NON-INTERVENTIONAL (NI) STUDY REPORT

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
Version identifier of the study report	1.0
Date	23 Aug 2024
EU Post Authorization Study (PAS)	EUPAS37691 HMA-EMA Study ID 41900
Active substance	ATC L01XC02
Medicinal product	PF-05280586 Ruxience (rituximab)
Product reference	H0004696
Procedure number	EMEA/H/C/004696/0000
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:** What are the incidence rates of safety events of special interest in patients with rheumatoid arthritis (RA) who are enrolled in the RABBIT register and initiate treatment with Ruxience? **Objectives:** To estimate incidence rates of infections, including serious infections, malignancies,

	cardiovascular events, and use during pregnancy among all patients with RA in the RABBIT register who initiate Ruxience.
Country(-ies) of study	Germany
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1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACPA	anti-citrullinated protein antibodies
BMI	body mass index
b/tsDMARD	biological or targeted synthetic disease modifying anti-rheumatic drug
CI	confidence interval
csDMARD	conventional synthetic disease modifying anti-rheumatic drug
CLL	Chronic lymphocytic leukemia
CRF	case report form
CV	cardiovascular
CVD	cardiovascular disease
DAS-28	Disease Activity Score in 28 joints
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	Hannover Functional Status Questionnaire
GC	glucocorticoid
GEP	Good Epidemiological Practice
GPA	Granulomatosis with polyangiitis
IEC	Independent Ethics Committee
IR	incidence rate
IRB	Institutional Review Board
MA	Market Authorisation
MAH	Market Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MPA	Microscopic polyangiitis
N	number
N/A	Not applicable
NHL	Non-Hodgkin’s lymphoma
NI	Non-interventional
NMSC	non-melanoma skin cancer
NRS	numeric rating scale

Abbreviation	Definition
NSAIDs	nonsteroidal anti-inflammatory drugs
PASS	Post-Authorization Safety Study
PV	Pemphigus Vulgaris
RA	rheumatoid arthritis
RABBIT	Rheumatoide Arthritis: Beobachtung der Biologika-Therapie
RMP	Risk Management Plan
TNF	Tumor necrosis factor

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
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4. OTHER RESPONSIBLE PARTIES

Responsible Party Name and Affiliation	Role in Study
Dr. Yvette Meißner Deutsches Rheuma-Forschungszentrum Berlin (German Rheumatism Research Centre Berlin), Programmbereich Epidemiologie und Versorgungsforschung,	Design, conduct and summary report, aside from the principal investigators
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5. MILESTONES

Milestone	Planned date	Actual date	Comments
Date of IEC approval	1 July 2021	5 July 2021	
Registration in the HMA-EMA Catalogues of RWD Studies	Prior to the start of data collection	21 October 2020	
Start of data collection^	30 April 2021	02 June 2021	
End of data collection#	31 December 2023	31 December 2023	.
Final report of study results	30 November 2024	XX Aug 2024	

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

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

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6. RATIONALE AND BACKGROUND

Rheumatoid arthritis (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.[1] RA is characterised by inflammation, joint destruction, and progressive disability. Joint destruction is frequently irreversible resulting in significant cumulative morbidity.[2] Patients experience a broad range of co-morbidities. Compared with the general population, RA patients are at a higher risk of infections, CV disease (CVD) and malignancies (including lymphoma).[3,4,5,6,7,8,9,10,11] These patients are also treated with multiple classes of agents, including nonsteroidal 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).[12]

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.[13] 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 antirheumatic drugs (DMARDs) including one or more tumour necrosis factor (TNF) inhibitor therapies.

PF-05280586 (Ruxience) was developed by Pfizer as a biosimilar to the licensed reference product MabThera and was approved in the EU on 01 April 2020.

Pfizer proposed the assessment of safety events of special interest based on the Ruxience EU RMP version 1.0 (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)).[14]

This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and was conducted voluntarily by Pfizer as a "Category 4 Additional Pharmacovigilance Activities" in line with the reference product.

7. RESEARCH QUESTION AND OBJECTIVES

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

Objectives:

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

8. AMENDMENTS AND UPDATES

None.

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. See Appendix 2.1 PROTOCOL.

This final report includes therapy and safety data from patients with RA enrolled and observed in the RABBIT register from the first Ruxience initiator in 2020 until 31 December 2023.

9.2. Setting

The setting of the study was the RABBIT register. Patients with RA are enrolled in RABBIT and observed in routine clinical care by the treating rheumatologists. The following inclusion criteria were fulfilled for this study:

- Age at enrolment in RABBIT **>17 years**
- Age at onset of RA **>15 years**
- Rheumatologist confirmed diagnosis of RA and indication of the number of fulfilled 1987 criteria of the American College of Rheumatology.[15] Until 2016: patients had to fulfill at least four of the seven 1987 criteria of the American College of Rheumatology.
- Initiating treatment with Ruxience either as the initial or subsequent treatment

Data are reported by physicians and patients at predefined time points of follow-up (enrolment, at 3 and 6 months, thereafter every 6 months). Once enrolled, patients are followed regardless of treatment changes, treatment cessation or treatment initiation. The type of treatment administered, and the conduct of individual therapy, including dosages, is solely determined by the treating physician in agreement with the patient. Patients are observed for at least five and up to ten years, however given the very low uptake of Ruxience for the treatment of RA as observed in the RABBIT register, the observation period for this study was approximated to 2 ½ years.

9.3. Subjects

All patients with RA who initiated Ruxience as their first or subsequent biologic treatment and were enrolled in RABBIT through 31 December 2023 were included in this study with entry defined as the start of treatment with Ruxience.

9.4. Variables

Safety events of special interest were primarily based on the safety events in the Ruxience risk management plan.[14] The following safety events of interest were defined a priori and investigated in the final report:

- Hospitalised infections overall.
- Serious cardiac disorders: heart failure, coronary artery disease, myocardial infarction, other cardiac disorders.
- Malignancies, excluding non-melanoma skin cancer (NMSC).
- NMSC.
- Events associated with use during pregnancy.

In RABBIT, the definition of safety events of special interest was based on pre-specified MedDRA codes. Details are given in **Table 1** below.

Table 1. Safety Events of Special Interest

Outcome	Outcome definition (MedDRA Preferred Terms)
INFECTIONS	
Hospitalised infections overall	Hospitalisation and/or use of parenteral antibiotics + MedDRA Infections and Infestations SOC 10021881
CARDIAC DISORDERS	
Cardiac disorders including heart failure, coronary artery disease, myocardial infarction, other cardiac disorders	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;

Table 1. Safety Events of Special Interest

Outcome	Outcome definition (MedDRA Preferred Terms)
	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; 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.
MALIGNANCIES	
Malignancies (excl. NMSC)	Malignant or unspecified tumours (SMQ)
Non-melanoma skin cancer (NMSC)	10004146 Basal cell carcinoma; 10004178 Basosquamous carcinoma; 10004179 Basosquamous carcinoma of skin; 10006059

Table 1. Safety Events of Special Interest

Outcome	Outcome definition (MedDRA Preferred Terms)
	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	
Events associated with use during pregnancy	The case report form asks about pregnancies which are flagged and coded. At the conclusion of pregnancy, pregnancy outcomes and complications are coded

SOC, system organ class

9.5. Treatment Exposure

Treatment exposure was defined as initiating treatment with Ruxience at enrolment in RABBIT or during follow-up. This group included both b/tsDMARD-naive and b/tsDMARD-experienced patients. If patients from the Ruxience group received concomitant treatment with csDMARD(s), they were still assigned to the Ruxience group.

The Index Date was defined as the date when the first dose of Ruxience was initiated. Patients who switched from another therapy to Ruxience while they were in RABBIT were eligible for enrolment, and the Index Date was the date of initiation of Ruxience. For patients initiating a treatment with Ruxience, different definitions for the time at risk (patient years (PY)) were applied.

- On-drug approach: Patients were evaluated for safety events of special interest while exposed to Ruxience and accrued patient years from Index Date until the first occurrence of the event of interest, death, loss to follow up or completion of follow up (End of Study Period). A 270-day risk window was applied for analyses of all outcomes. The 270 day (e.g. 9 months) risk window period was implemented for Ruxience in part to accommodate ongoing exposure to treatments with longer half-lives, and to ensure that any subclinical or undiagnosed illness at time of end of treatment is captured.
- Ever-exposed approach: Time at risk was calculated from drug initiation until the occurrence of the event of interest, death, end of follow-up, or end of data collection, whichever occurred first. A patient was considered as once exposed, always at risk, despite switching to another drug.
- Ever-exposed approach plus induction period: Time at risk was calculated starting six months after drug initiation until the occurrence of the event of interest, death, end of follow-up, or end of data collection, whichever occurred first. A patient was considered as once exposed, always at risk, despite switching to another drug.

Events were allocated to Ruxience if the event occurred during the time at risk for Ruxience.

Depending on the outcome of interest, different approaches were applied:
- On-drug approach: applied to all outcomes
- Ever-exposed approach: applied only to malignancy outcomes
- Ever-exposed approach plus induction period: applied only to malignancy outcomes.

9.6. Confounders

The reported incidence rates (IR) are crude and not adjusted for any confounders. As this study was focused solely on Ruxience-exposed patients, no comparative analysis was planned and therefore, confounder-adjusted risk estimation by Cox regression was not part of this final report.

9.7. Data sources and measurement

The RABBIT register served as the only data source for this final report.

9.8. Bias

A common problem of observational studies is the lack of randomisation of patients to treatment arms resulting in effect measures being possibly confounded by indication to a therapy.[16] Treatment decision and therefore exposure to a DMARD are usually based on the availability of drugs, the physician's experience to treat patients and on patients' characteristics such as age, severity of symptoms, the individual disease course and specific comorbidities. On the other hand, patients are individually susceptible to develop a particular adverse event depending on characteristics such as age, inflammatory activity of the RA, smoking habits, comorbid conditions or co-medication.

The reported incidence rates are crude and not adjusted for any confounders.

9.9. Study Size

This active surveillance study was not intended to test a pre-specified statistical hypothesis. The size of the active surveillance population depends on use of Ruxience for RA in Germany. All eligible patients enrolled in the RABBIT cohort between the first initiator of Ruxience in 2020 through 31 December 2023 were included in the analyses.

9.10. Data transformation

The Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. Obesity was defined according to the definition of the World Health Organization as BMI $\geqslant$30 kg/m2. The disease activity score based on 28 tender and swollen joints, erythrocyte sedimentation rate (ESR) and patient's global health assessment was calculated (DAS28).[17] Disability was assessed using the Funktionsfragebogen Hannover (FFbH), which is highly correlated to the Health Assessment Questionnaire.[18]

9.11. Statistical methods

9.11.1. Main summary measures

Patient characteristics at Index Date: As summary measures, mean with standard deviation (for continuous variables) or numbers and their according proportion (for categorical variables) were calculated.

Incidence rates (IR): Pre-defined safety events of special interest were listed as cumulative number of incident events during the time of observation, total PY (person-years), IR per 1,000 PY, and 95% confidence interval (CI). The calculation of PY was based on the sum of the months at risk per patient and Ruxience exposure group divided by twelve. For patients

without events, the total time at risk during the observation period was included in the calculation of PY. For calculating IRs, the first event per patient was taken into account. To calculate CI, a Poisson distribution was assumed.[19]

9.11.2. Main statistical methods

Not applicable

9.11.3. Missing values

Proportion of missing data are provided for the main baseline variables.

9.11.4. Sensitivity analyses

None

9.11.5. Amendments to the statistical analysis plan

None

9.12. Quality control

Results for this final report consist of anonymized data provided to Pfizer from the RABBIT register. The administrators of the RABBIT register follow specific quality control measures as described below.

All data from questionnaires (CRFs) are sent to the RABBIT register holder by fax. After having received them, the initial plausibility checks are performed. Missing or implausible variables are stratified into different groups: for some variables, missing values or implausible values are always queried, for other variables, missing or implausible values are only queried when values of other variables are also queried, and for some variables, missing or implausible values are not queried at all. Disease related information (joint count, inflammation markers, physician reported disease activity, etc.) and information related to DMARD treatment (start and stop dates, reasons for discontinuation of DMARDs, etc.) are always queried. There are no inquiries if physician reported weight or any patient reported variables (e.g., general health state, functional state, fatigue, pain, smoking habits, etc.) are missing. After the first monitoring steps, data are entered into the database. At regular intervals (every eight weeks) a new dataset is created by adding the new data. After this process the next monitoring steps are performed, mainly regarding longitudinal data plausibility.

If more than two follow-up time points are missing in one patient, an intensive drop out inquiry starts. First, the physician is queried to determine if anything is known about the patient's whereabouts. Secondly, the patient (or his/her relatives living in the same household) is contacted to determine why there have been no visits to the rheumatologist and whether the patient is still in rheumatologic care. If insufficient information is received after these first steps, authorities are asked (e.g., registration office) about new addresses, or whether the patient has died. In the latter case, health authorities are subsequently contacted to obtain causes of death.

9.13. Protection of human subjects

Subject information and consent

Results for this study were provided to Pfizer in the form of anonymized data. Patients provided written informed consent to the administrators of the RABBIT register before study entry in RABBIT.

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

The original study protocol was approved on 1 March 2001 by the ethics committee of the Charité University Medicine, Berlin, Germany (Protocol number 1508/2001). A revised and updated study protocol received approval on 5 July 2021 (Protocol number EA4/123/21).

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 followed generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology, and Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association.

10. RESULTS

10.1. Patients

After applying the inclusion and exclusion criteria of this study, 19 patients initiated a treatment with Ruxience either at enrolment (n=1) or during follow-up (n=18) and were therefore eligible for this analysis. Of note, patients receiving Ruxience were enrolled from 2020 onwards when Ruxience received its marketing authorisation in the European Union.

10.2. Descriptive data

Characteristics of patients at the time of Ruxience initiation are given in **Table 2**. This final report includes therapy and safety data for Ruxience-exposed patients with RA enrolled and observed in the RABBIT register from the first Ruxience initiator in 2020 through 31 December 2023. For the purposes of this study, patients with RA in the Ruxience cohort were followed-up from the time of their initiation of Ruxience and the mean time on treatment was 8.9 months. Table 2 also shows the total follow up of these patients in the RABBIT register overall. These patients had a mean age of 64.5 years and 68.4% were female. Duration of RA disease was on average 13.1 years and all of the patients were rheumatoid factor or anti-citrullinated protein antibodies (ACPA) positive. The mean disease activity at the time of Ruxience initiation as measured by the Disease Activity Score (DAS 28) was 3.2. Patients had received a mean of 1.5 different csDMARDs and 3.1 different bDMARDs or tsDMARDs prior to Ruxience initiation. The majority of patients received concomitant glucocorticoids (73.7%), and about half received concomitant methotrexate (47.4%). The mean number of comorbid conditions was 3.7, whereas 84.2% of patients with at least 3 comorbidities were reported. Most of the patients were former or current smokers (77.9%).

Table 2. Characteristics of patients at the time of initiation of Ruxience

Characteristics	Statistics	Ruxience
No. of patients	n	19
Total follow-up in the RABBIT register		
Total years of follow-up in RABBIT	Mean (SD)	5.0 (1.4)
<3 years of follow-up in RABBIT	n (%)	2 (10.5)
3 - <4 years of follow-up in RABBIT	n (%)	4 (21.1)
4 - <5 years of follow-up in RABBIT	n (%)	2 (10.5)
⩾5 years of follow-up in RABBIT	n (%)	11 (57.9)
Time on Ruxience		
Total time on treatment (years)	Mean (Std)	8.9 (2.4)
Years of follow-up since first initiation of Ruxience	Mean (Std)	1.7 (0.9)
<1 year of follow-up since first initiation of Ruxience	n (%)	8 (42.1)
1 - <2 years of follow-up since first initiation of Ruxience	n (%)	0 (0)
⩾2 years of follow-up since first initiation of Ruxience	n (%)	11 (57.9)
Demographics and clinical information		
Age (years)	Mean (SD)	64.5 (11.7)
	n miss (%)	0 (0)
Age <65 years	n (%)	10 (52.6)
Age 65-74 years	n (%)	4 (21.1)
Age ≥75 years	n (%)	5 (26.3)
Female	n (%)	13 (68.4)
	n miss (%)	0 (0)
Disease duration (years)	Mean (SD)	13.1 (10.2)
	n miss (%)	0 (0)
Rheumatoid factor and/or ACPA positive	n (%)	19 (100.0)
	n miss (%)	0 (0)
Disease activity DAS28-ESR	Mean (SD)	3.2 (1.3)
	n miss (%)	4 (21.1)
ESR (mm/h)	Mean (SD)	18.7 (23.3)
	n miss (%)	1 (5.3)
CRP (mg/l)	Mean (SD)	11.3 (16.4)
	n miss (%)	1 (5.3)
28 Swollen joint count	Mean (SD)	1.0 (2.6)
	n miss (%)	0 (0)
28 Tender joint count	Mean (SD)	3.6 (6.5)
	n miss (%)	0 (0)
Joint erosions	n (%)	13 (68.4)
	n miss (%)	0 (0)
FFbH (% of full physical function, 0-100)	Mean (SD)	51.9 (22.8)

Table 2. Characteristics of patients at the time of initiation of Ruxience

Characteristics	Statistics	Ruxience
	n miss (%)	0 (0)
Patient reported global health (NRS 0-10)	Mean (SD)	4.6 (2.4)
	n miss (%)	3 (15.8)
Patient reported fatigue (NRS 0-10)	Mean (SD)	4.1 (2.8)
	n miss (%)	1 (5.3)
Patient reported pain (NRS 0-10)	Mean (SD)	4.2 (2.7)
	n miss (%)	0 (0)
Previous treatments		
No. of previous csDMARDs	Mean (SD)	1.5 (1.4)
	n miss (%)	0 (0)
No. of previous b/tsDMARDs	Mean (SD)	3.1 (1.1)
	n miss (%)	0 (0)
Previous bDMARDs ≥2	n (%)	18 (94.7)
Oral GC, 6 months prior to enrolment	n (%)	9 (47.4)
	n miss (%)	0 (0)
Oral GC dose, 6 months prior to enrolment (mg/d)	Mean (SD)	3.1 (5.5)
	n miss (%)*	0 (0)
Oral GC dose, 6 months prior to enrolment (mg/d)		
<5 mg/d	n (%)	14 (73.7)
5 - <10 mg/d	n (%)	3 (15.8)
≥10 mg/d	n (%)	2 (10.5)
Concomitant medications		
Oral GC	n (%)	14 (73.7)
	n miss (%)	0 (0)
Oral GC dose (mg/d)	Mean (SD)	4.1 (4.8)
	n miss (%)*	0 (0)
Oral GC dose (mg/d)		
<5 mg/d	n (%)	8 (42.1)
5 - <10 mg/d	n (%)	8 (42.1)
≥10 mg/d	n (%)	3 (15.8)
NSAID or Cox-II-Inhibitor	n (%)	6 (50.0)
	n miss (%)	7 (36.8)
csDMARD (including Methotrexate)	n (%)	9 (47.4)
	n miss (%)	0 (0)
Methotrexate	n (%)	9 (47.4)
	n miss (%)	0 (0)
Comorbidities		

Table 2. Characteristics of patients at the time of initiation of Ruxience

Characteristics	Statistics	Ruxience
No. of comorbidity	n (%)	3.7 (2.4)
≥3 comorbidities	n (%)	16 (84.2)
	n miss (%)	0 (0)
Hypertension	n (%)	12 (63.2)
Coronary heart disease	n (%)	4 (21.1)
History of heart failure	n (%)	1 (5.3)
Hyperlipoproteinaemia	n (%)	4 (21.1)
Diabetes mellitus	n (%)	3 (15.8)
History of malignancy	n (%)	0 (0)
History of lymphoma	n (%)	0 (0)
Chronic renal disease	n (%)	3 (15.8)
Osteoporosis	n (%)	7 (36.8)
History of tuberculosis	n (%)	0 (0)
Chronic obstructive pulmonary disease	n (%)	3 (15.8)
History of total joint replacement	n (%)	4 (21.1)
Body mass index (kg/m^2)	Mean (SD)	30.3 (4.9)
Body mass index ≥30 kg/m^2	n (%)	6 (31.6)
	n miss (%)	0 (0)
Smoking		
Never	n (%)	5 (33.3)
Former	n (%)	11 (57.9)
Occasionally	n (%)	0 (0)
Current	n (%)	3 (20.0)
	n miss (%)	4 (21.1)

Characteristics refer to the time of initiation of Ruxience unless otherwise indicated.

10.3. Outcome data

The overall numbers of incident events, PY and crude, non-adjusted IR with 95% CI for pre-defined safety events of special interest in patients exposed to Ruxience were calculated. For all investigated events, numbers are given for the on-drug approach in **Table 3**. For malignancy outcomes, an ever-exposed approach was applied and additionally an induction period of 180 days was considered as described in **Table 4**.

10.4. Main results

Hospitalised infections

One hospitalised infection occurred in the Ruxience group resulting in an IR of 67.8 (95% CI 1.72; 377.74) events per 1,000 PY (**Table 3**).

Serious Cardiac disorders

Two events of the composite outcome cardiac disorders occurred in the Ruxience group resulting in an IR of 136.4 (95% CI 16.51; 492.48) events per 1,000 PY (**Table 3**).

Malignancies
No events of malignancies or NMSC occurred in the Ruxience group (**Table 3**, **Table 4**).

Events associated with use during pregnancy
No patients were exposed to Ruxience before or during pregnancy.(Table 3).

Table 3. Crude, unadjusted incidence rates for pre-defined safety events of interest stratified by treatment applying the on-drug approach

Outcome	No.	PY	IR	LCL	UCL
On-drug approach (Total PY: 14.83)					
Hospitalised infections	1	14.75	67.80	1.72	377.74
Serious Cardiac disorders	2	14.67	136.36	16.51	492.48
Malignancies, excluding NMSC	0	14.83	0.00	0.00	248.74
NMSC	0	14.83	0.00	0.00	248.74
Events associated with use during pregnancy	0	0	-	-	-

Incidence rates are given per 1,000 patient years.
Abbreviations: IR, incidence rate; LCL, 95% lower confidence limit; NMSC, non-melanoma skin cancer; No., number of events; PY, patient years; UCL, 95% upper confidence limit.

Table 4. Crude, unadjusted incidence rates for pre-defined safety events of interest stratified by treatment applying the ever-exposed approach and the ever-exposed approach plus induction period

Outcome	No.	PY	IR	LCL	UCL
Ever-exposed approach (Total PY: 38.00)					
Malignancies, excluding NMSC	0	38.00	0.00	0.00	97.08
NMSC	0	38.00	0.00	0.00	97.08
Ever-exposed approach considering an induction period (Total PY: 28.83)					
Malignancies, excluding NMSC	0	28.83	0.00	0.00	127.95
NMSC	0	28.83	0.00	0.00	127.95

Incidence rates are given per 1,000 patient years.
Abbreviations: IR, incidence rate; LCL, 95% lower confidence limit; NMSC, non-melanoma skin cancer; No., number of events; PY, patient years; UCL, 95% upper confidence limit.
Not applicable

10.5. Other analyses

None

10.6. Adverse events / adverse reactions

For this study, Pfizer received data from RABBIT in an anonymized, structured format. Thus, the minimum criteria for reporting an adverse event (AE) (ie, identifiable patient, identifiable reporter, a suspect product, and event) were not met.

11. DISCUSSION

11.1. Key results

This final report analysed and summarised data collected during the observation of patients with RA treated with Ruxience in daily rheumatologic care who were enrolled and observed in the German biologics RABBIT register between the time of Ruxience availability in 2020 through December 2023. The aim of this PASS was to investigate relevant safety events of special interest associated with Ruxience treatment. Crude IRs were assessed.

A total of 19 patients with RA initiated treatment with Ruxience during their observation time in the RABBIT register. These patients had a mean total follow-up time in the RABBIT register of 5 years and a mean duration of Ruxience exposure of 8.9 months. The total exposure time amounted to 14.8 PY in the on-drug approach adding a three-month risk window, 38.0 PY in the ever-exposed approach without induction period, and 28.8 PY in the ever-exposed approach considering an induction period (see Table 3 and Table 4). At the time of Ruxience initiation, patients were on average 65 years old, and 68% were female (see Table 2).

With regard to the occurrence of prespecified safety events of interest, one event of hospitalised infections and two events of serious cardiac disorders were reported in patients exposed to Ruxience. Due to the low number of PY, the respective IRs were high and CIs were large. No events were reported for the outcomes malignancies and NMSC, or events associated with use during pregnancy. Without a comparator group and given the very small number of patients and events, IRs could only be enumerated descriptively but not interpreted.

11.2. Limitations

General limitations lie within the study design upon which this final report is based. Observational cohort studies on drug treatment examine unselected patients in daily care. Due to non randomisation of patients to defined treatment arms, these studies are prone to confounding by indication.[16] Treatment decision and therefore exposure to a DMARD are usually based on the availability of drugs, the provider's experience treating patients with them and on patients' characteristics such as age, severity of symptoms, disease course and specific comorbidities. There might be a channelling of patients with a more severe disease of RA to certain therapies. Even after careful adjustment, such confounding can never be entirely ruled out. Since observational studies follow patients over very long time periods, they are also prone to attrition bias, i.e. selective loss to follow-up. However, drop-out rates in the RABBIT register are rather low. Only 6% of patients drop out per annum.[20]

11.3. Interpretation

Since Ruxience's availability in Germany, only a very small number of persons with RA initiated Ruxience either as the first or subsequent biologic, hence, no meaningful interpretation of these data is possible.

11.4. Generalizability

In general, RABBIT is a nationwide, population-based cohort study including non-selected patients with established RA in daily routine rheumatological care. No inclusion or exclusion criteria are applied, except that patients must be at least 18 years of age at enrolment, have RA disease onset after 15 years of age and start a new DMARD treatment. Results are therefore generalisable to this patient population. However, therapeutic decision making may vary across countries according to the health care system and its requirements

12. OTHER INFORMATION

Not applicable

13. CONCLUSIONS

This report describes the uptake of Ruxience for the treatment of RA since its availability in 2020 in rheumatology units in Germany participating in the RABBIT register. All a priori defined serious safety events of special interest up to 31 December 2023 under Ruxience treatment reported to and collected and assessed by the RABBIT register are included. During the reporting period, the uptake of Ruxience as a treatment option for patients with RA was very low (n=19), therefore, no conclusions can be drawn from these data.

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Document Approval Record

Document Name:	B3281012 RABBIT Final Study Report_23AUG2024
Document Title:	B3281012 FINAL STUDY REPORT_23AUG2024

Signed By:	Date(GMT)	Signing Capacity
Younus, Muhammad	23-Aug-2024 14:47:24	Final Approval
De Bernardi, Barbara	27-Aug-2024 19:41:40	EUQPPV Approval
De Bernardi, Barbara	27-Aug-2024 19:42:30	EUQPPV Approval
Younus, Muhammad	27-Aug-2024 20:26:17	Final Approval