful" or "Somewhat useful"	Attitude towards the aRMM Materials	

[QUESTION APPLIES TO ALL COUNTRIES] **Source of HCPs' Information on the Safety of Xeljanz**			
Question No.	Question	Desired Response	Question Category
Q12	Which of the following is your **primary source** of safety and prescribing information for tofacitinib? Please select one	N/A	Source of HCPs' Information on the Safety of Xeljanz

Appendix 5. Number of Anticipated HCPs* in the OneKey Database, by Country and by Specialty

	Rheumatology	3.5% Response Rate	1.7% Response Rate	Dermatology	3.5% Response Rate	1.7% Response Rate	Gastroenterology	3.5% Response Rate	1.7% Response Rate
France	2,847	100	48	4,094	143	70	4,367	153	74
Germany	1,478	52	25	7,841	274	133	4,350	152	74
Netherlands	397	14	7	761	27	13	762	27	13
Poland	691	24	12	2,308	81	39	502	18	9
Romania	367	13	6	1027	36	17	566	20	10
Spain	1,480	52	25	2,686	94	46	3,842	134	65
Sweden	370	13	6	589	21	10	357	12	6
United Kingdom	1,502	53	26	1,793	63	30	2,706	95	46
Total	**9,132**	**321**	**155**	**21,099**	**739**	**358**	**17,452**	**611**	**297**

* "HCPs" refers to HCPs in the OneKey database whose *primary* specialty is recorded as either dermatology, gastroenterology, or rheumatology (versus any specialty). These counts represent the highest and most relevant possible number of specialists in the OneKey database to be invited to participate in the HCP survey. A proportion of the specialists represented in this table are expected to be eligible to prescribe Xeljanz and/or to treat their patients with Xeljanz.

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