NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

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
Version identifier of the final study report	9.0
Date	02 December 2022
EU Post Authorization Study (PAS) register number	EUPAS43143
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 Authorization 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), psoriatic arthritis (PsA) or ulcerative colitis (UC)? The objectives of this study were 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
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2. 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)
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GEP	Good Epidemiological Practice
GORD	Gastroesophageal reflux disease
GVP	Good Pharmacovigilance Practices
HCP(s)	Healthcare professional(s)
IEA	International Epidemiological Association
IEC	Independent ethics committee
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
MAH	Marketing Authorisation Holder

Abbreviation	Definition
MTX	Methotrexate
NI	Non-interventional
NIS	Non-interventional study
P	Proportion
PAS	Post-authorisation study
PASS	Post-authorisation safety study
PE	Pulmonary embolism
PRAC	Pharmacovigilance Risk Assessment Committee
PsA	Psoriatic arthritis
Q	Question
QC	Quality control
RA	Rheumatoid arthritis
RMP	Risk Management Plan
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SD(s)	Standard deviation(s)
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedures
TB	Tuberculosis
TNF	Tumor necrosis factor
UC	Ulcerative colitis
UK	United Kingdom

Abbreviation	Definition
VTE	Venous thromboembolism
WHO	World Health Organization
YRR	Your Reporting Responsibility

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
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Subcontractor acting as contracted principal investigator:

Name, degree(s)	Title	Affiliation
Krystal Cantos, PhD	Associate Principal, Epidemiology & Drug Safety	IQVIA

4. OTHER RESPONSIBLE PARTIES

Not applicable.

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Registration in the EU PAS register	Prior to the start of data collection in the first survey country (May 2021)	29 September 2021	EU PAS registration number: EUPAS43143
Start of data collection	31 May 2021	01 November 2021	The start of data collection was contingent upon PRAC's endorsement of the protocol amendment and local submissions of the final study protocol.
End of data collection	31 August 2021	24 June 2022	There was variability in start dates (e.g., related to submissions/approvals from local Health Authorities and other privacy and/or disclosure organisations) such that the first survey countries started data collection on 01 November 2021 and the final survey country started data collection 01 April 2022. Thus the end of data collection could not occur until 12 weeks after the latest survey launch date in April 2022.
Final study report	31 August 2022		

6. RATIONALE AND BACKGROUND

Xeljanz® (tofacitinib citrate) is an oral Janus kinase inhibitor first 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] RA is a chronic systemic autoimmune disease that affects approximately 6.2 million people in Europe.[2] It is characterised by inflammation, joint destruction, and progressive disability. Despite a number of treatment options available, many patients do not sustain remission.[3] In December 2019, the EC also approved for RA a prolonged-release film-coated tablet (11 mg), taken once a day (QD).

In June 2018, Xeljanz 5-mg tablet (immediate-release) was approved by the EC, in combination with methotrexate (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.[4] In July 2021, prolonged-release 11 mg QD was also approved for PsA. In July 2018, Xeljanz 5-mg tablet and 10-mg tablet (immediate-release) were approved by the EC for the treatment of moderately-to-severely active ulcerative colitis (UC), a bowel disease characterised by inflammation and ulcers in the colon and rectum, in patients with an inadequate response, a loss of response, or an intolerance to conventional therapy or a biologic agent.

To provide an appropriate tool designed to enhance the awareness and knowledge of HCPs and patients about safety concerns as outlined in the Xeljanz Risk Management Plan [RMP] (version 30.2),[a] the Marketing Authorisation Holder (MAH) implemented additional risk minimisation measure (aRMM), which consists of an educational program intended to enhance the communication of the key risk messages and risk minimisation practices to patients and healthcare professionals (HCPs). The program includes the following 4 components (only 3 in Germany because treatment initiation and maintenance checklists were combined into one checklist):

- Xeljanz Prescriber Brochure;

[a] Safety concerns include: 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.

- Xeljanz Prescriber Treatment *Initiation* Checklist:[b] 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 where a combined Xeljanz Treatment Initiation and Maintenance Checklist was distributed**);

- 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 where a combined Xeljanz Treatment Initiation and Maintenance Checklist was distributed**); and

- Xeljanz Patient Alert Card: to be distributed to patients by HCPs.

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 indication(distribution beginning in August 2018).

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 venous thromboembolism (VTE) events, both for deep venous thrombosis as well as pulmonary embolism, especially in patients with risk factors for VTE. 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. PRAC also concluded that, based on the interim analyses of Study A3921133: *Phase 3b/4 Randomized Safety Endpoint Study of 2 Doses of Tofacitinib in Comparison to A Tumor Necrosis Factor (TNF) Inhibitor in Subjects with Rheumatoid Arthritis*, there is a potential increased risk of mortality. 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]

[b] 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.

The aRMM materials were updated to reflect the findings from the CHMP's re-assessment of the benefit-risk of Xeljanz and were distributed after February 2020 (January 2020 for Poland); the specific distribution date of the updated aRMM materials (hereafter referred to as the "*current aRMM materials*") for each survey country can be found in Table 1.

The MAH evaluated the effectiveness of the aRMM program per the good pharmacovigilance practices (GVP) module XVI. The effectiveness of the aRMM materials was quantitatively evaluated among HCPs who prescribe Xeljanz to patients with RA, PsA, or UC.[c] Data from this study were 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. HCPs are 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 was, "Are the aRMM materials implemented across Europe effective in communicating the key risk messages associated with the use of Xeljanz to healthcare professionals (HCPs) treating patients with RA, PsA or UC?"

Specifically, the objectives of this study were 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.

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

8. AMENDMENTS AND UPDATES

Appendix 8a outlines all amendments to the protocol. Key amendments to the protocol include the following:

- The date for start of data collection was changed due to the Agency's request to review changes to the survey instrument post-user testing; the MAH submitted the updated English version questionnaire;
- The protocol was changed to reflect the changes made to the survey instruments as indicated in Appendix 1 and Appendix 2 of the protocol (primarily to increase readability and clarity); and
- The dates for the registration in the EU PAS register, statistical analysis plan (SAP) finalisation, start of data collection, end of data collection and final study report submission were updated to match the RMP. Justification for milestone changes was communicated to the EMA in a regulatory response as part of Procedure EMEA/H/C/004214/IB/0042/G.

9. RESEARCH METHODS

9.1. Study design

This was a cross-sectional, non-interventional, multimodal survey study conducted among HCPs who prescribed Xeljanz for RA and/or PsA or UC in the 12 months preceding survey administration in 8 European countries.

There were 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"). The surveys were split because some survey questions were specific to prescribing Xeljanz to patients with ulcerative colitis (e.g., related to initiation and maintenance dosing).

The survey study was 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 sufficient time for HCPs to familiarise themselves with the materials and Xeljanz uptake (as applicable), respectively. The dates of survey launch by country are presented in Table 1. The time window for data collection in each country was originally planned for 12 weeks after survey launch but 2 weeks were added to each country's timeline except Romania to account for winter holidays that occurred during the data collection period.

9.2. 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 such as operational feasibility to implement the survey and likeliness to yield a

meaningfully large and representative sample of HCPs treating patients for RA, PsA, or UC. These factors included:

- Highest numbers of potential Xeljanz prescribers (e.g., rheumatologists, dermatologists, and gastroenterologists);
- Highest projected number of patients to be treated with Xeljanz;
- Timing of Xeljanz reimbursement and aRMM materials distribution; and
- Geographic location (the selected countries represent Western, Northern, Southern, and Eastern Europe).

Table 1. Xeljanz Availability with Full Reimbursement, Current aRMM Materials Distribution, and Windows for Survey Data Collection

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)
Germany	RA	May 2017	20 March 2020	23 November 2021 – 02 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	September 2020		
	UC	September 2020		

Table 1. Xeljanz Availability with Full Reimbursement, Current aRMM Materials Distribution, and Windows for Survey Data Collection

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)
Romania	RA	December 2019	26 August 2020	01 April 2022 – 24 June 2022
	PsA	August 2021[d]		
	UC	August 2021[d]		

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

9.3. Subjects

9.3.1. Selection criteria for targeted HCPs

The target study population was specialist HCPs in Europe who are prescribers of Xeljanz for the treatment of RA, PsA, or UC (i.e., rheumatologists, dermatologists, and gastroenterologists), as these were the HCPs who were targeted for the aRMM materials distribution by the MAH. All HCPs from the proprietary IQVIA OneKey database who met the eligibility criteria were invited to participate in the survey (i.e., the **Targeted HCPs**). A description of the IQVIA OneKey database can be found in Section 9.5.

9.3.1.1. Inclusion criteria

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

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

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

3. HCPs who were located in the selected countries.

9.3.1.2. Exclusion criteria

The following was the study exclusion criterion for the **Targeted HCPs**. HCPs were excluded if they met the following criterion:

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

[d] Conditionally reimbursed through cost volume contract with the National Institute of Health.

9.3.2. Inclusion and exclusion criteria for the final study population

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

9.3.2.1. Inclusion criteria

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

1. HCPs who were **Targeted HCPs**;[e]
2. HCPs who agreed 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).

9.3.2.2. Exclusion criterion

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

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

9.4. Variables

9.4.1. Primary endpoints/study outcomes

The following is a summary of the variables that were derived from the survey data to address the primary endpoints/study outcomes. Operational definitions for the primary endpoints/study outcomes are outlined in **Appendix 8b, Table 1**.

1. Objective 1 outcome variables included:
    - Receipt of each of the aRMM materials *ever;*
    - Receipt of each of the current aRMM materials (after February 2020 [January 2020 for Poland]);
    - Number of aRMM materials received *ever;*

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

- Number of current aRMM materials received;
- Utilisation of each of the aRMM materials;
- Number of aRMM materials utilised;
- Awareness of a prescriber website for tofacitinib; and
- Utilisation of the prescriber website for tofacitinib.

1. Objective 2 outcome variables included:
    - Correct answer *to each* of the Knowledge Questions 1-18 (1-20 for the UC survey);
    - Proportion of correct Knowledge Questions in the categories: <70%, 70% to <80%, 80% to <90%, 90% to <100%, 100%; and
    - Number of correct answers to Knowledge Questions 1-18 (1-20 for the UC survey).
2. Objective 3 outcome variables included:
    - Answer that adheres to the risk minimisation practices *for each* of the Adherence Questions 1-17;
    - Proportion of answers that adhere to the risk minimisation practices in the categories: <70%, 70% to <80, ⩾80% to <90%, ⩾90% to <100%, 100%; and
    - Number of answers that adhere to the risk minimisation practices for Adherence Questions 1-17.

9.4.2. Secondary endpoints/study outcomes

The operational definitions for the secondary endpoints/study outcomes are outlined in detail in **Appendix 8b, Table 2**. The following is a summary of the variables that were derived from the survey data to address the secondary endpoints/study outcomes:

- Primary source of HCPs' information on the safety and prescribing information for tofacitinib (for all countries in the RA/PsA survey; for all countries except Germany in the UC survey);
- Attitude toward each of the aRMM materials; and
- Attitude toward the prescriber website for tofacitinib.

9.4.3. Covariates

The operational definitions for study covariates are outlined in detail in **Appendix 8b, Table 3**. The following HCP characteristic variables were derived from the survey data to be used as study covariates:

- HCP specialty;
- Number of years in practice;
- Experience prescribing tofacitinib within the past 12 months for RA and/or PsA (for the RA/PsA survey only);
- Self-reported approximate number of tofacitinib prescriptions written for RA and/or PsA or UC in the past 12 months;
- Self-reported approximate number of patients treated with tofacitinib for RA and/or PsA or UC in the past 12 months;
- Role in providing tofacitinib treatment (i.e., initiation, maintenance, or both); and
- Prior participation in a Pfizer-sponsored tofacitinib clinical trial as a healthcare provider.

9.4.4. Overall effectiveness of aRMM program

The following variables described in Table 2 were derived from the survey data to determine the overall effectiveness of the aRMM program. The operational definitions for the overall effectiveness of the aRMM program are outlined in **Appendix 8b, Table 4**.

Table 2. Overall Effectiveness of aRMM Program

Variable	Effectiveness Criteria
Overall effectiveness of the aRMM program	
Awareness (receipt) ever	Effectiveness threshold: ≥80% of HCPs reporting that they ever received all aRMM materials
Awareness (receipt) for current aRMMs (after February 2020 [January 2020 for Poland])	Effectiveness threshold: ≥80% of HCPs reporting that they received all current aRMM materials
Knowledge	*For the RA/PsA survey:* Effectiveness threshold: ≥80% of HCPs correctly answering ≥14 out of 18 (≥78% [or approximately 80%]) of the knowledge questions *For the UC survey:*

Table 2. Overall Effectiveness of aRMM Program

Variable	Effectiveness Criteria
	Effectiveness threshold: ≥80% of HCPs correctly answering ≥16 out of 20 (≥80%) of the knowledge questions
Adherence	Effectiveness threshold: ≥80% of HCPs providing desirable responses for ≥14 out of 17 (≥82% [or approximately 80%]) of the adherence questions

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

9.4.5. Survey administration and study participation

The operational definitions for the survey administration statistics and study participation are outlined in detail in **Appendix 8b, Table 5**. The following variables were derived from the survey data to assess survey administration and study participation:

- Number of HCPs sent survey invitations (I) – i.e., the "Targeted HCPs";
- Number of HCPs with survey invitations returned as undeliverable (R);
- Number of HCPs who did not respond to the survey invitation;
- Number of HCPs who interacted with the survey;
- Number of HCPs screened for participation (S);
- Survey response proportion (S/[I-R]);
- Number of HCPs eligible for participation (E);
- Eligibility proportion (E/S);
- Number of eligible HCPs who completed the survey (C); and
- Completion proportion (C/E).

9.5. Data sources and measurement

This study involved primary data collection. All data for analyses were collected from HCPs directly via a multimodal survey instrument including closed-ended questions or statements with multiple response choices (i.e., a structured survey questionnaire implemented via Web portal or phone interview; **Appendix 5** [Sample Case Report Form (CRF) / Data Collection Tool (DCT)]) that was written to follow the principles of health literacy and readability. The questionnaire collected information on survey respondent characteristics, the implementation of the aRMM program, HCPs' knowledge of the key risk messages, and HCPs' self-reported adherence to the risk minimisation practices.

9.5.1. Prescriber recruitment

The list of HCPs invited to participate in the survey was 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.[5] Initially created for marketing purposes, it is used in research to recruit HCPs [6-8] and by international organisations to construct HCP census data.[9] 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).

Invitations were issued to HCPs primarily by email, if available; by postal mail; or by phone, according to the country. Invitation letters included an overview of the rationale for the survey and the secure URL to be copied and pasted into their browser.

9.5.2. Subject withdrawal

Each subject was informed that he/she could withdraw from the study at any time and for any reason. Only HCPs with completed surveys were included in the main analysis.

9.5.3. Screening process

HCPs answered a series of screening questions to assess their eligibility to take the survey. Depending on the answers provided for the screening questions, an HCP's survey was either terminated or progressed to the next survey question. Thus, if an HCP was determined to be *ineligible* to continue with the survey study, they were immediately notified with a "thank you" message that survey participation ended. If an HCP was determined to be *eligible*, they were allowed to continue with survey participation.

9.5.4. Data collection process

IQVIA Primary Intelligence was responsible for conducting the survey across all study countries. Data collection lasted 12 weeks in Romania and 14 weeks in all other countries as 2 weeks were added to all data collection windows that included December (to account for winter holidays). The data collection start dates were 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/or other privacy and disclosure organisations, as needed (see Table 1 for study country timelines).

Operators of a call centre specialised in health surveys were assigned to the project and trained on the survey methodology prior to fieldwork. The postal mailings, email contacts, and phone calls were traced using management software. Access to the web survey interface was strictly limited to the invited HCPs, with the possibility to participate only once, which was monitored using a traceability system. The same procedure was followed if the invited HCPs took the survey over the phone.

Data were collected using a data collection tool (DCT) (**Appendix 5**). IQVIA (the study vendor) ensures that the completed DCTs are securely stored on the IQVIA internal server in encrypted electronic form and are password protected to prevent access by unauthorised third parties.

9.5.4.1. User testing of the survey questions

In December 2020, prior to fielding the survey, the survey instrument was pilot tested by Northwestern University or Research Support Services in the UK using a sample of HCPs including two each of rheumatologists, dermatologists, and gastroenterologists, who can potentially prescribe Xeljanz. This qualitative testing assessed comprehension among HCPs of the words, phrases, and response options used in the survey to ensure that the intended content of the questions was adequately conveyed. The feedback received from the pilot testing was incorporated into the final version of the survey instrument (**Appendix 5**).

9.5.4.2. Follow-up reminders

After each contact attempt by IQVIA Primary Intelligence, the OneKey database was cross checked with any correspondence that had an invalid address or incorrect contact details, or that bounced back. An HCP was considered unreachable if they could not 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).

9.6. Bias

Selection bias (volunteer bias)

Since participation in the survey was voluntary, HCPs self-selected into the study resulting in the potential for selection bias such that HCPs willing to participate in the survey may differ in how they respond to survey questions from those who did not participate. Due to the low response rates and possibility of selection bias, the results of this survey may not be generalisable to the entire population of HCPs who prescribe Xeljanz.

To minimise selection bias and to increase the number of responses, the following efforts have been made:

- A paragraph in the introduction to the survey 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 Europe;
- The survey was pilot tested for clarity and surveys were conducted in local languages;
- A multimodal recruitment approach: all HCPs were sent an email, a postal mailing, and/or contacted by phone, when available; and

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

Limitation of human recall

A limitation inherent in most survey research is reliance on a respondent's recall as to whether or not she/he had received materials. If respondents replied that they did not receive a particular tool, the risk minimisation program was evaluated as not having been optimally implemented, though it is possible that prescribers simply did not recall having received the tools that were sent and received. Respondents may also have had an acceptable understanding of the risks and appropriate behaviours despite not having received (or recalled receipt of) the aRMMs.

Additionally, though the administration of surveys to HCPs was planned 6-12 months after the distribution of the current aRMMs to allow sufficient time for aRMM uptake, local regulatory submissions and approvals delayed survey launch to an average of 20 months after the distribution of the current aRMMs in each country. This likely contributed to greater recall error.

Measurement error in survey response

Measurement error refers to the accuracy of survey responses, which may vary depending on HCPs' comprehension of the questions. To reduce measurement error, a pilot testing was conducted which assessed comprehension among HCPs of the words, phrases, and response options used in the survey to ensure that the intended content of the questions was adequately conveyed. The feedback received from the pilot testing were incorporated into the final version of the survey instrument.

Social desirability bias

As in all self-reported surveys, this survey may have suffered from social desirability bias, which refers to the tendency of respondents to give socially desirable/expected responses instead of choosing those reflecting their current knowledge or behaviour.[10] 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 structured questions with pre-defined response choices in the survey could/tends to reduce this bias.[11] Further, for survey questions where the response options were presented in a list, the response options were randomised to minimise positional bias.

9.7. Study size

This was a descriptive study and no comparative analyses were conducted. Thus, the purpose of the sample size calculations provided below was 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 9.4 [Variables]). As P was not known in advance, we considered it to be 50% (maximum uncertainty). Such an assumption yielded the most conservative, i.e., the largest, sample size for a specified margin of error.

Table 3, 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 3. 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 9.4 [Variables]).

Across the 8 survey countries, the MAH aimed 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 was applied, and all completed surveys received during the data collection window were included in the study.

The target sample size proposed was based on the above precision considerations, as well as on the operational feasibility of achieving it. While there were an estimated 47,000 total specialist HCPs (i.e., rheumatologists, dermatologists, gastroenterologists) across the survey

countries, the number of HCPs who *participated* in the survey was limited by the following factors:

- Only a proportion of HCPs met the inclusion/exclusion criteria for **Targeted HCPs** (i.e., have contact information available in OneKey and did not participate in pilot testing of the survey); note that all **Targeted HCPs** were invited to participate;

- An unknown proportion of specialist HCPs were 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 were 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 HCPs who manage patients indicated for Xeljanz, an unknown proportion *would* 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 proportion of 1.5-10% (depending on the country) was expected for this type of survey, with response proportions on the lower end expected as an honorarium was not provided.

Given the sample size that the study achieved (n=164 for PsA/RA survey and n=81 for UC survey), the margins of error were, on average, around 6% and 9%, respectively, though these varied depending on the parameters being estimated.

9.8. Data transformation

Detailed methodology for data transformations, particularly complex transformations (e.g., many raw variables used to derive an analytic variable), were documented in the SAP, which was dated, filed and maintained by the sponsor (**Appendix 4**).

9.9. Statistical methods

9.9.1. Main summary measures

Detailed methodology for summary and statistical analyses of data collected in this study was documented in the SAP (**Appendix 4**).

Categorical variables were presented using frequencies and proportions. For outcome measures of the three main objectives, associated 95% CIs were also calculated; 95% CIs were *not* calculated for other outcomes such as attitude towards the aRMM materials and

Xeljanz Prescribe Website and source of HCPs' information on the safety of Xeljanz. Continuous variables were presented using means, standard deviations (SDs), minimums, 25th percentiles, medians, 75th percentiles, and maximums.

9.9.2. Main statistical methods

The data collected from the RA/PsA survey were analysed separately from the data collected from the UC survey. All primary analyses were conducted using *pooled* data across all countries. For the RA/PsA survey, analyses were additionally pooled across specialties and indications. Analyses were descriptive in nature, and no statistical comparisons within or between countries, specialties, and/or indications were conducted.

Since the distribution of HCPs who prescribe Xeljanz for RA, PsA, or UC in each survey country in the sample of HCPs who completed the survey was different from the underlying population, 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 were weighted to reflect the proportion of HCPs who prescribe Xeljanz across the countries, and *within* each country to reflect the proportion of each HCP specialty authorised to prescribe Xeljanz in that country (applies to the RA/PsA survey only). Because the true number of HCPs who prescribe tofacitinib for RA, PsA, or UC in each survey country is unknown, the number of rheumatologists, dermatologists (for the RA/PsA survey), and gastroenterologists (for the UC survey) identified in the OneKey database was used as a proxy for the true number.

Both unweighted and weighted results are presented in the final study results. The details of the weighting schema are included in the SAP (**Appendix 4**).

9.9.3. Missing values

Only HCPs with completed surveys were included in the main analysis.

9.9.4. Sensitivity analyses

None.

9.9.5. Amendments to the statistical analysis plan

All unplanned, post-hoc analyses and the rationale are described below.

1. In the weighted and unweighted population, HCP self-reported utilisation of the aRMM materials was restricted to those who received the aRMM materials.

   The purpose of this analysis was to avoid an underestimation of utilisation by assessing self-reported utilisation of the aRMM materials among HCPs who self-reported actually receiving the aRMM materials.

2. In the weighted and unweighted population, HCP self-reported utilisation of Xeljanz prescriber website was restricted to those who self-reported being aware of the website.

   The purpose of this analysis was to avoid an underestimation of utilisation by assessing self-reported utilisation of Xeljanz prescriber website among HCPs who self-reported being aware of the website.

3. Analysis for the perceived usefulness of an aRMM material was restricted to HCPs who indicated *ever* receiving the aRMM material.

   The purpose of this analysis was to provide a more meaningful estimate of usefulness because those HCPs who did not receive the aRMM materials would not be able to rate the usefulness of aRMMs.

4. In the unweighted population, HCPs who reported they did not receive or did not remember receiving aRMM materials were reported separately for aRMM materials *ever* or current aRMMs.

   The purpose of this analysis was to gain additional insight into whether HCPs truly reported not receiving aRMM materials versus not remembered receiving them.

5. Analysis for the primary source of HCPs' information on the safety and prescribing information for Xeljanz was restricted to HCPs who self-reported *ever* receiving aRMM materials.

   The purpose of this analysis was to provide a more meaningful estimate of whether aRMMs were an important source of information for HCPs because those HCPs who did not receive the aRMM materials would not report aRMMs as the primary source of information.

The following post-hoc analyses were conducted in the RA/PsA survey only:

6. Selected unweighted analyses (i.e., implementation of the aRMM program, HCPs' knowledge of the key risk messages, HCPs' self-reported adherence to the risk minimisation practices, and overall effectiveness of the aRMM program) were stratified by HCPs' primary source on the safety and prescribing information for Xeljanz (aRMMs, SmPC, and other).

   The purpose of this analysis was to provide additional insight into the effectiveness of aRMMs by comparing the aforementioned measures in HCPs who identified the aRMM educational materials as their primary source of information compared to HCPs who identified the SmPC or other sources.

7. In the unweighted population, HCPs' adherence to key risk messages for select questions with negative responses (False/No) was analysed by utilisation of the aRMM materials.

   The purpose of this analysis was to assess whether the magnitude of social desirability bias varied among those who reported utilising all, some, or none of the aRMM materials. The hypothesis was that HCPs who self-reported utilising all aRMM materials were more susceptible to social desirability bias and thus were more likely to answer 'Yes' to adherence questions with negative responses (False/No).

9.10. Quality control

Quality control (QC) was 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, were conducted within the framework of the IQVIA Quality Management System.

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

- The study QC plan established ownership for the execution of the individual QC steps;
- The Principal in Charge of the study ensured that individuals responsible for the execution of specific QC steps 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 was documented, and included the required corrective actions, if any. The execution of any required corrective action was also documented.

The QC plan was subjected to a final review and approval for sufficiency and completeness from the Principal in Charge of the study. IQVIA had a qualified individual external to the writing team conduct QC reviews of all final deliverables, including 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.

9.11. Protection of human subjects

Subject information and consent

Written informed consent (**Appendix 6**) was obtained prior to the subject entering the study (before initiation of study protocol-specified procedures) by study personnel; the nature, purpose, and duration of the study was explained to each subject. Each subject was informed that he/she could withdraw from the study at any time and for any reason. Each subject was given sufficient time to consider the implications of the study before deciding whether to participate. Subjects who chose to participate signed an informed consent document.

Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

IRB/IEC review was not required in any study countries and a waiver was received from a German IEC.

The following agencies were notified of or reviewed and approved the final protocol, any amendments, and informed consent documentation: L'Agence nationale de sécurité du médicament et des produits de santé (ANSM) in France; the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK; The Federal Institute for Drugs and Medical Devices (BfArM), German Association of Private Health Insurance Funds (PKV), Central Federal Association of the Health Insurance Funds (GKV) and the Federal Association of Panel Doctors (KVB) in Germany; the Medical Product Agency (MPA) in Sweden; and the National Agency for Medicines and Medical Devices (NAMMD) in Romania. No local submissions were required in the Netherlands, Spain, and Poland.

Ethical conduct of the study

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in:

- European Pharmaceutical Marketing Research Association Code of Conduct [12];
- Module XVI of the EMA's Guideline on GVP – Risk minimisation measures: selection of tools and effectiveness indicators [13];
- *Good Pharmacoepidemiology Practices* issued by the International Society for Pharmacoepidemiology [14];
- *Guidelines for Good Epidemiological Practice (GEP)* issued by the International Epidemiological Association (IEA) [15];

- *Good Practices for Outcomes Research* issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) [15];
- *International Ethical Guidelines for Epidemiological Research* issued by the Council for International Organizations of Medical Sciences in collaboration with the World Health Organization (WHO) [16];
- EMA European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology [17]; and
- The US Food and Drug Administration's Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment.[18]

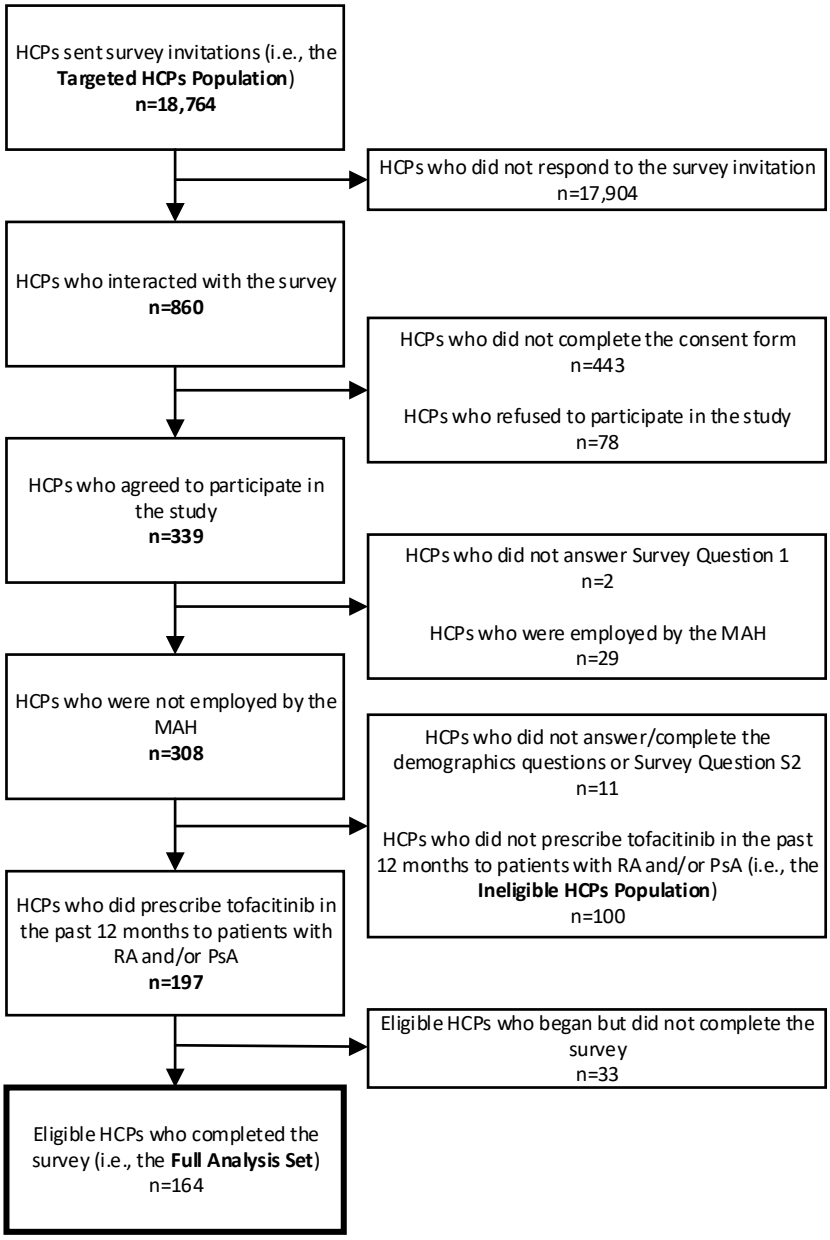
10. RESULTS

10.1. Participants

10.1.1. RA/PsA

As shown in Figure 1 and **Results Table 1-A** (see Section 15 for full set of results tables) for the RA/PsA study, survey invitations were sent to 18,764 HCPs (the Targeted HCPs Population). 17,904 (95.4%) HCPs did not respond to the survey invitation, while 860 (4.6%) HCPs interacted with the survey. 339 (1.8%) HCPs agreed to participate in the study and 326 (1.7%) were screened for participation. Of the 197 (1.0%) eligible HCPs who had prescribed Xeljanz in the past 12 months to patients with RA and/or PsA, 164 HCPs completed the survey. The survey response proportion (i.e., the proportion screened for participation out of those invited to participate) was 1.7% (326/18,764), the eligibility proportion was 60.4% (197/326), and the completion proportion was 83.2% (164/197).

Figure 1. Survey Administration Statistics and Study Population – RA/PsA Survey

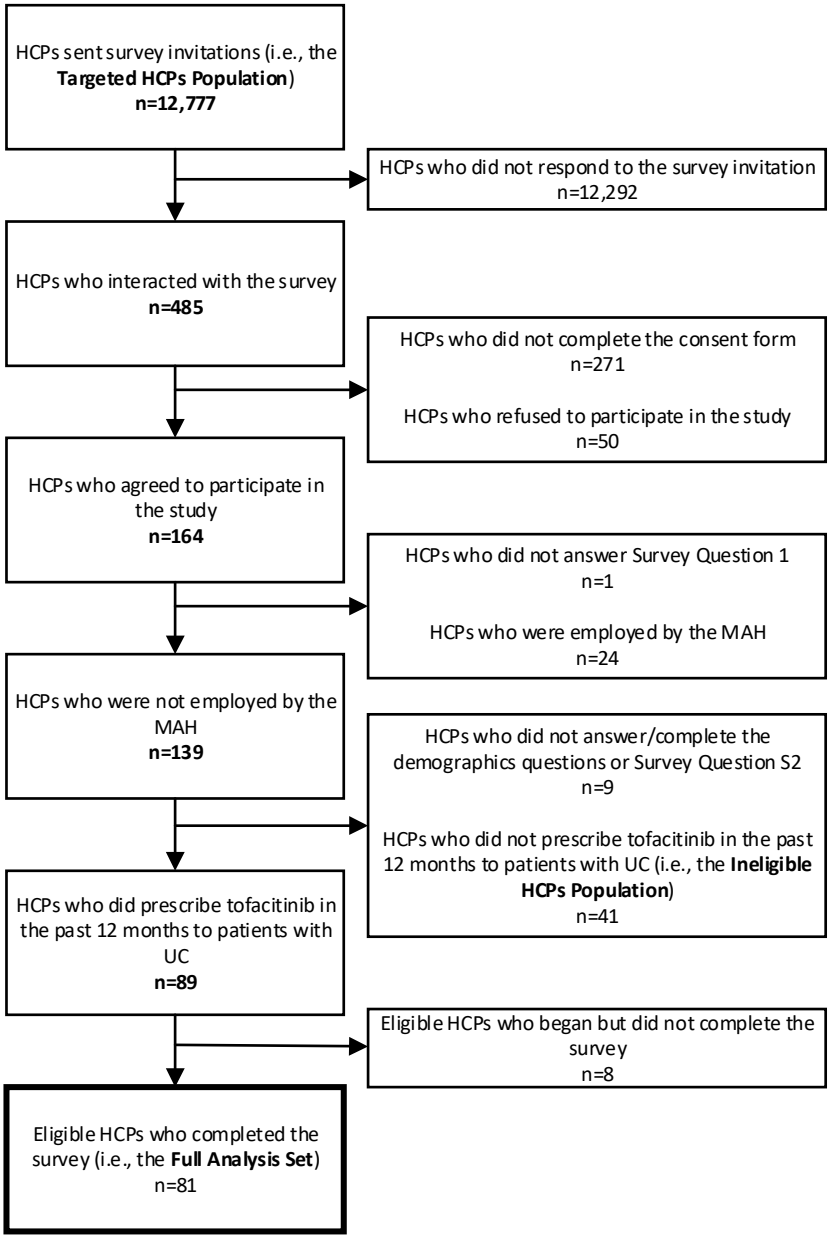


10.1.2. UC

As shown in Figure 2 and **Results Table 1-B** for the UC study survey, invitations were sent to 12,777 HCPs (the Targeted HCPs Population). 12,292 (96.2%) HCPs did not respond to the survey invitation, while 485 (3.8%) HCPs interacted with the survey. 164 (1.3%) HCPs agreed to participate in the study and 154 (1.2%) were screened for participation. Of the 89 (0.7%) eligible HCPs who had prescribed Xeljanz in the past 12 months to patients with UC, 81 (0.6%) HCPs completed the survey. The survey response proportion was 1.2%

(154/12,777), the eligibility proportion was 57.8% (89/154), and the completion proportion was 91.0% (81/89).

Figure 2. Survey Administration Statistics and Study Population – UC Survey

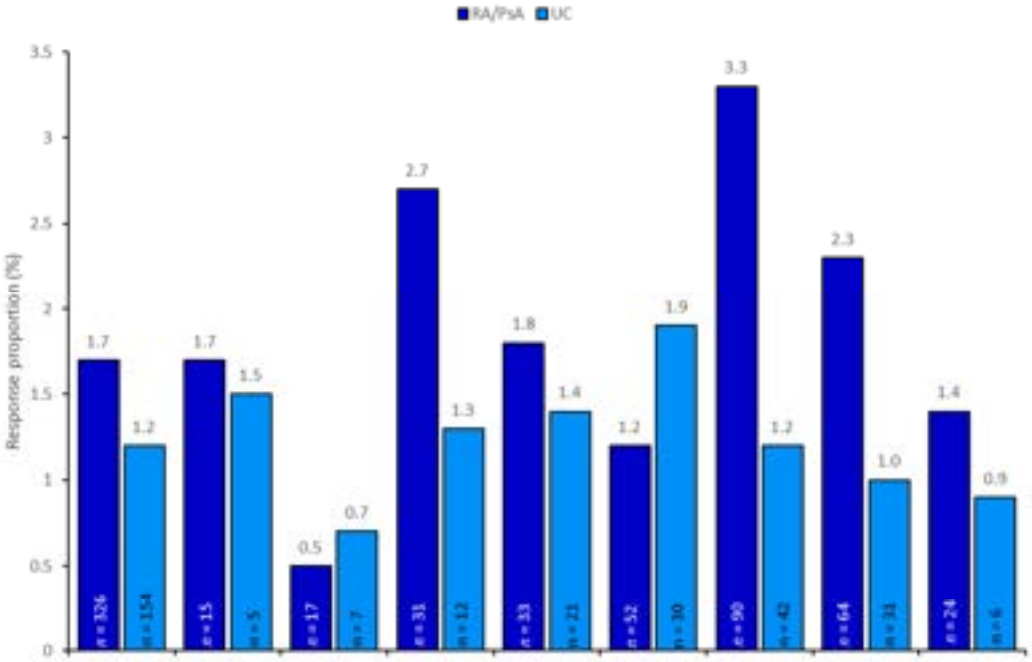


10.1.3. Survey Participation by Country

As shown in Figure 3, while the overall response proportions for the RA/PsA and UC surveys were 1.7% and 1.2%, respectively, country-specific response proportions ranged from 0.5% in Poland to 3.3% in Spain for the RA/PsA survey, and from 0.7% in Poland to 1.9% in France for the UC survey. The countries with the largest HCPs invited to participate

in the RA/PsA survey were France (n=4,464), followed by Poland (n=3,140) and Germany (n=2,791). The countries with the largest HCPs invited to participate in the UC survey were Spain (n=3,611), followed by Germany (n=3,204) and France (n=1,607). Spain had the highest number of HCPs completing the RA/PsA survey (n=61), followed by Germany (n=37) and France (n=28). Germany had the highest number of HCPs completing the UC survey (n=22), followed by Spain (n=21) and the UK (n=13).

Figure 3. Response Proportion, by Survey and Country



		Overall	Sweden	Poland	Netherlands	UK	France	Spain	Germany	Romania
Invited	RA/PsA	18764	869	3140	1137	1845	4464	2760	2791	1758
	UC	12777	326	948	904	1473	1607	3611	3204	704
Screened	RA/PsA	326	15	17	31	33	52	90	64	24
	UC	154	5	7	12	21	30	42	31	6
Completed	RA/PsA	164	3	4	9	18	28	61	37	4
	UC	81	4	4	4	13	11	21	22	2

10.2. Descriptive data

Weighted results are reported for descriptive data unless otherwise noted. Both weighted and unweighted results can be found in the results tables (Section 15).

10.2.1. RA/PsA survey respondent characteristics

The most common HCP specialty in the *unweighted* Final Study Population (n=164) was rheumatologist (65.9%). In the *weighted* Final Study Population, HCPs most commonly had more than 10 years in practice (59.0%), had prescribed fewer than 10 medications in the past 12 months (59.5%), and had prescribed Xeljanz for fewer than 5 patients in the past 12

months (41.9%). HCPs were most commonly involved in both the initiation and maintenance of Xeljanz treatment (83.0%). Most HCPs had experience prescribing Xeljanz for PsA only within the past 12 months (59.9%), while 22.8% had prescribed Xeljanz for both RA and PsA, and the remaining 17.3% prescribed Xeljanz for RA only. 91.8% of HCPs had not participated in a Pfizer-sponsored Xeljanz clinical trial as an HCP [**Results Table 2-A**].

Among the Ineligible HCPs Population (n=100), the most common HCP specialty was dermatologist (81.0%, unweighted), and HCPs most commonly had more than 10 years in practice (60.0%, unweighted) [**Results Table 2-A].**

10.2.2. UC survey respondent characteristics

In the *unweighted* Final Study Population, gastroenterologist was the only HCP specialty reported in the UC survey (n=81;100.0%). HCPs most commonly had more than 10 years in practice (74.5%), had prescribed fewer than 10 medications in the past 12 months (46.0%), and had prescribed Xeljanz for fewer than 5 patients in the past 12 months (36.1%). HCPs were most commonly involved in both the initiation and maintenance of Xeljanz treatment (93.3%). 91.8% of HCPs had not participated in a Pfizer-sponsored Xeljanz clinical trial as an HCP [**Results Table 2-B]**.

Among the Ineligible HCPs Population (n=41), HCPs most commonly had more than 10 years in practice (51.2%, unweighted) [**Results Table 2-B].**

10.3. Outcome data

Not applicable.

10.4. Main results

Weighted results for survey questions are reported for outcome data unless otherwise specified. Both weighted and unweighted results can be found in the results tables (Section 15). Criteria for the evaluation of overall effectiveness of aRMMs program are specified in Section 9.4.4.

10.4.1. Primary analysis

10.4.1.1. Implementation of aRMM program

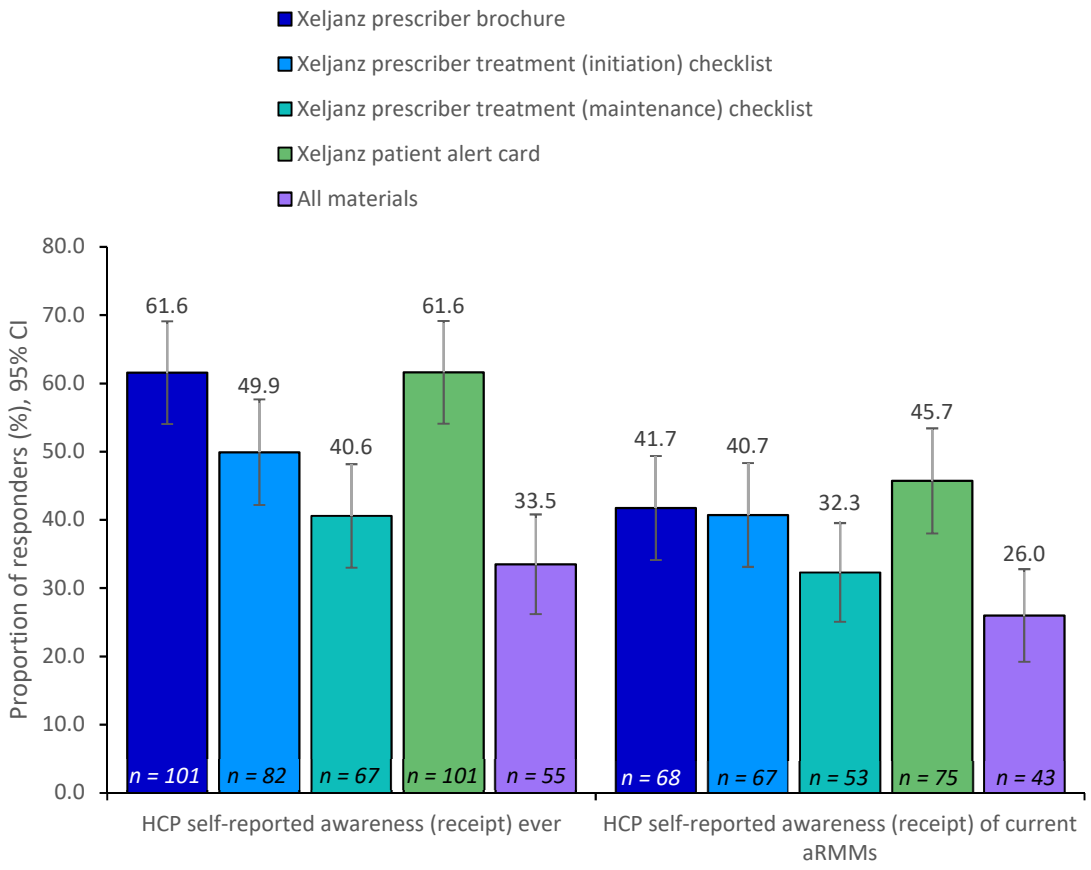
10.4.1.1.1. RA/PsA

Self-reported receipt of aRMMs:

As shown in Figure 4, among RA/PsA survey completers (n=164), HCPs' self-reported awareness (receipt) of individual aRMM materials *ever* ranged from 40.6% (95% CI, 33.0-48.2%; n=67) (Xeljanz prescriber treatment [maintenance] checklist) to 61.6% (95% CI, 54.1-69.1%; n=101) (Xeljanz prescriber brochure and Xeljanz patient alert card). Out of 4 total aRMM materials, the mean number of aRMM materials received *ever* was 2.1 (Interquartile range [IQR]: 1.0-4.0). As shown in Figure 4, the HCP self-reported awareness

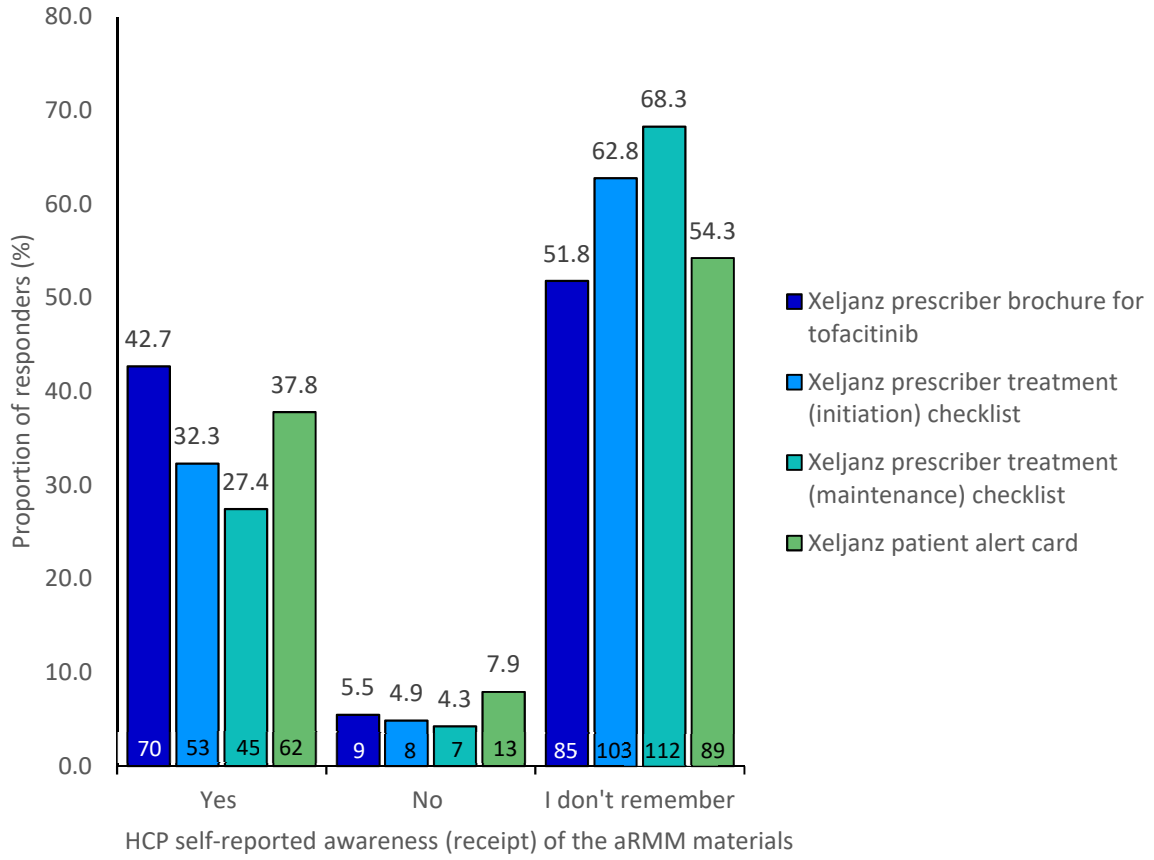
(receipt) of individual current aRMM materials ranged from 32.3% (95% CI, 25.1-39.5%; n=53) (Xeljanz prescriber treatment [maintenance] checklist) to 45.7% (95% CI, 38.0-53.4%; n=75) (Xeljanz patient alert card). Out of 4 total current aRMM materials, the mean number of current aRMM materials received was 1.6 (IQR: 0.0-4.0) [**Results Table 3-A**].

Figure 4. HCP Self-Reported Awareness (Receipt) of aRMMs Ever and of Current aRMMs, RA/PsA Survey



In a **post-hoc** analysis, HCPs who reported they did not receive or did not remember receiving aRMM materials were reported separately in the *unweighted* population to determine if more HCPs reported not receiving versus not remembering receiving aRMM materials. As shown in Figure 5, for the receipt of the current aRMM materials, HCPs more commonly responded that they *did not remember* whether they received the aRMM materials (ranging from 51.8% to 68.3%, unweighted) rather than reporting that they *did not receive* the aRMM materials (ranging from 4.3% to 7.9%, unweighted). HCPs more commonly responded "I don't remember" for the prescriber treatment checklists compared to the prescriber brochure and patient alert card [**Results Table 3-A-i**]

Figure 5. HCP Self-Reported Awareness (Receipt) of the Current aRMM Materials, RA/PsA Survey



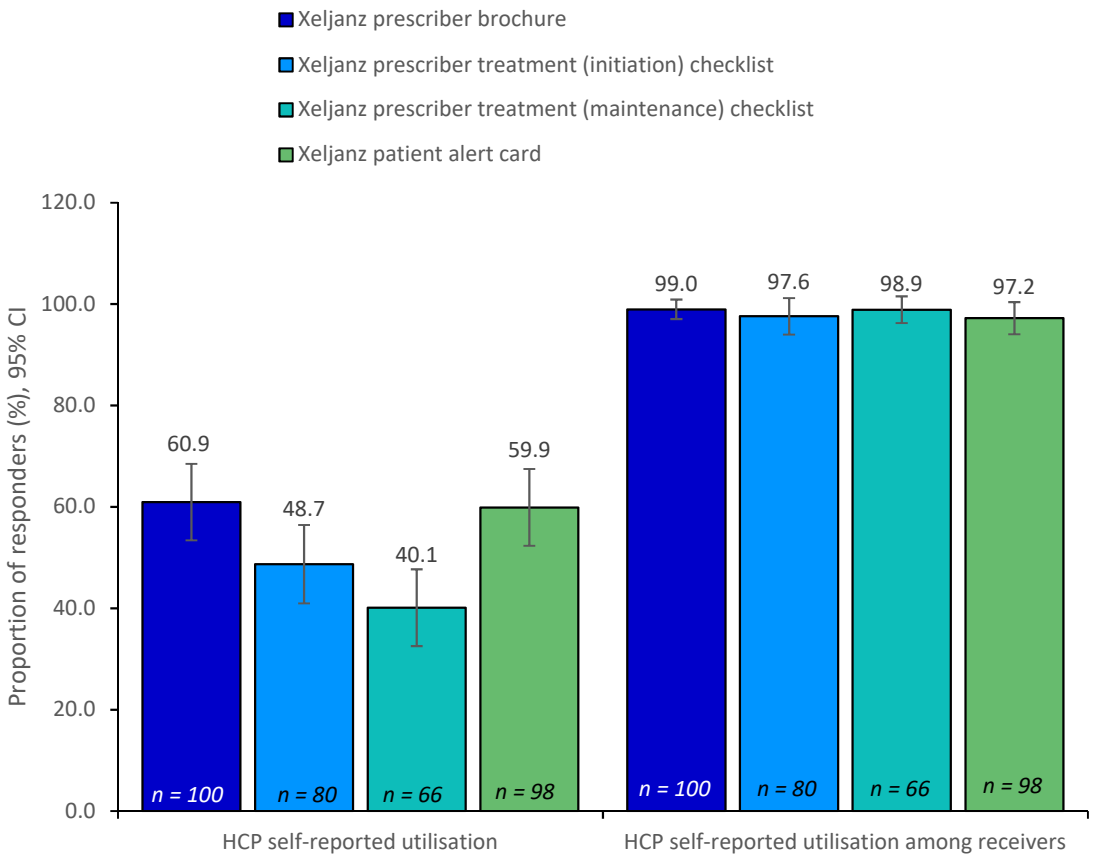
Note: Results using unweighted data.

Self-reported utilisation of aRMMs:

As shown in Figure 6, out of all RA/PsA survey completers (n=164; including those who did not receive the material), HCPs' self-reported utilisation of the aRMM materials ranged from 40.1% (95% CI, 32.5-47.7%; n=66) (Xeljanz prescriber treatment [maintenance] checklist) to 60.9% (95% CI, 53.4-68.5%; n=100) (Xeljanz prescriber brochure). The mean number of aRMM materials utilised was 2.1 (IQR: 0.0-4.0) [**Results Table 3-A**]. In the *unweighted* population, 80.4% (132/164) of HCPs reported utilising all or some of the aRMM materials [**Stratified Results Tables 3-A-iii, 5-A-iii, 7-A-iii, 8-A-iii**].

As shown in Figure 6, in a **post-hoc** analysis, HCP self-reported utilisation of the aRMM materials, among HCPs who indicated receiving the aRMM materials, ranged from 97.2% (95% CI, 94.0-100.0%; n=98) (Xeljanz patient alert card) to 99.0% (95% CI, 97.1-100.0%; n=100) (Xeljanz prescriber brochure). The mean number of aRMM materials utilised among those who received the aRMM materials was 3.1 (IQR: 2.0-4.0) [**Results Table 3-A**].

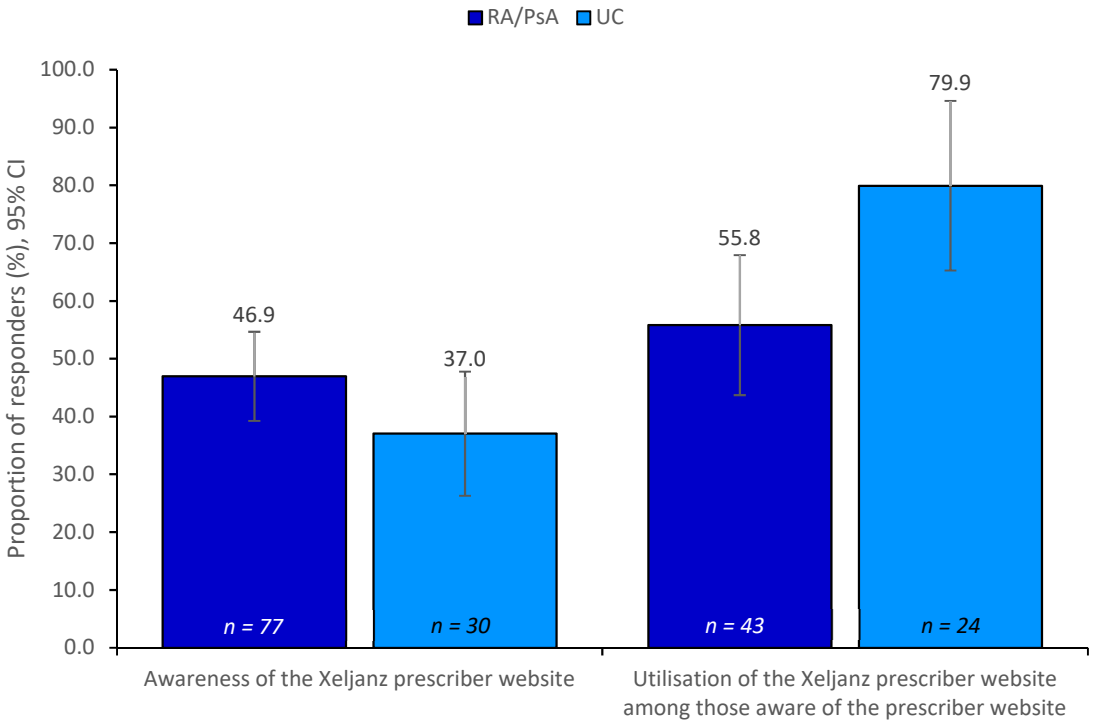
Figure 6. Overall Utilisation and Utilisation among HCPs who Indicated Receiving an aRMM Material, RA/PsA Survey



Awareness and utilisation of Xeljanz prescriber website:

As shown in Figure 7, of RA/PsA survey completers (n=164), self-reported awareness of the Xeljanz prescriber website was 46.9% (95% CI, 39.2-54.7%; n=77) while utilisation of the website (including those who were reportedly not aware of the website) was 26.2% (95% CI, 19.4-33.0%; n=43). In a **post-hoc** analysis restricted to HCPs (n=77) who reportedly were aware of the website, utilisation increased to 55.8% (95% CI, 43.7-67.9%; n=43) [**Results Table 3-A**].

Figure 7. Awareness of and Utilisation of Xeljanz Prescriber Website among HCPs Aware of the Prescriber Website, by Survey



Effectiveness for the implementation of aRMM program:

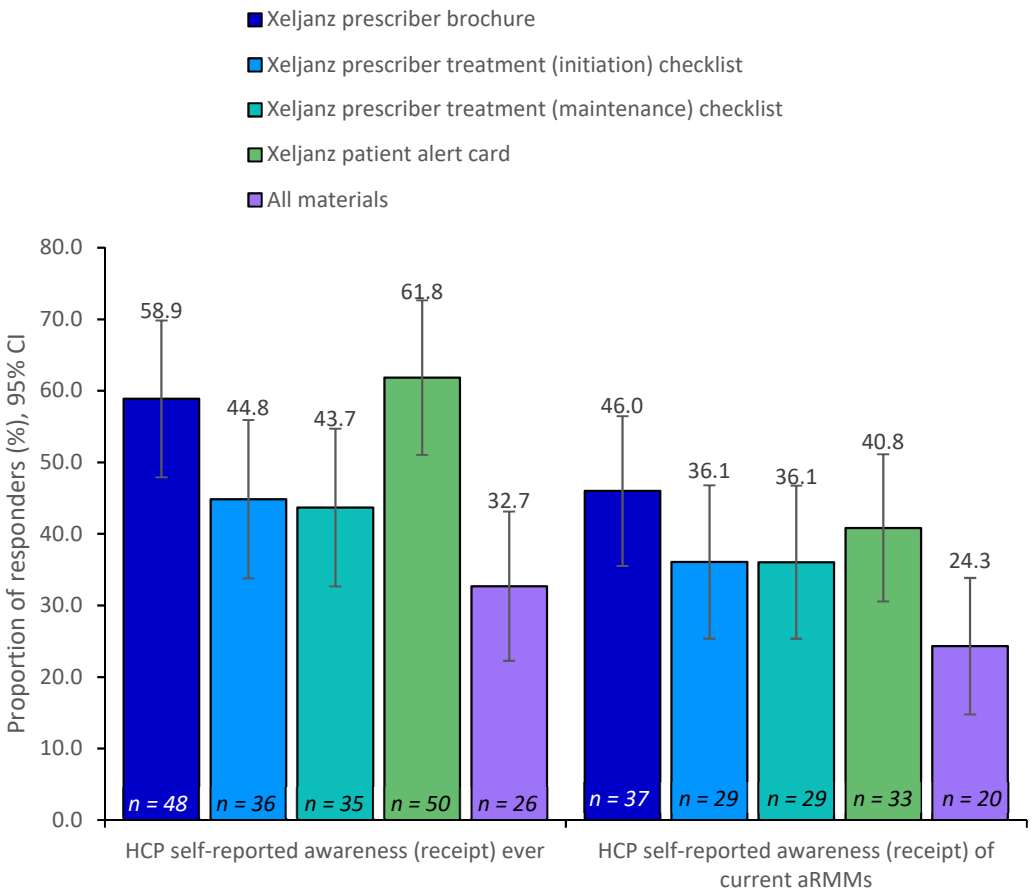
Among RA/PsA survey completers (n=164), **33.5%** (95% CI, 26.2-40.8%; n=55) of HCPs indicated receiving all (4 out of the 4) aRMM materials *ever*, and **26.0%** (95% CI, 19.2-32.7%; n=43) of HCPs indicated receiving all (4 out of the 4) current aRMM materials [**Results Table 8-A**], both of which were below the pre-defined 80% effectiveness threshold.

10.4.1.1.2. UC

Self-reported receipt of aRMMs:

As shown in Figure 8, among UC survey completers (n=81), HCPs' self-reported awareness (receipt) of the aRMM materials *ever* ranged from 43.7% (95% CI, 32.6-54.7%; n=35) (Xeljanz prescriber treatment [maintenance] checklist) to 61.8% (95% CI, 51.0-72.7%; n=50) (Xeljanz patient alert card). Out of 4 total aRMM materials, the mean number of aRMM materials received *ever* was 2.1 (IQR: 1.0-4.0). As shown in Figure 8, the HCP self-reported awareness (receipt) of the current aRMM materials ranged from 36.1% (95% CI, 25.4-46.8%; n=29) (Xeljanz prescriber treatment [initiation] checklist and Xeljanz prescriber treatment [maintenance] checklist) to 46.0% (95% CI, 34.9-57.1%; n=37) (Xeljanz prescriber brochure). Out of 4 total aRMM materials, the mean number of current aRMM materials received was 1.6 (IQR: 0.0-3.0) [**Results Table 3-B**].

Figure 8. HCPs Self-Reported Awareness (Receipt) of aRMMs Ever and of Current aRMMs, UC Survey

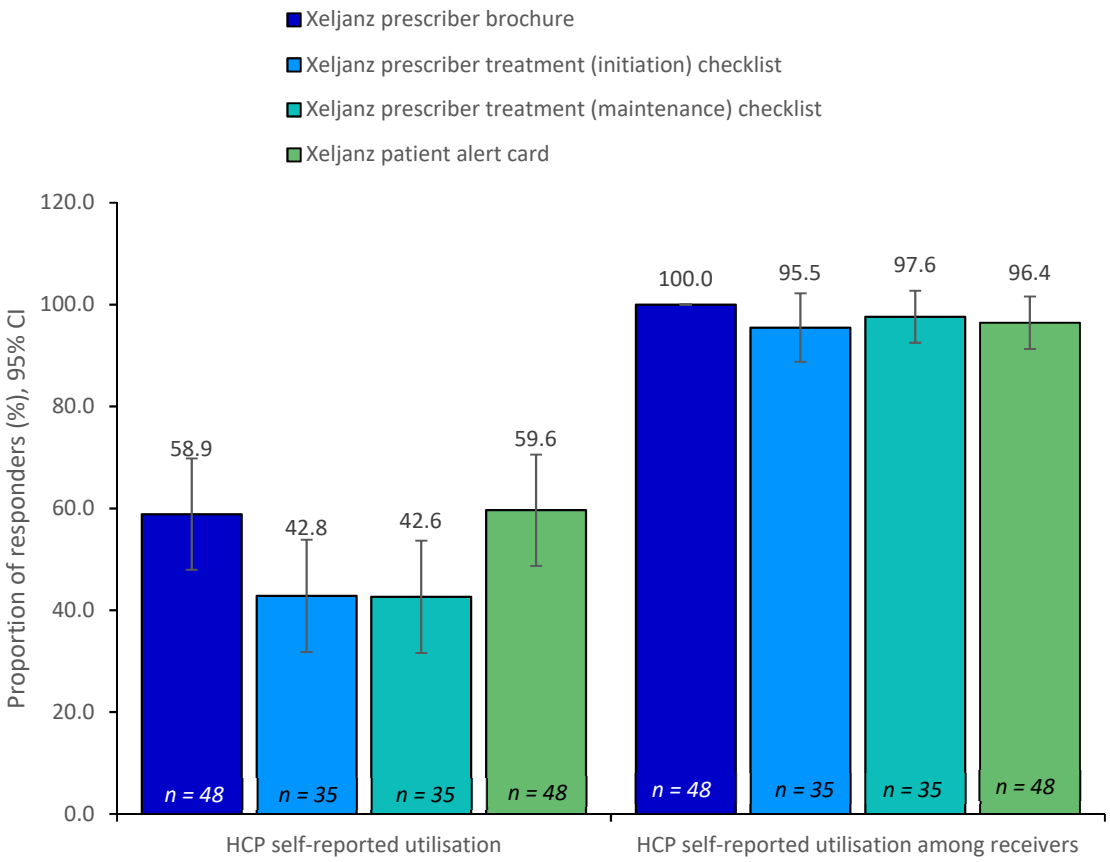


Self-reported utilisation of aRMMs:

As shown in Figure 9, out of all UC survey completers (n=81; including those who did not receive the material), HCPs' self-reported utilisation of the aRMM materials ranged from 42.6% (95% CI, 31.6-53.6%; n=35) (Xeljanz prescriber treatment [maintenance] checklist) to 59.6% (95% CI, 48.7-70.6%; n=48) (Xeljanz patient alert card). The mean number of aRMM materials utilised was 2.0 (IQR: 0.0-4.0) [**Results Table 3-B]**.

As shown in Figure 9, in a **post-hoc** analysis, HCPs' self-reported utilisation of the aRMM materials, among HCPs who indicated receiving the aRMM materials, ranged from 95.5% (95% CI, 88.8-100.0%; n=35) (Xeljanz prescriber treatment [initiation] checklist) to 100.0% (Xeljanz prescriber brochure; n=48). The mean number of aRMM materials utilised among those who received the aRMM materials was 3.1 (IQR: 2.0-4.0) [**Results Table 3-B**].

Figure 9. Overall Self-Reported Utilisation and Utilisation among HCPs who Indicated Receipt of an aRMM Material, UC Survey



Awareness and utilisation of Xeljanz prescriber website:

Of UC survey completers (n=81), HCPs' self-reported awareness of Xeljanz prescriber website was 37.0% (95% CI, 26.3-47.8%; n=30) (see Figure 7) while utilisation of the website (including those who were reportedly not aware of the website) was 29.6% (95% CI, 19.4-39.8%; n=24). In a **post-hoc** analysis restricted to HCPs (n=30) who reportedly were aware of the website, utilisation increased to 79.9% (95% CI, 65.2-94.6%; n=24) (see Figure 7) [**Results Table 3-B**].

Effectiveness for the implementation of aRMM program:

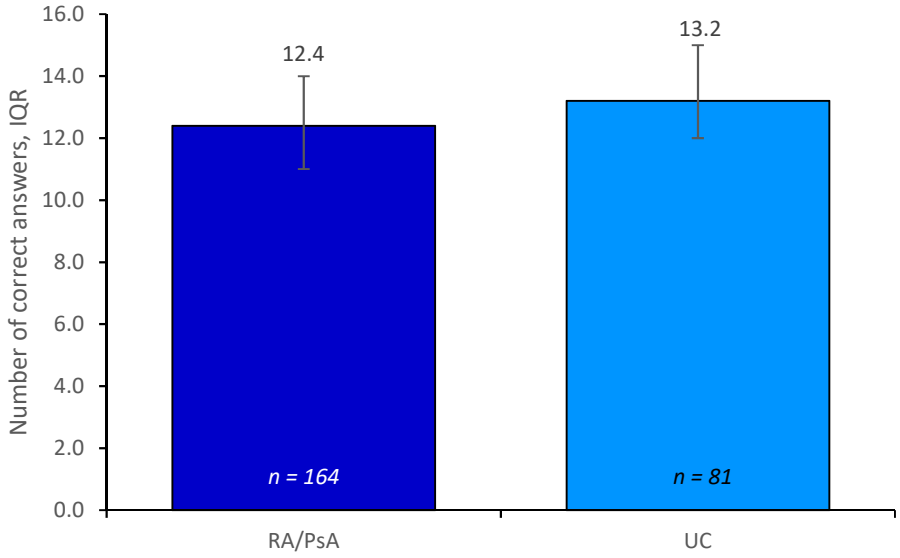
Among UC survey completers (n=81), **32.7%** (95% CI, 22.2-43.1%; n=26) of HCPs recalled receiving all (4 out of the 4) aRMM materials *ever*, **24.3%** (95% CI, 14.8-33.9%; n=20) of HCPs recalled receiving 4 out of the 4 (100%) current aRMM materials [**Results Table 8-B**], both of which were below the pre-defined 80% effectiveness threshold.

10.4.1.2. HCPs' knowledge of the key risk messages

10.4.1.2.1. RA/PsA

Among RA/PsA survey completers (n=164), there was large variation in the proportion of HCPs correctly answering each of the Knowledge Questions 1-18, ranging from 37.3% to 96.3%, with 10 out of 18 questions having < 80% of HCPs answering correctly [**Results Table 4-A**]. HCPs most commonly answered <13 out of 18 (<70%) knowledge questions correctly (44.5%; 95% CI, 36.8-52.1%; n=73). As shown in Figure 10, the mean number of correct answers to Knowledge Questions 1-18 was 12.4 (IQR: 11-14), or about 69% [**Results Table 5-A**].

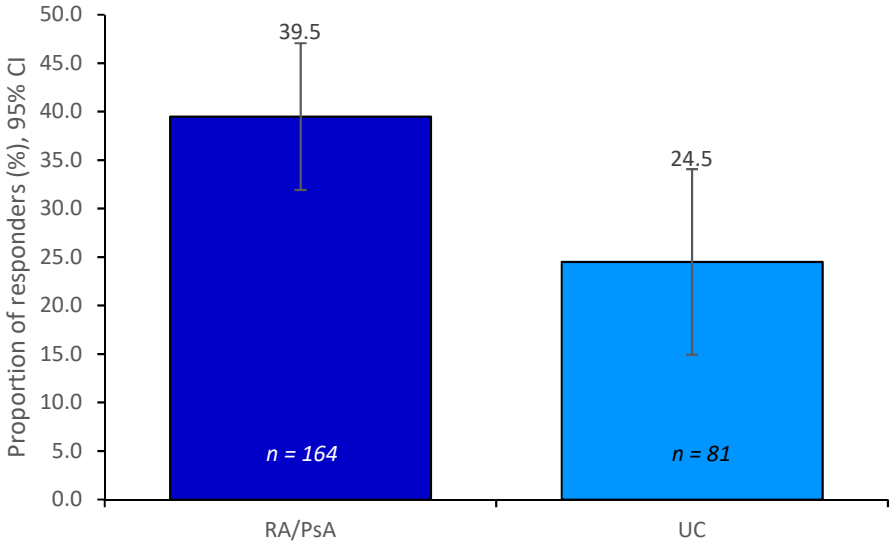
Figure 10. Mean Number of Correct Answers to Knowledge Questions, by Survey



The question with the lowest proportion of HCPs answering correctly (37.3%; n=61) was whether Xeljanz can be used in combination with other biologics or potent immunosuppressants (Q7a). Other questions with <60% of HCPs answering correctly were related to decisions HCPs need to make (i.e., discontinue Xeljanz, interrupt dosing, lower the dose, and no action) when a patient experiences unusual lab results (Q10a, Q10b, Q10e) or develops certain adverse events (i.e., serious infection [Q10c]; suspected VTE [Q10f]). Finally, 61.5% of HCPs answered the following question correctly: *"(Q7g) Xeljanz should only be considered in patients who are 65 years of age or older if there is no suitable alternative (True, False, I don't know)"*, and this is one of the important key risk messages highlighted in the current aRMMs [**Results Table 4-A**].

Effectiveness for the aRMMs in the knowledge domain: As shown in Figure 11, among RA/PsA survey completers (n=164), **39.5%** (95% CI, 31.9-47.1%; n=65) of HCPs had at least 14 out of 18 (≥78% [or approximately 80%]) correct answers to knowledge questions [**Results Table 8-A**], which was below the pre-defined 80% effectiveness threshold.

Figure 11. Proportion of HCPs with at Least Approximately 80% Correct Answers to Knowledge Questions, by Survey



10.4.1.2.2. UC

Among UC survey completers (n=81), there was large variation in the proportion of HCPs answering correctly across Knowledge Questions 1-20, ranging from 36.3% to 94.0%. Fourteen out of the 20 questions had < 80% of HCPs answering correctly [**Results Table 4-B**]. HCPs most commonly answered <14 out of 20 (<70%) knowledge questions correctly (47.8%, 95% CI, 36.7-58.9%; n=39). The mean number of correct answers to Knowledge Questions 1-20 was 13.2 (IQR: 12-15) or about 66% (see Figure 10) [**Results Table 5-B**].

Questions with the lowest proportions of HCPs providing desirable responses asked about actions to take when patients develop severe renal impairment while taking *10 mg* Xeljanz twice a day (Q10e, 36.3%; n=29) or when developing a serious infection, an opportunistic infection or sepsis (Q10d, 38.6%; n=31). Similar to the RA/PsA survey, questions concerning lab monitoring (Q10a-c, g) and use of Xeljanz in combination with other drugs (Q7a) had <60% of HCPs providing desirable responses, while 62.6% of HCPs provided a correct response for use in patients ≥ 65 years old (Q7g) [**Results Table 4-B**].

Effectiveness for the aRMMs in the knowledge domain: Among UC survey completers (n=81), a quarter (**24.5%**; 95% CI, 14.9-34.1%; n=20) of HCPs had at least 16 out of 20 (≥80%) correct answers to knowledge questions (see Figure 11) [**Results Table 8-B**], which was below the pre-defined 80% effectiveness threshold.

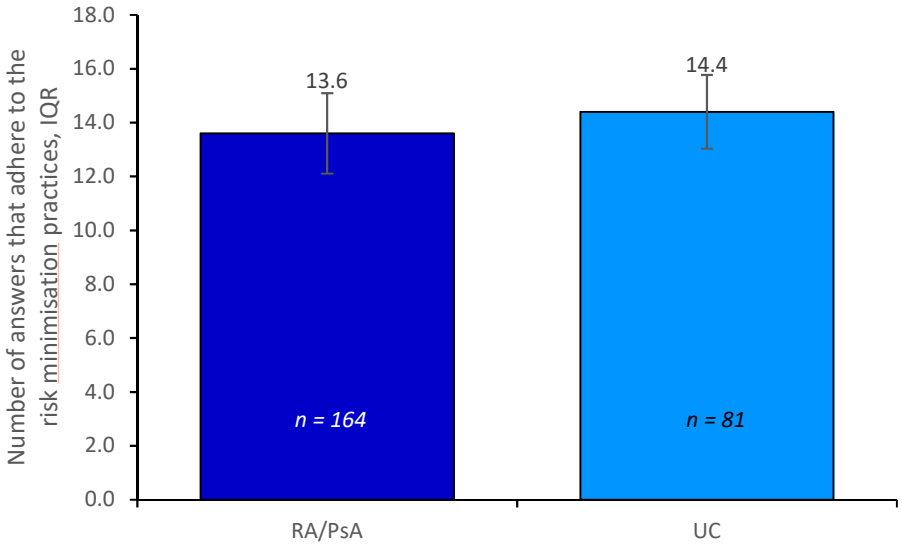
10.4.1.3. HCPs' self-reported adherence to the risk minimisation practices

10.4.1.3.1. RA/PsA

Among RA/PsA survey completers (n=164), the proportion of HCPs providing desirable answers to adherence questions was higher than for knowledge questions, with 12 of 17

adherence questions having at least 80% of HCPs providing desirable answers [**Results Table 6-A**]. As shown in Figure 12, the mean number of answers that adhered to the risk minimisation practices for Adherence Questions 1-17 was 13.6 (IQR: 13-14) or about 80% [**Results Table 7-A**].

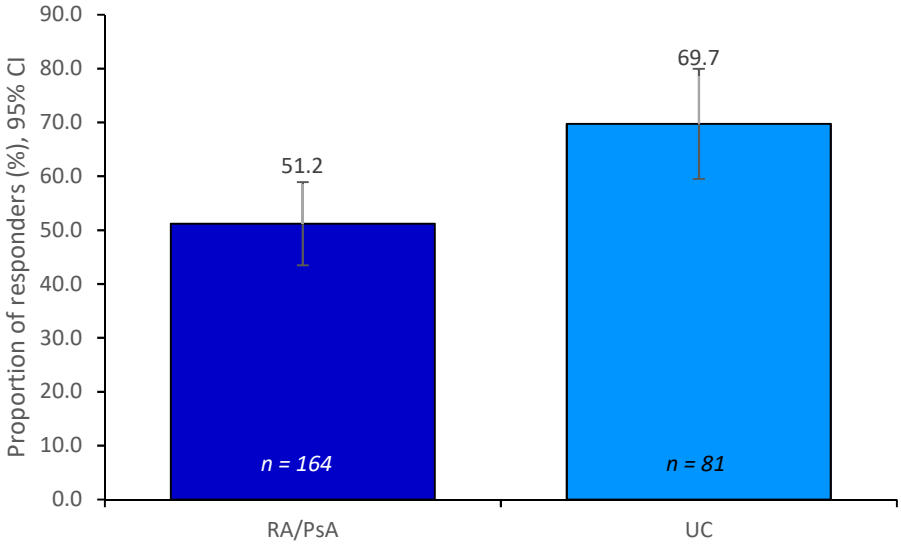
Figure 12. Mean Number of Answers that Adhere to the Risk Minimisation Practices, by Survey



Four negative response questions had <50% of HCPs providing desirable responses (Q8a, Q8d, Q9b, Q9g). These questions ask HCPs about certain lab tests (i.e., urinalysis, blood glucose level) or medical history (i.e., gastroesophageal reflux disease [GORD], hyperthyroidism) that need *not* be checked prior to Xeljanz initiation [**Results Table 6-A**].

Effectiveness for the aRMMs in the adherence domain: As shown in Figure 13, among RA/PsA survey completers (n=164), half (**51.2%**; 95% CI, 43.5-58.9%; n=84) of HCPs had at least 14 out of 17 (≥82% [or approximately 80%]) desirable answers to adherence questions [**Results Table 8-A**], which was below the pre-defined 80% effectiveness threshold.

Figure 13. Proportion of HCPs with at Least Approximately 80% Answers that Adhere to the Risk Minimisation Practices for Adherence Questions, by Survey



10.4.1.3.2. UC

Among UC survey completers (n=81), the proportion of HCPs providing desirable answers to adherence questions was higher than for knowledge questions. The mean number of answers that adhered to the risk minimisation practices for Adherence Questions 1-17 was 14.4 (IQR: 13-16) or about 85% (see Figure 12) [**Results Table 7-B**].

Like HCPs in the RA/PsA survey, <80% of HCPs provided desirable responses to the 4 negative response questions. Furthermore, another question with only 66% of HCPs providing desirable responses asked whether HCPs should check patients at increased risk for skin cancer prior to Xeljanz initiation (Q8b) [**Results Table 6-B**].

Effectiveness for the aRMMs in the adherence domain: Among UC survey completers (n=81), **69.7%** (95% CI, 59.5-80.0%; n=56) of HCPs had at least 14 out of 17 (≥82% [or approximately 80%]) desirable answers to adherence questions, which was below the pre-defined 80% effectiveness threshold (see Figure 13). [**Results Table 8-B**].

10.4.2. Secondary analysis

10.4.2.1. HCPs' perceived usefulness of the aRMM materials

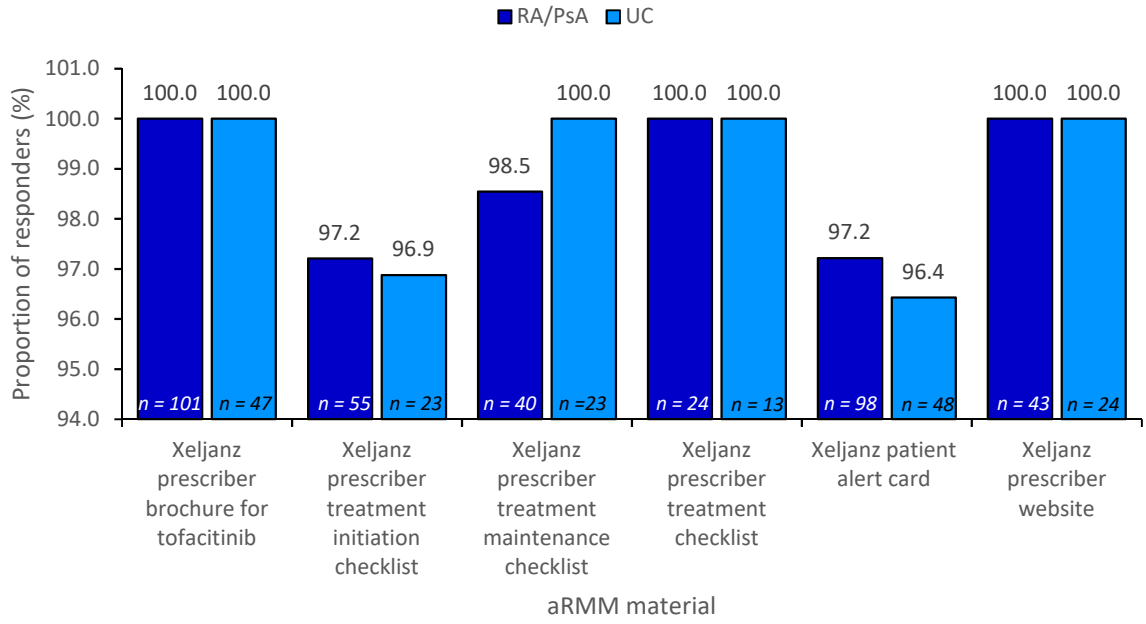
10.4.2.1.1. RA/PsA

Among RA/PsA survey completers (n=164), HCPs who found individual aRMM materials very useful ranged from 26.4% (n=34) (Xeljanz prescriber treatment maintenance checklist [for all countries expect Germany]) to 43.1% (n=71) (Xeljanz prescriber brochure) and to 50.9% (n=19) (Xeljanz prescriber treatment checklist [for Germany only]). These

percentages were out of all HCPs, including those who did not report *ever* receiving the aRMM materials [**Results Table 9-A**].

In a **post-hoc** analysis restricting to HCPs who reported *ever* receiving the aRMM materials, about 70-85% of HCPs found the individual aRMM materials very useful and, as shown in Figure 14, >95% found them useful (very and somewhat useful) [**Results Table 9-A**].

Figure 14. HCPs' Perceived Usefulness (Very Useful or Somewhat Useful) of the aRMM Materials among Those who Received the Materials, by Survey



10.4.2.1.2. UC

Among UC survey completers (n=81), HCPs who found the individual aRMM materials very useful ranged from 24.0% (n=14) (Xeljanz prescriber treatment maintenance checklist [for all countries expect Germany]) to 43.5% (n=35) (Xeljanz prescriber brochure) and to 45.5% (n=10) (Xeljanz prescriber treatment checklist [for Germany only]). These percentages were out of all HCPs, including those who did not report *ever* receiving the aRMM materials [**Results Table 9-B**].

In a **post-hoc** analysis restricting to HCPs who reported *ever* receiving the aRMM materials, about 61-77% of HCPs found the individual aRMM materials very useful and >95% found them useful (very and somewhat useful) (see Figure 14) [**Results Table 9-B**].

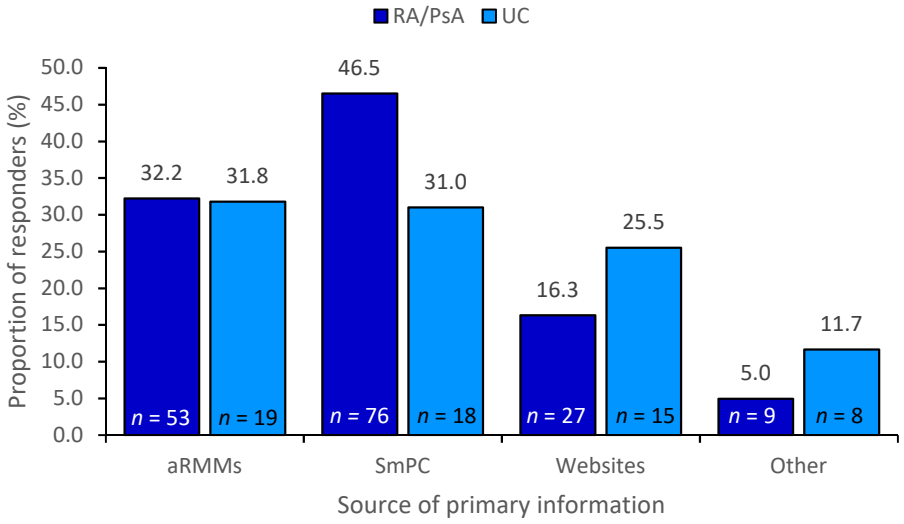
10.4.2.2. Source of HCPs' information on the safety of Xeljanz

10.4.2.2.1. RA/PsA

As shown in Figure 15, among RA/PsA survey completers (n=164), the most common primary source of HCPs' information on the safety and prescribing information for Xeljanz was the SmPC (46.5%; n=76) followed by the aRMM educational materials (32.2%; n=53) [**Results Table 10-A**].

In the **post-hoc** analysis restricting to HCPs who reported *ever* receiving the aRMM materials (n=137), the proportion was 38.0% (n=52) primarily using the SmPC versus 32.1% (n=44) primarily using the aRMMs [**Results Table 10-A-i**].

Figure 15. Primary Source of HCPs' Information on the Safety and Prescribing Information for Xeljanz, by Survey



"Websites" include "National Health Authority website" and "National formulary website"
"Other" includes "Pharmaceutical company website", "Do not know/recall the source", and "Other".

10.4.2.2.2. UC

Among UC survey completers (n=59)[f], the most common primary source of HCPs' information on the safety and prescribing information for Xeljanz was aRMMs (31.8%; n=19), though the SmPC was similar with 31.0% (n=18) of HCPs using this as their primary source of information (see Figure 15) [**Results Table 10-B**].

[f] Survey Q12 (source of HCP's information on the safety of tofacitinib) was not asked in Germany for the UC survey, and therefore Germany is excluded from this analysis.

In the **post-hoc** analysis restricting to HCPs who reported *ever* receiving the aRMM materials (n=45)[f], the same proportion (33.3%; n=15) reported the SmPC and the aRMMs as their primary source of information on Xeljanz [**Results Table 10-B-i**].

10.5. Other analyses (stratified analyses)

Select unweighted RA/PsA analyses were also stratified by the following variables: HCP experience prescribing Xeljanz within the past 12 months (RA only, PsA only, or both RA and PsA); receipt of current aRMM materials (received all materials, received some materials, or received no materials); utilisation of the aRMM materials (utilised all materials, utilised some materials, or utilised no materials); and HCPs' primary source on the safety and prescribing information for Xeljanz (aRMM educational materials, SmPC [label], and other).

Stratification variables were selected from a pre-defined list of variables based on a threshold of 30 or more HCPs per stratum, which was pre-specified in the SAP (**Appendix 4**). The last stratification variable, HCPs' primary source on the safety and prescribing information for Xeljanz, however, was added as an analysis **post-hoc**. Select questions with negative responses (False/No) from the RA/PsA survey were stratified by utilisation of the aRMM materials as a **post-hoc**, **exploratory** analysis. Stratified analyses can be found in the second set of results tables (Section 15). Sample sizes for many of the strata were too small to see meaningful differences and results are described qualitatively below.

10.5.1. Implementation of the aRMM Program

1. Stratified analysis by HCP experience prescribing Xeljanz within the past 12 months for RA only, PsA only, and both RA and PsA

- The proportion of HCPs who self-reported receipt of the current aRMMs and aRMM materials *ever* was highest in HCPs who prescribed Xeljanz for both RA and PsA within the past 12 months [**Stratified Results Table 3-A-i**].

- Correspondingly, utilisation of aRMM materials was also highest in HCPs who prescribed Xeljanz for both RA and PsA [**Stratified Results Table 3-A-i**].

- The prescriber brochure and patient alert card were the most commonly received and utilised aRMM materials across strata [**Stratified Results Table 3-A-i**].

- The proportion of HCPs who indicated receiving *all* aRMM materials *ever* and current aRMMs, respectively, was highest in HCPs who prescribed Xeljanz for both RA and PsA (37.5%, 25.0%), followed by PsA only (30.9%, 21.8%) and RA only (13.3%, 8.9%) [**Stratified Results Table 8-A-i**].

2. Stratified analysis by receipt of the current aRMM materials after February 2020 (January 2020 for Poland)

- Awareness and utilisation of the Xeljanz prescriber website was highest among HCPs who self-reported receipt of all current aRMMs, followed by those who received some and no materials [**Stratified Results Table 3-A-ii**].

3. Stratified analysis by utilisation of aRMM materials

- HCPs who utilised all aRMM materials had the highest awareness and utilisation of the Xeljanz prescriber website [**Stratified Results Table 3-A-iii**].

4. Stratified analysis by HCPs' primary source of information on the safety and prescribing information for Xeljanz

- HCPs who reported aRMM materials as their primary source of information appeared to have higher receipt of various aRMM materials compared to HCPs who reported the SmPC and other sources (National Health Authority website, Pharmaceutical company website, etc.) as their primary source of information [**Stratified Results Table 3-A-iv**].

- HCPs who reported aRMM materials as their primary source of information also tended to have the highest utilisation of various aRMM materials. Interestingly, HCPs who identified other sources as the primary source of information also reported similarly high utilisation of the prescriber brochure and patient alert card [**Stratified Results Table 3-A-iv**].

- There was higher awareness and utilisation of the Xeljanz prescriber website for HCPs who reported aRMM materials as their primary source of information [**Stratified Results Table 3-A-iv**].

10.5.2. HCPs' knowledge of the key risk messages

1. Stratified analysis by HCP experience prescribing Xeljanz within the past 12 months for RA only, PsA only, and both RA and PsA

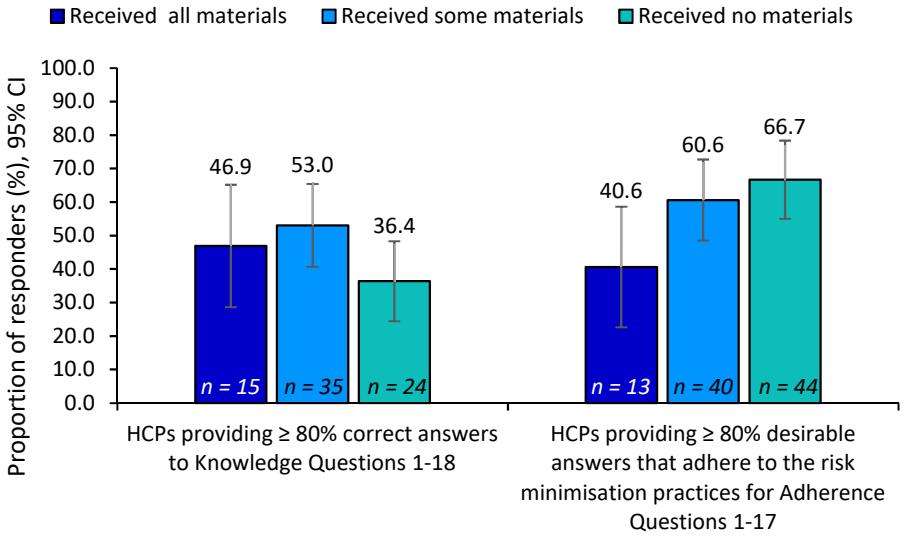
- HCPs who prescribed Xeljanz in the past 12 months for RA only and who prescribed Xeljanz for both RA and PsA tended to have a higher number of correct answers (mean number of correct answers, 13.3) for Knowledge Questions 1-18 compared to those who prescribed Xeljanz for PsA only (mean, 12.1) [**Stratified Results Table 5-A-i & 8-A-i**].

2. Stratified analysis by receipt of the current aRMM materials after February 2020 (January 2020 for Poland)

- HCPs who self-reported receiving some materials (mean number of correct answers, 13.3) had slightly more correct answers to Knowledge Questions 1-18 compared to those who received all or no (both means, 12.6) materials [**Stratified Results Table 5-A-ii**].

- As shown in Figure 16, The proportion of HCPs who provided ≥ 80% correct answers to knowledge questions was highest in HCPs who self-reported receiving some materials (53%), followed by those who received all materials (46.9%), and those who received no materials (36.4%) [**Stratified Results Table 8-A-ii**].

Figure 16. HCPs' Performance on Knowledge and Adherence Questions Stratified by Receipt of the Current aRMM Materials after February 2020 (January 2020 for Poland), RA/PsA Survey

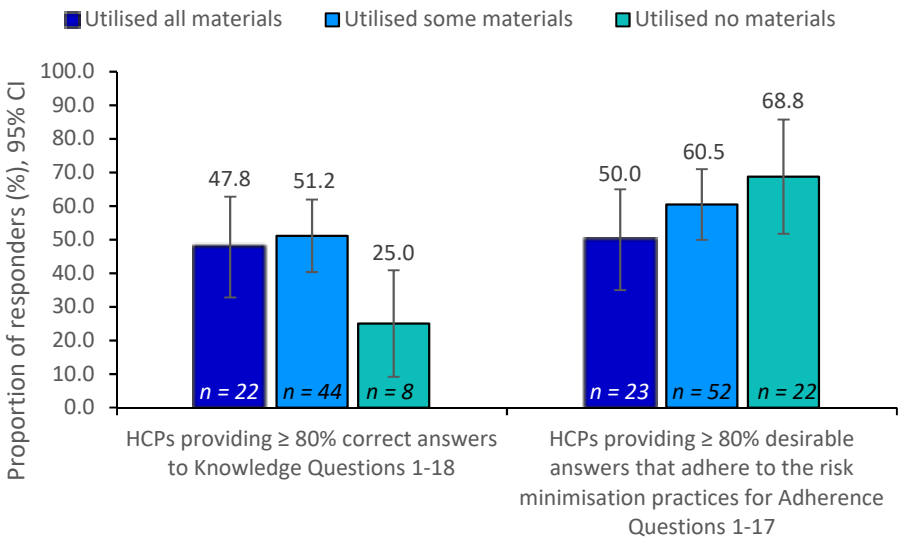


3. Stratified analysis by utilisation of the aRMM materials

- HCPs who utilised all materials (mean, 12.8) and some materials (mean, 13.2) tended to have a higher number of correct answers to Knowledge Questions 1-18 than those who utilised no materials (mean, 12.0) [**Stratified Results Table 5-A-iii**].

- As shown in Figure 17, the proportion of HCPs who provided ≥ 80% correct answers to knowledge questions was highest in HCPs who indicated utilising some materials (51.2%), followed by those who utilised all materials (47.8%), and those who utilised no materials (25.0%) [**Stratified Results Table 8-A-iii**].

Figure 17. HCPs' Performance on Knowledge and Adherence Questions Stratified by Utilisation of the aRMM Materials, RA/PsA Survey



4. Stratified analysis for selected knowledge questions with negative responses (False/No) by utilisation of the aRMM materials [**Stratified Results Table 5-A-iii-a**]

- In the *unweighted* population, HCPs' adherence to key risk messages for select questions with negative responses (False/No) was analysed by utilisation of the aRMM materials. HCPs who reported utilising all aRMM materials tended to respond correctly to the selected questions with negative responses less often [**Results Table 5-A-iii-a**].

5. Stratified analysis by HCPs' primary source of information on the safety and prescribing information for Xeljanz

- The mean number of correct answers to knowledge questions was similar across strata (aRMMs, SmPC and other) [**Stratified Results Table 5-A-iv**].

- The proportion of HCPs who provided ≥ 80% correct answers to knowledge questions was highest in HCPs whose primary source of information was SmPC (52.2%), followed by aRMMs (45.8%), and other sources (34.7%) [**Stratified Results Table 8-A-iv**].

10.5.3. HCPs' self-reported adherence to the risk minimisation practices

1. Stratified analysis by HCP experience prescribing Xeljanz within the past 12 months for RA only, PsA only, and both RA and PsA

- The mean number of desirable answers to adherence questions was similar across HCPs who prescribed Xeljanz in the past 12 months for RA only, PsA only or both RA and PsA [**Stratified Results Table 7-A-i**].

- The proportion of HCPs who provided ≥ 80% desirable answers to adherence questions was highest in HCPs who prescribed Xeljanz in the past 12 months for RA only (66.7%), followed by RA and PsA (59.4%), and PsA only (52.7%) [**Stratified Results Table 8-A-i**].

2. Stratified analysis by receipt of the aRMM materials after February 2020 (January 2020 for Poland) [**Stratified Results Table 7-A-ii**]

- The mean number of desirable answers to adherence questions appears slightly higher in HCPs who received some or no materials than those who received all materials [**Stratified Results Table 7-A-ii**].

- As shown in Figure 16, the proportion of HCPs who provided ≥ 80% desirable answers to adherence questions was highest in HCPs who received no materials (66.7%), followed by some materials (60.6%), and all materials (40.6%) [**Stratified Results Table 8-A-ii**].

3. Stratified analysis by utilisation of the aRMM materials

- The mean number of desirable answers to adherence questions was slightly higher in HCPs who utilised some and no materials than those who utilised all materials [**Stratified Results Table 7-A-iii**].

- As shown in Figure 17, the proportion of HCPs who provided ≥ 80% desirable answers to adherence questions was highest among those who utilised no materials (68.8%), followed by some materials (60.5%), and all materials (50.0%) [**Stratified Results Table 8-A-iii**].

4. Stratified analysis by HCPs' primary source of information on the safety and prescribing information for Xeljanz

- The mean number of desirable answers to adherence questions was similar across HCPs whose primary source of information was aRMMs, SmPC, or other sources [**Stratified Results Table 7-A-iv**].

- The proportion of HCPs who provided ≥ 80% desirable answers to adherence questions was highest in HCPs whose primary source of information was other

sources (67.3%), followed by SmPC (58.2%), and aRMMs (52.1%) [**Stratified Results Table 8-A-iv**].

10.6. Adverse events / adverse reactions

This study did not involve data collection on individual patients by their treating HCPs and the DCT used in this study (i.e., the survey instrument) did not intend to identify product safety information. The DCT for this study was completed online via a secure website. The DCT did 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 (i.e., IQVIA) was not expected during the conduct of the study. However, it is possible that a study participant could have volunteered product safety information to study vendor staff while in conversation about the survey instrument for any other reason (e.g., seeking information about the purpose of the study); this information would be reported as described in the study protocol (**Appendix 2**) and below.

The following safety events must be reported on the noninterventional 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 volunteered product safety information, study vendor staff at IQVIA were required to 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 were the study participant's contact information; complete contact information was required so that, once the NIS AEM Report Form was sent to Pfizer, the NIS AEM Report Form could be assessed and processed according to Pfizer's SOPs, including requests for follow-up with the study participant.

All study vendor staff at IQVIA who were available to study participants to address any query from participants about the study or who conducted the survey over the phone were required to complete the following Pfizer training requirements:

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

This training was completed by study vendor staff at IQVIA prior to the start of data collection. All Pfizer trainings included a "Confirmation of Training Certificate" (for signature by the trainee [paper-based training only]) as a record of completion of the training, which has been stored in a retrievable format. IQVIA also provided copies of all signed training certificates to Pfizer. Re-training was completed on an annual basis using the most current Your Reporting Responsibilities training materials.

11. DISCUSSION

11.1. Key results

Participants:

Between the RA/PsA (n=164) and UC surveys (n=81), participation proportions were similar. The response proportions were 1.7% and 1.2%, eligibility proportions were 60.4% and 57.8%, and completion proportions were 83.2% and 91.0% for the RA/PsA and UC surveys, respectively. Although the response proportion was low, it was not unexpected considering participation in the survey was voluntary and honoraria were not provided. The low response proportion was consistent with a prior prescriber survey study for voriconazole aRMMs in the EU conducted by the MAH (response proportion, 1.7%).[19]

Implementation of aRMM program:

Among survey completers, recollection of receipt of aRMM materials was low: 33.5% of HCPs in the RA/PsA survey and 32.7% in the UC survey reported having *ever* received all aRMM materials and 26.0% of HCPs in the RA/PsA survey and 24.3% in the UC survey reported receiving all current aRMM materials. These proportions did not meet the pre-determined threshold for effectiveness of the aRMM program implementation: ≥80% of HCPs reporting that they received all current aRMMs and all aRMM materials *ever*. There are several possible explanations for the low receipt of aRMM materials. The distribution of current aRMMs occurred during the COVID-19 pandemic, so it is possible that aRMMs, although delivered, did not properly reach the prescribers due to delivery restrictions in the healthcare setting or administering staff filtering. It is also possible that the aRMMs were received, but HCPs did not recall receiving them as they completed this survey about 20 months after the distribution of the current aRMMs and even longer after receiving the original aRMMs. Post-hoc analyses showed that more than half of HCPs answered, *"I don't remember"* to receiving the current aRMMs. Although the survey was intended to launch 6-12 months after the distribution of the current aRMMs to minimise recall error, local authority submission and approval processes delayed survey launch dates, likely leading to greater recall error.

Among survey completers, variations in recall of receipt of individual aRMM materials were noted; prescriber brochures and patient alert cards were more commonly received than treatment (initiation and maintenance) checklists. Since all aRMM materials were distributed in one batch, differences in the recollection of receipt of those materials is likely reflective of prescribers' selected utilisation of the individual materials. For example, the patient alert card was more likely to be remembered by prescribers as it was handed to the patients. Higher proportions of HCPs answered *"I don't remember"* for the receipt of initiation and maintenance checklists than for prescriber brochures and patient alert cards.

Although the recall of receipt of aRMM materials was low, almost all HCPs who recalled receiving the aRMM materials utilised them, and two-third of HCPs that recalled receiving aRMMs found the materials very useful.

HCPs' knowledge of the key risk messages:

Among RA/PsA and UC survey completers, 39.5% and 24.5% of HCPs answered ≥ 80% of knowledge questions correctly, respectively, which was far below the pre-determined effectiveness threshold of ≥ 80% of HCPs answering ≥ 80% of knowledge questions correctly.

There was large variation in HCPs' performance across all knowledge questions. HCPs seemed most confused about whether Xeljanz could be used in combination with other biologics or immunosuppressants. Additionally, HCPs tended to answer correctly less often for questions where they had to decide between multiple treatment options (i.e., discontinue treatment, interrupt dose, lower dose and no action) when patients experienced certain unusual lab values or adverse events during treatment. This may be because HCPs had no experience with patients meeting these conditions, and thus would typically consult sources such as the SmPC or aRMM materials if and when patients experienced them during treatment.

HCPs' adherence to the risk minimisation practices:

Among RA/PsA survey completers and UC survey completers, 51.2% and 69.7% of HCPs provided desirable answers to ≥ 80% of adherence questions, respectively, which was also below the pre-determined effectiveness threshold. However, the overall performance for adherence with risk minimisation practices questions was higher than knowledge questions.

The difference in HCPs' performance between adherence and knowledge questions could partly be due to the design of survey questions. Unlike knowledge questions where there was only one correct answer, multiple answers were accepted as desirable answers for some of the adherence questions.

For adherence with risk minimisation practices questions, HCPs had fewer desirable answers for the negative response questions *not* associated with key risk messages. Those questions asked prescribers whether they should check certain labs or medical conditions that are not necessary to check before initiating Xeljanz. If those questions were excluded, HCPs' performance for the adherence questions would have been much higher and met the effectiveness threshold. However, HCPs' response to those negative response questions is indicative of social desirability bias, a type of response bias commonly found in survey studies where survey respondents tend to provide 'favorable' answers instead of answering truthfully (see Section 11.2.5 for further discussion). Therefore, HCPs' overall performance for adherence questions that included responses to negative response questions were took into account this social desirability bias.

11.2. Limitations

11.2.1. Low response proportion

It has been noted in the literature that participation rates in epidemiologic studies have been decreasing over the past 30 years, with greater decline in recent years.[20-24] For surveys evaluating program effectiveness in particular, it is not uncommon for the response proportion to be below 10%.[25]

The minimum target sample size of 300 HCPs (i.e., completed surveys) for each survey (RA/PsA and UC) was not achieved for a number of possible reasons including those outlined below.

- **Challenge in identifying Xeljanz prescribers**: Although one of the survey inclusion criteria was that the HCP must have prescribed Xeljanz within the 12 months preceding the survey, per protocol, survey invitations were sent to all specialists who were potential prescribers of Xeljanz in the 8 European countries. Due to local privacy regulations, it is challenging to know beforehand the proportion of specialists that (1) manage patients indicated for Xeljanz treatment on a regular basis and (2) have the necessary certification to prescribe Xeljanz as the OneKey database does not contain this information.

- **Low market penetrance**: While the survey did not begin in each survey country until at least 12 months had passed from the distribution of the current aRMM materials, it is possible that market penetrance was still low at the start of data collection, especially for the survey countries where Xeljanz reimbursement was more recent (e.g., Romania for the PsA and UC indications). Low market penetrance means there are fewer HCPs with experience prescribing Xeljanz and thus a smaller base of HCPs eligible to participate in the survey.

- **Low interest in responding**: Physicians may have competing priorities; lack of interest in participating in studies, particularly with the lack of an honorarium offered to survey participants.

- **Logistic challenges**: The postal mail invitations may not have reached or been opened by the intended recipient. For example, based on available addresses, it may have been delivered only to the central hospital mail hub; or the office staff may have reviewed and discarded the invitation; and/or it was discarded without opening by the intended recipient.

Despite these limitations, the MAH employed survey design-based approaches to increase participation. Effective survey design-based approaches include the use of a short survey and surveys personalised and approved by professional associations.[26] It must be emphasized that the MAH has taken all possible measures to enhance HCP participation as has been previously described in Section 9.6.

11.2.2. Unreachable HCPs

The number of HCPs with survey invitations returned as undeliverable could not be reliably ascertained. HCPs were contacted multiple times and via multiple methods including by phone and email, and thus it would be challenging to categorise these HCPs as those with survey invitations returned as undeliverable if they did not respond to either mode of communication.

11.2.3. Absence of pre-aRMM data on HCPs' knowledge and prescribing patterns

The MAH's ability to measure the extent to which HCPs' knowledge or behaviours can be attributed to the aRMM program was 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 were available. To gain some insights, the knowledge and behaviour of the HCPs who self-reported having received and/or utilised the aRMM materials was compared with the knowledge and behaviour of the HCPs who self-reported having not received and/or utilised the aRMM materials. However, the interpretability of the subgroup analyses is limited by small size in the subgroups.

11.2.4. Limitation of human recall

Reliance on respondents' recall is another inherent limitation of survey research. The HCPs were asked if they recalled having received the aRMM materials. Because the MAH had no way to verify true receipt of materials (original or current), it is possible that HCPs who reported never having received the materials did, in fact, received them and vice versa. It is noteworthy for the RA/PsA survey that HCPs differentially recalled receiving the individual components of aRMM materials, even though they were distributed in one package. For the current aRMM materials, it was also worth noting that more than half of HCPs stated they did not remember receiving the various materials.

11.2.5. Social desirability bias with self-reported data

Stratification by receipt of the current aRMM materials and utilisation of the aRMM materials uncovered possible social desirability bias as HCPs performed particularly poorly on specific negative response adherence to risk miminisation questions. For instance, one negative response adherence question asks HCPs, "in your clinical practice, do you perform the following tests to make a decision about whether to initiate a patient on tofacitinib (Yes/No)? Check blood glucose level?" The desired response for this question is "No" (i.e., it is *not* best practice to check for blood glucose level prior to starting a patient on Xeljanz based on the risk minimisation practices). However, about 60% of HCPs answered "Yes" in both surveys likely because they assume this is the expected answer.

In stratified analyses, HCPs who reported utilising all aRMM materials tended to perform even more poorly on these negative response adherence questions while those who reported utilising no materials performed the best. It is possible that HCPs who wish to provide socially desirable answers are more likely to report receiving all aRMM materials (even when they did not, assuming this is the socially desirable answer) and are also more likely to

report positively that all possible comorbidities and/or labs should be examined before prescribing Xeljanz because they assume this is the socially desirable answer.

11.3. Interpretation

Among survey completers, the survey results did not achieve the pre-determined threshold for effectiveness across any of the four domains for awareness (receipt) of all aRMM materials *ever*; awareness (receipt) of all current aRMM materials; knowledge; and adherence to risk minimisation measures. HCPs' overall performance for the adherence questions were higher than the knowledge questions. Though only about one-third of HCPs reported receiving all of the aRMM materials *ever*, a much higher percentage indicated receiving individual aRMM materials, with the prescriber brochure receiving the highest recall and also reported as the most useful among HCPs. Among those who did report receiving an aRMM material, utilisation was quite high (≥ 95%), and about one-third of HCPs reported the aRMM materials were their primary source on the safety and prescribing information for Xeljanz.

11.4. Generalisability

Despite efforts to maximise the number of responses, the survey response proportion (1.7% for RA/PsA survey and 1.2% for UC survey) remained low. Thus, there is a possibility that participants may differ in terms of characteristics, motivations, awareness of the aRMMs, and knowledge of Xeljanz' risks from those who did not respond to the survey. For instance, Poland had a high number of HCPs invited to participate in the RA/PsA survey but only contributed a small number of survey respondents. Thus, selection bias cannot be ruled out and the generalisability of the study results to all Xeljanz prescribers is unknown.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSIONS

Among 164 completers of the RA/PsA survey and 81 completers of the UC survey, the Xeljanz aRMM materials did not achieve the pre-determined threshold (80%) for effectiveness across any of the domains for awareness (receipt) of all aRMM materials, knowledge, or adherence to risk minimisation practices. HCPs' overall performance for the adherence questions tended to be higher than those for the knowledge questions. However, the true effectiveness of the aRMMs cannot be meaningfully inferred from the results due to the low survey response proportion of less than 2%. It must be emphasized that the MAH has taken all possible measures to enhance HCP participation such as employing a multimodal recruitment approach (email, postal mailing, and/or phone calls) that incorporates multiple follow-ups (each HCP was emailed or called at least 3 times before being considered "unreachable"). Due to the low response proportion, the study results may be subject to selection bias (i.e., survey respondents may differ from survey non-respondents in terms of characteristics, awareness of aRMMs, prescribing experience and knowledge of Xeljanz

risks) which may limit the generalisability of results to all Xeljanz prescribers in European countries.

Although an a priori threshold of 80% was used to define the success of each domain of the aRMMs program, the selection of this threshold for success was subjective and not based on established scientific criteria in the education or risk communication literature (as acknowledged by EMA: 7 May 2015 PRAC Rapporteur PASS Protocol Assessment Report; Procedure no.: EMEA/H/C/000387/MEA 087.2). It was expected that knowledge may differ by key risk message, clinical practice, HCP specialties, and countries. Although the MAH could not confirm the difference in knowledge according to HCP specialties or countries given the sample size, knowledge did vary substantially by risk message. In particular, HCPs had less knowledge of Xeljanz' use in combination with other biologics or immunosuppressants, and the preferred treatment course when patients experienced certain unusual lab values or adverse events. This may be because HCPs had no experience with patients meeting these conditions, and thus would typically consult sources such as the SmPC or aRMM materials if and when patients experienced them during treatment.

Among survey completers, low recollection of receipt of aRMM materials by HCPs should likely be interpreted as a limitation of human recall, given more than half of HCPs responded they did not remember receiving the current aRMM materials as opposed to not receiving them in a post-hoc analysis. It is possible that the length of time that passed between dissemination of current aRMMs and the survey may be a potential factor in low recall of receipt of aRMMs materials. Though the administration of surveys to HCPs was planned 6-12 months after the distribution of the current aRMMs to allow sufficient time for aRMM uptake, local regulatory submissions and approvals delayed survey launch to an average of 20 months after the distribution of the current aRMMs in each country. Variability in the recollection of receipt of individual components of aRMMs may be due to select utilisation of the materials. More frequently utilised materials such as the patient alert card and prescriber brochure were more likely to be remembered by HCPs.

Finally, among survey completers, the aRMM program still appears to be a useful tool in clinical practice. Almost all HCPs who indicated receiving the aRMMs utilised them and found them useful, and about a third of HCPs reported using the aRMM materials as their primary source of information for Xeljanz. However, due to the low response rate of less than 2%, whether all Xeljanz prescribers in Europe find the aRMM program useful is unknown.

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15. LIST OF SOURCE TABLES AND FIGURES

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