NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS Information

Title	An Active Surveillance, Post-Authorization Safety Study (PASS) to Estimate Incidence Rates of Serious Infection, Malignancy, Cardiovascular (CV) and Other Safety Events of Interest among all Patients Treated with Ruxience for Rheumatoid Arthritis (RA) within the German Registry Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT)
Protocol number	B3281012
Protocol version identifier	1
Date	14 October 2020
EU Post Authorisation Study (PAS) register number	TBD
Active substance	PF-05280586 Rituximab
Medicinal product	Ruxience (rituximab)
Product reference	H0004696
Procedure number	EMEA/H/C/004696/0000
Marketing Authorisation Holder (MAH)	Pfizer Europe MA EEIG
Joint PASS	No
Research question and objectives	**Research Question:** What are the incidence rates of safety events of special interest in patients with rheumatoid arthritis who initiate treatment with Ruxience and are

	enrolled in the RABBIT register? **Objectives:** To estimate incidence rates of infections, including serious infections, malignancies, cardiovascular events, and events associated with use during pregnancy among patients with rheumatoid arthritis in the RABBIT register who initiate Ruxience.
Country(ies) of study	Germany
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Marketing Authorisation Holder(s)

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1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Rheumatology
AE	adverse event
BSRBR	British Society of Rheumatology Biologics Register
CI	confidence interval
CLL	Chronic lymphocytic leukaemia
CRF	Case Report Form
CRP	C-reactive protein
csDMARD	Conventional Synthetic Disease Modifying Anti-rheumatic Drug
CV	Cardiovascular
CVD	cardiovascular disease
DALYS	Daily-adjusted Life Years
DAS-28	Disease Activity Score-28
DRFZ	Deutsches Rheuma-Forschungszentrum (German Rheumatism Research Center)
DMARD	Disease Modifying Anti-rheumatic Drug
EEIG	European Economic Interest Grouping
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ESR	erythrocyte sedimentation rate
EU	European Union
FFbH	Funktionsfragebogen Hannover
GPA	Granulomatosis with polyangiitis
HAQ	Health Assessment Questionnaire
HRQoL	Health-related Quality of Life
HZ	herpes zoster
ICD	International Classification of Diseases
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MA	Market Authorisation
MACE	major adverse cardiovascular event
MAH	Market Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MPA	Microscopic polyangiitis
NHL	Non-Hodgkins lymphoma
NI	Non-Interventional
NMSC	Non-melanoma Skin Cancer
NRS	Pain Visual Analog Scale

Abbreviation	Definition
NSAIDs	non-steroidal anti-inflammatory drugs
PAS	Post-Authorisation Study
PASS	Post-Authorisation Safety Study
PV	Pemphigus Vulgaris
QALY	Quality-adjusted Life Year
RA	Rheumatoid Arthritis
RABBIT	Rheumatoide Arthritis: Beobachtung der Biologika-Therapie
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
SMQ	Standardised MedDRA Queries
TNF	tumour necrosis factor

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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Country Coordinating Investigators

Not applicable.

4. ABSTRACT

Title: An Active Surveillance, Post-Authorisation Safety Study (PASS) to Estimate Incidence Rates of Serious Infection, Malignancy, Cardiovascular (CV) and other Safety Events of Interest among all Patients Treated with Ruxience for Rheumatoid Arthritis (RA) within the German Registry Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT).

Version: 1

Date: 14 October 2020

Main Author: Cynthia de Luise, PhD, MH, Pfizer, Inc.

Rationale and background:

Rituximab is a genetically engineered chimeric mouse/human monoclonal IgG1k antibody targeting the transmembrane CD20 antigen. CD20 is a 32-kDa, non-glycosylated transmembrane phosphoprotein, located on the surface of normal precursor-B cells, mature B lymphocytes and malignant B cells. The natural ligand for CD20 has not been identified, and the biological function of CD20 remains unclear. Rituximab binds to a discontinuous conformational epitope on CD20 and initiates multiple immune effector functions leading to target cell lysis. The currently approved indications for licensed rituximab (MabThera) are for Rheumatoid arthritis (RA), Non-Hodgkin's lymphoma (NHL), Chronic lymphocytic leukaemia (CLL), Granulomatosis with polyangiitis (GPA), Microscopic polyangiitis (MPA) and Pemphigus Vulgaris (PV).[1]

Licensed as MabThera in the European Union (EU) in 1998, rituximab was the first biologic on the market for RA for specific B cell targeting therapy. Rituximab in combination with methotrexate is indicated for the treatment of adult patients with severe active RA who have had an inadequate response or intolerance to other disease modifying anti-rheumatic drugs (DMARDs) including one or more tumour necrosis factor (TNF) inhibitor therapies. Approved in the EU on 1 April 2020, PF-05280586 (Ruxience) has been developed by Pfizer as a biosimilar to the licensed reference product, MabThera. Pfizer proposes the assessment of safety events of special interest based on the Ruxience EU Risk Management Plan (RMP v. 1.0 (eg, infections including serious infections (Important Identified Risk), malignancies (Important Potential Risk), impact on cardiovascular disease (CVD) (Important Potential Risk) and use in pregnancy (Missing Information).[2] This protocol describes a Post-Authorisation Safety Study (PASS) of Ruxience-exposed patients using actively collected prospective data included in the established the German Registry Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT). This study is designated as a Category 4 "Additional Pharmacovigilance Activities" in line with the reference product.

Research question: What are the incidence rates of safety events of special interest in patients with rheumatoid arthritis enrolled in the RABBIT register who initiate treatment with Ruxience?

Objectives: To estimate incidence rates of infections, including serious infections, malignancies, cardiovascular events, and events associated with use during pregnancy among patients with rheumatoid arthritis in the RABBIT register who initiate Ruxience.

Study design: This active surveillance study will use data from the established RABBIT register, an ongoing prospective observational cohort study started in 2001 with the primary aim of studying the safety of new therapies for RA during routine post-marketing clinical use.

Population: The study population will comprise all patients >16 years at the time of disease onset with RA enrolled within the RABBIT register who initiate treatment with Ruxience.

Data sources: RABBIT is an independent long-term observational cohort study of the safety and effectiveness of biologic agents in rheumatoid arthritis (RA). The aim of the register is to provide safety and effectiveness data on all licensed biologic drugs available for the treatment of RA. RABBIT has been active since May 2001 under the auspices of the "Kompetenznetz entzündlich-rheumatische Systemerkrankungen" ("Competence Network Rheumatology"). RABBIT is overseen by the Deutsches Rheuma-Forschungszentrum (German Rheumatism Research Center) (DRFZ). The content of the original study protocol as well as the extension protocol was agreed to by the Deutsche Gesellschaft für Rheumatologie (German Society for Rheumatology).

Variables: This study will focus on specific variables routinely captured in the RABBIT registry and include baseline patient characteristics (ie, clinical and demographic characteristics, comorbidities and current and past therapies), and safety events of special interest including serious infections, malignancies, CVD events, and events associated with use during pregnancy.

Study size: This is a descriptive study. All Ruxience-treated patients in the RABBIT register during the study period will be included in this study.

Study period: The Study Start Date is defined as the date when the first patient entered in RABBIT with RA initiates Ruxience. The Study End Date will be defined as 3 years after the Study Start Date.

Data analysis: Annual reports will consist of counts of patients exposed to Ruxience and descriptive summaries of baseline variables. The final study report will include incidence rates of safety events of interest described above for Ruxience-treated patients. No comparative analyses with other cohorts will be performed.

Milestones: The first annual report describing the number and characteristics of patients initiating Ruxience will be prepared beginning approximately 31 July 2021 and annually thereafter through 31 July 2023. A final report reflecting incidence rates of events of special interest will be prepared by 31 July 2024.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Registration in the EU PAS register	TBD
Start of data collection (estimated)	30 April 2021^
First annual report (estimated)	31 July 2021
Second annual report (estimated)	31 July 2022
Third annual report (estimated)	31 July 2023
End of data collection (estimated)	31 October 2023#
Final study report* (estimated)	31 July 2024×

^ Start of data collection is the planned date for starting data extraction for the purposes of the primary analysis.

End of data collection is the planned date on which the analytical dataset will be first completely available; the analytic dataset is the minimum set of data required to perform the statistical analysis for the primary objective(s).

x Final report must be submitted within 11 months of end of data collection.

7. RATIONALE AND BACKGROUND

RA is a chronic and systemic inflammatory disease with an estimated prevalence of 0.5-1.0% and a mean annual incidence of 0.02-0.05% within Northern European and North American populations.[3] RA is characterised by inflammation, joint destruction, and progressive disability. Joint destruction is frequently irreversible resulting in significant cumulative morbidity. Patients experience a broad range of co-morbidities.[4] Compared with the general population, RA patients are at a higher risk of infections, CVD and malignancies (including lymphoma).[5,6,7,8,9,10,11,12,13] These patients are also treated with multiple classes of agents, including non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and DMARDs including biologicals, each of which carry significant risks as well as benefits.

Rituximab is a genetically engineered chimeric mouse/human monoclonal IgG1k antibody targeting the transmembrane CD20 antigen. CD20 is a 32-kDa, non-glycosylated transmembrane phosphoprotein, located on the surface of normal precursor-B cells, mature B lymphocytes and malignant B cells. The natural ligand for CD20 has not been identified, and the biological function of CD20 remains unclear. Rituximab binds to a discontinuous conformational epitope on CD20 and initiates multiple immune effector functions leading to target cell lysis. The currently approved indications for licensed rituximab (MabThera) are for Rheumatoid arthritis (RA), Non-Hodgkin's lymphoma (NHL), Chronic lymphocytic leukaemia (CLL), Granulomatosis with polyangiitis (GPA), Microscopic polyangiitis (MPA) and Pemphigus Vulgaris (PV).[2]

Licensed as MabThera in the European Union (EU) in 1998, rituximab was the first biologic on the market for RA for specific B cell targeting therapy.[14] Rituximab in combination with methotrexate is indicated for the treatment of adult patients with severe active RA who have had an inadequate response or intolerance to other disease modifying anti-rheumatic drugs (DMARDs) including one or more tumour necrosis factor (TNF) inhibitor therapies.

Biosimilars and non-originator biologicals of rituximab have been approved in several additional countries as of July 2018, including Turkey, Russia, Argentina, South Korea, Australia, and India.[15] The European Medicines Agency (EMA) approved two rituximab biosimilars from 2 MAHs including Rixathon (Sandoz) in June 2017, and Truxima (Celltrion) in November 2018. PF-05280586 (Ruxience) has been developed by Pfizer as a proposed biosimilar to the licensed reference product MabThera and was approved in the EU on 1 April 2020.

The Market Authorisation Holder (MAH) proposes the assessment of safety events of special interest based on the Ruxience EU RMP v. 1.0 (infections including serious infections (Important Identified Risk), malignancies (Important Potential Risk), impact on CVD (Potential Risk) and use in pregnancy (Missing Information).[2] This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is conducted voluntarily by Pfizer. This study is designated as a "Category 4 Additional Pharmacovigilance Activities" in line with the reference product.

8. RESEARCH QUESTION AND OBJECTIVES

Research question:

What are the incidence rates of safety events of special interest in patients with rheumatoid arthritis enrolled in the RABBIT register who initiate treatment with Ruxience?

Objectives:

To estimate incidence rates of infections, including serious infections, malignancies, cardiovascular events, and events associated with use during pregnancy among patients with rheumatoid arthritis in the RABBIT register who initiate Ruxience.

9. RESEARCH METHODS

9.1. Study Design

This is an active surveillance study using existing data within the German register Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT), an ongoing prospective observational cohort study started in 2001 with the primary aim of studying the safety of new therapies for RA during routine post-marketing clinical use.

9.2. Setting

The German Biologics Register RABBIT has been active since May 2001. The content of the original study protocol as well as the extension protocol was agreed with the Deutsche Gesellschaft für Rheumatologie (German Society for Rheumatology). Physicians who wish to take part in RABBIT must sign a contract with the DRFZ. There is no influence on any treatment decision from the principal investigators, scientific advisory board or pharmaceutical companies sponsoring the study. The type of treatment administered, and the details of individual therapy, including dosages, is determined by the treating physician only. Participating patients have provided informed consent, have definite RA, diagnosed by a rheumatologist, have an age at onset of RA of 16 or older, and are initiating an approved therapy for the treatment of RA.

9.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Included in RABBIT.[1]
2. Newly initiated Ruxience.

[1] Patients included in RABBIT must have a rheumatologically confirmed diagnoses of RA and a disease onset after the age of 16.

3. Age >16 years at the time of disease onset.

9.2.2. Exclusion Criteria

There are no exclusion criteria for this study.

9.3. Variables

This study will focus on specific variables routinely captured in the RABBIT registry which include baseline patient characteristics (ie, clinical and demographic characteristics, comorbidities and current and past therapies), and safety events of special interest including serious infections, malignancies, CVD events, and events associated with use during pregnancy.

9.3.1. Baseline Data

The following information is collected within RABBIT, having been reported by the recruiting clinician, using a standardized form:

1. Diagnosis (including the presence or absence of those features listed in 1987 American College of Rheumatology criteria for RA).

2. Age at treatment start, gender, year of recalled symptom onset, year of diagnosis.

3. Previous drug history of immunosuppressive conventional synthetic Disease Modifying Anti-rheumatic Drug (csDMARDs) and biologics, biosimilar or other new advanced therapy roughly before enrolment and in detail during follow-up after enrolment, including duration of therapy recorded as start month/year and reasons for interruption.

4. Co-morbidities.

5. All current therapy.

6. Baseline disease activity including Disease Activity Score-28 (DAS-28), Funktionsfragebogen Hannover (FFbH) which can be transformed to the Health Assessment Questionnaire (HAQ); Pain Visual Analog Scale (NRS), Global Health NRS, Tender Joint Count, Swollen joint count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), American College of Rheumatology (ACR-20), ACR-50, ACR-70.

7. Baseline history of disease including malignancy, heart failure.

9.3.2. Follow-up

Follow up data in RABBIT occur at months 3, 6, 12, 18, 24, 30, 36, 48, 54, and 60.

9.3.3. Endpoints

The following events of interest have been pre-specified for this study.

1. Hospitalized infections overall.
2. Non-melanoma skin cancer (NMSC).
3. Cardiac disorders: heart failure, coronary artery disease, myocardial infarction, other cardiac disorders.
4. Malignancies, excluding NMSC.
5. Events associated with use during pregnancy

Rates of these endpoints of interest and their 95% CI will be reported for Ruxience-exposed patients. See Table 2 in ANNEX 1. LIST OF STAND ALONE DOCUMENTS for a list of Medical Dictionary for Regulatory Activities (MedDRA) codes for safety events of interest.

9.4. Data Sources

RABBIT is an independent long-term observational cohort study of the safety and effectiveness of biologic agents in rheumatoid arthritis (RA). The aim of the register is to provide safety and effectiveness data on all licensed biologic drugs available for the treatment of RA. RABBIT has been active since May 2001 under the auspices of the "Kompetenznetz entzündlich-rheumatische Systemerkrankungen" ("Competence Network Rheumatology"). RABBIT is overseen by the Deutsches Rheuma-Forschungszentrum (German Rheumatism Research Center) (DRFZ). The content of the original study protocol as well as the extension protocol was agreed to by the Deutsche Gesellschaft für Rheumatologie (German Society for Rheumatology).

9.5. Study Size

This is a descriptive study not intended to test a pre-specified statistical hypothesis. All Ruxience-treated patients in the RABBIT register during the study period will be included in this study. Table 1 displays the 95% confidence intervals around the reported incidence proportions for safety events in the Ruxience RMP.

Table 1. Precision Estimates around Reported Incidence Proportions for Safety Events in the Ruxience RMP[2]

Condition	Incident Count	Population at Risk	Incidence Proportion	Lower Bound of 95% CI	Upper Bound of 95% CI
Any infection (including serious infection)	22	73	0.301	0.199	0.420
Serious infection	3	73	0.041	0.009	0.115

Table 1. Precision Estimates around Reported Incidence Proportions for Safety Events in the Ruxience RMP[2]

Condition	Incident Count	Population at Risk	Incidence Proportion	Lower Bound of 95% CI	Upper Bound of 95% CI
Malignancy#	1	73	0.014	0.000	0.074
NMSC	0	73	0.000	0.000	0.049
CV events	3	73	0.041	0.009	0.115
Events during pregnancy	0	73	0.000	0.000	0.049

Software used: PASS v15.0.8; Method: Exact (Clopper-Pearson); # excluding NMSC; NMSC, non-melanoma skin cancer; CV, cardiovascular; CI, confidence interval.

9.6. Data Management

All data management activities occur within the overarching RABBIT study.

Data will be archived for at least ten years after the end of the study at the DRFZ in Berlin. No selected data or entire data sets will be disclosed without authorization to third parties, including the sponsors, but the sponsors will receive upon request additional analyses on their own products separate from the joint evaluations. The study management, advisory board and sponsors will decide jointly whether data may be passed on for pooling (international studies).

9.7. Data Analysis

The Index Date is the date when the first dose of Ruxience was initiated. Patients who switch from another therapy to Ruxience while they are in RABBIT are eligible for enrolment, and the Index Date will be the date of initiation of Ruxience. Patients will be evaluated for safety events of interest while exposed to Ruxience and accrue person-time from Index Date until the first occurrence of the event of interest, death, loss to follow up or completion of 3 years of follow up (End of Study Period). A 270-day risk window will be applied for analyses regarding serious infections. The 270 day (eg, 9 months) risk window period is implemented for Ruxience in part to accommodate its very long half live, and to ensure that any subclinical or undiagnosed illness at time of end of treatment is captured. In addition, a once exposed always at risk period will be applied for analyses regarding cardiovascular disease and malignancies.

Annual reports will consist of counts of patients exposed to Ruxience and descriptive summaries of baseline variables. The final study report will include incidence rates of safety events of interest and their 95% confidence intervals. No comparative analyses with other cohorts will be performed.

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

protocol amendment. The approved SAP will also describe the a priori determined common set of MedDRA codes and the MedDRA version to define serious infections, major adverse cardiovascular events (MACE) and malignancies. In case of pooling data or performing comparative analyses with other registers, the codes and version will be harmonised among those registers. A draft set of MedDRA codes is included in Table 2 in ANNEX 1. LIST OF STAND ALONE DOCUMENTS.

All serious and non-serious events occurring during the observation are regularly reported from the rheumatologist and captured in the register (with judgement from the rheumatologist on: severity (mild, moderate, severe) and seriousness according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) criteria for seriousness, and causality to given medication). For events of special interest (eg, serious infections, malignancies, heart failure, lymphomas) detailed queries are sent out to the reporting rheumatologists, to get more information on the events (and additional discharge letters from hospitals, or results from biopsies etc).

There is no possibility to link RABBIT data with other data sources in Germany due to strict data protection rules and due to the fact that there is no national cancer register or death register in Germany with the possibility of linkage. However, all events are carefully monitored, and if necessary, several national offices are contacted to get more information.

9.8. Quality Control

All questionnaires (CRFs) are sent to RABBIT by fax. Missing or implausible variables are stratified in different groups and queried for additional information if feasible and necessary. At regular intervals (every 8 weeks) a new dataset is created with the addition of new data. Thereafter, the subsequent monitoring steps are performed, this time mainly regarding longitudinal data plausibility. If more than two follow-up visits are missed in a patient, the physician is queried about the patient's whereabouts. If necessary, the patient or relative(s) of the patient in the same household is/are contacted (via contact information). If insufficient information is available, authorities are asked (eg, registration office) about any new addresses, and/or whether the patient has died. In the latter case, health authorities are subsequently contacted to obtain the cause of death.

9.9. Limitations of the Research Methods

This study is designed to assess the safety of Ruxience within the clinical practice setting utilizing RABBIT, a well-established Germany-based rheumatology register. Despite the strengths of the register, data must be interpreted in light of some limitations. For example, consistent with most observational studies, endpoint misclassification is a key limitation. While RABBIT has an established system to identify and capture endpoint data, it is not feasible in such an observational study to verify all events via source documentation. However, several activities are employed by RABBIT investigators to mitigate outcome misclassification.[16] One is to request additional information in case of serious events of interest; another is a multi-step procedure in case of missing information or when a patient drops out of the registry.

The RA treatment landscape has evolved over time with the introduction of new therapies, treatment recommendations, and approaches to managing adverse events (AEs). The rates of safety events of interest and their distribution among patient-types may have changed over time.

This study will continue for approximately three years from the Study Start Date which is defined as the date when the first patient entered in RABBIT with RA initiates Ruxience (assuming it is feasible to continue participation and that a sufficient number of Ruxience-treated patients can be enrolled). This amount of follow-up may not be sufficient to adequately evaluate some safety events of interest in this study, particularly malignancies. Conclusions may not be generalizable outside of the 3 year period. Another limitation is the lack of a control group which does not allow the results in Ruxience-exposed patients to be compared to patients exposed to other treatments.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

This study involves data that exist in anonymized structured format and contain no patient personal information.

10.2. Patient Consent

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required. Institutional Review Board/Independent Ethics Committee.

10.2.1. Cooperation Between Study Management, Advisory Board, and Sponsors

The study management team is supported by a scientific advisory board comprising four experienced community and hospital rheumatologists. The scientific advisory board was appointed by the governing board of the German Society for Rheumatology in agreement with the Professional Association of German Rheumatologists. The advisory board's duties are: regular review of the reports, consultation in case of serious events, discussion of the research agenda and the SAPs/intended analyses. The advisory board members meet personally every 6 months, at least once annually with the principal investigators and the study physicians and additionally communicate by telephone conferences and email.

Each company participating in RABBIT can send two delegates to the meetings of the scientific advisory board.

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

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (eg, informed consent forms if applicable) from the relevant Institutional Review Board (IRB)/Independent Ethics Committee (IEC). All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

RABBIT has a valid vote received from the Ethics Committee of the Charité in March 2001 (EK Vorg. 1508/2001).

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology, EMA, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology. ANNEX 2. ENCePP checklist for study protocols.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start or a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an AE (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Annual summary reports will be provided to Pfizer and may be included in regulatory updates regarding the benefit risk surveillance of Ruxience. A final dataset, to include 3 years of enrolment, (contingent upon ability to enroll sufficient patients) will be the basis for a final report. Data may be used in regulatory communications external to Germany for contextualization purposes. Manuscripts based on specific endpoints of interest may be developed for publication purposes.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol of which the investigator becomes aware.

13. REFERENCES

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14. LIST OF TABLES

15. LIST OF FIGURES

Not applicable.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Table 2. ICD and MedDRA Codes for Select Safety Endpoints

BIOBADASER, BSRBR, RABBIT	
Event	**Operationalization (Final list TBD based on reported endpoints)**
Serious infections	Hospitalization and/or use of parenteral antibiotics+ MedDRA Infections and Infestations SOC 10021881
CV Risk	Fatal and non-fatal 10000891 Acute myocardial infarction; 10006147 Brain stem infarction; 10006148 Brain stem ischaemia; 10008034 Cerebellar infarction; 10008088 Cerebral artery embolism; 10008120 Cerebral ischaemia; 10008190 Cerebrovascular accident; 10014498 Embolic stroke; 10019005 Haemorrhagic cerebral infarction; 10019016 Haemorrhagic stroke; 10024033 Lateral medullary syndrome; 10028596 Myocardial infarction; 10028602 Myocardial necrosis; 10033697 Papillary muscle infarction; 10043647 Thrombotic stroke; 10049768 Silent myocardial infarction; 10051078 Lacunar infarction; 10055677 Haemorrhagic transformation stroke; 10056237 Migrainous infarction; 10059613 Stroke in evolution; 10060839 Embolic cerebral infarction; 10060840 Ischaemic cerebral infarction; 10061256 Ischaemic stroke; 10062573 Brain stem thrombosis; 10064961 Thalamic infarction; 10066591 Post procedural stroke; 10066592 Post procedural myocardial infarction; 10067167 Cerebellar embolism; 10067347 Thrombotic cerebral infarction; 10067462 Millard-Gubler syndrome; 10068621 Cerebellar ischaemia; 10068644 Brain stem stroke; 10069020 Basal ganglia infarction; 10070671 Cerebral septic infarct; 10070754 Inner ear infarction; 10071043 Basal ganglia stroke; 10071260 Carotid angioplasty; 10073945 Perinatal stroke; 10074422 Brain stem embolism; Fatal only 10002886 Aortic aneurysm rupture; 10003173 Arterial rupture; 10003210 Arteriosclerosis; 10003212 Arteriosclerosis moenckeberg-type;;10006145 Brain stem haemorrhage; 10007522 Cardiac asthma; 10007554 Cardiac failure; 10007556 Cardiac failure acute; 10007558 Cardiac failure chronic; 10007559 Cardiac failure congestive; 10007559 Cardiac failure congestive; 10007560 Cardiac failure high output; 10007625 Cardiogenic shock; 10007684 Carotid arterial embolus; 10007686 Carotid artery aneurysm; 10007688 Carotid artery thrombosis; 10008023 Cerebellar artery thrombosis; 10008030 Cerebellar haemorrhage; 10008076 Cerebral aneurysm ruptured syphilitic; 10008086 Cerebral arteriovenous malformation haemorrhagic; 10008089 Cerebral artery occlusion; 10008092 Cerebral artery thrombosis; 10008111 Cerebral haemorrhage; 10008118 Cerebral infarction; 10008132 Cerebral thrombosis; 10018985 Haemorrhage intracranial; 10022758 Intracranial aneurysm; 10022840 Intraventricular haemorrhage; 10022841 Intraventricular haemorrhage neonatal; 10024119 Left ventricular failure; 10024242 Leriche syndrome; 10034476 Pericardial haemorrhage; 10036511 Precerebral artery occlusion; 10039163 Right ventricular failure; 10039330 Ruptured cerebral aneurysm; 10042316 Subarachnoid haemorrhage; 10042434 Sudden death; 10047279 Ventricle rupture; 10048380 Aneurysm ruptured; 10048761 Atrial rupture; 10049418 Sudden cardiac death; 10049993 Cardiac death; 10050403 Carotid artery dissection; 10051093 Cardiopulmonary failure; 10051328 Carotid aneurysm rupture;

Table 2. ICD and MedDRA Codes for Select Safety Endpoints

BIOBADASER, BSRBR, RABBIT	
Event	**Operationalization (Final list TBD based on reported endpoints)**
CV risk	10052019 Femoral artery occlusion; 10053633 Cerebellar artery occlusion; 10053649 Vascular rupture; 10053949 Vascular pseudoaneurysm ruptured; 10055803 Haemorrhage coronary artery; 10058178 Aortic occlusion; 10060874 Aortic rupture; 10060953 Ventricular failure; 10060964 Arterial haemorrhage; 10062585 Peripheral arterial occlusive disease; 10062599 Arterial occlusive disease; 10063081 Acute left ventricular failure; 10063082 Acute right ventricular failure ; 10063083 Chronic left ventricular failure; 10063084 Chronic right ventricular failure; 10064595 Haemorrhagic arteriovenous malformation; 10064601 Iliac artery occlusion; 10065441 Venous haemorrhage; 10065558 Aortic arteriosclerosis; 10067057 Basal ganglia haemorrhage; 10067116 Carotid arteriosclerosis; 10068119 Aortic dissection rupture; 10068119 Aortic dissection rupture; 10068230 Cardiorenal syndrome; 10069694 Brachiocephalic artery occlusion; 10069695 Subclavian artery occlusion; 10069696 Coeliac artery occlusion;10071716 Vertebral artery dissection; 10072043 Central nervous system haemorrhage; 10072789 Iliac artery rupture; 10073565 Intracranial artery dissection; 10073565 Intracranial artery dissection; 10073681 Epidural haemorrhage; 10075449 Brachiocephalic arteriosclerosis; 10076203 Radiation associated cardiac failure.
NMSC	10004146 Basal cell carcinoma; 10004178 Basosquamous carcinoma; 10004179 Basosquamous carcinoma of skin; 10006059 Bowen's disease; 10007390 Carcinoma in situ of skin; 10064055 Lip squamous cell carcinoma; 10063693 Malignant neoplasm of eyelid; 10040808 Skin cancer; 10055115 Skin cancer metastatic 10041834 Squamous cell carcinoma of skin
Pregnancy	The case report form asks about pregnancies which are flagged and coded. At the conclusion of pregnancy, pregnancy outcomes and complications are coded
Malignancy	Malignant or unspecified tumours (SMQ)

Abbreviations: BIOBADASER= Spanish Registry for Adverse Events of Biological Therapy in Rheumatic Diseases; BSRBR= The British Society of Rheumatology Biologics Register; CV= cardiovascular; HZ= herpes zoster; ICD= International Classification of Disease; MedDRA= Medical Dictionary for Regulatory Activities; NMSC= non-melanoma skin cancer; RABBIT= Rheumatoide Arthritis: Beobachtung der Biologika Therapie; SMQ= Standardised MedDRA Queries.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

bDoc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: An Active Surveillance, Post Authorization Safety Study (PASS) of Serious Infection, Malignancy, Cardiovascular (CV) and Other Safety Events of Interest among Patients Treated with Ruxience for Moderately to Severely Active Rheumatoid Arthritis (RA) within the German Registry Rheumatoide Arthritis: Beobachtung der Biologika Therapie (RABBIT).

EU PAS Register® number:
Study reference number (if applicable):B3281012

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☐	☐	☒	
1.1.2 End of data collection[2]	☐	☐	☒	
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6

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

Section 1: Milestones	Yes	No	N/A	Section Number
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	9.7

Comments:

Section 3: Study design	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.2
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	
4.2.2 Age and sex	☐	☐	☒	

ENCePP Checklist for Study Protocols (Revision 4) Page 2/6

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.3 Country of origin	☒	☐	☐	9.2
4.2.4 Disease/indication	☒	☐	☐	9.2
4.2.5 Duration of follow-up	☒	☐	☐	9.5.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1 and 9.2.1.1

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	Section 9
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☒	☐	☐	Section 9
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	Section 9
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	Section 9
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.5.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	Apppendix 1
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

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

Comments:

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

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☐	☐	☒	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.6
9.1.3 Covariates and other characteristics?	☐	☐	☒	
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	Section 9
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	Section 9
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☒	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	Section 9
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	Appendix 1
9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.9
10.2 Is study size and/or statistical precision estimated?	☐	☐	☒	
10.3 Are descriptive analyses included?	☒	☐	☐	9.9
10.4 Are stratified analyses included?	☐	☐	☒	
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.10
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	N/A

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☒	
12.1.2 Information bias?	☒	☐	☐	9.11
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☐	☒	

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.4
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10.4
13.3 Have data protection requirements been described?	☒	☐	☐	10.1

Comments:

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

Comments:

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

Comments:

Name of the main author of the protocol: Cynthia de Luise

Date: 25 Sept 2020

Signature: 

ANNEX 3. ADDITIONAL INFORMATION

Not Applicable.

Document Approval Record

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