NON-INTERVENTIONAL STUDY REPORT

Study 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 British Society for Rheumatology Biologics Register-Rheumatoid Arthritis (BSRBR-RA)
Protocol number	B3281011
Version identifier of the study report	1.0
Date	22 February 2024
EU Post Authorization Study (PAS) register number	EUPAS37688
Active substance	PF-05280586 Rituximab
Medicinal product	Ruxience (rituximab)
Research question and objectives	**Research question** What are the incidence rates of safety events of special interest in patients with rheumatoid arthritis who are enrolled in the BSRBR-RA and 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 BSRBR-RA who initiate Ruxience.
Country(-ies) of study	United Kingdom

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TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

Annex 1. List of stand-alone documents

Appendix 1. SIGNATURES

Appendix 2. PROTOCOL

Appendix 4. STATISTICAL ANALYSIS PLAN

Not applicable

1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Rheumatology
ACS	Acute coronary syndrome
ADA	Adalimumab
AE	adverse Event
BSRBR	British Society for Rheumatology Biologics Register
BSRBR-RA	British Society for Rheumatology Biologics Register Rheumatoid Arthritis
CI	confidence interval
CLL	Chronic lymphocytic leukaemia
csDMARD	Conventional Synthetic Disease Modifying Anti-rheumatic Drug
CV	cardiovascular
CVD	cardiovascular disease
DALYS	Daily-adjusted Life Years
DAS-28	Disease Activity Score 28
DMARD	disease modifying anti-rheumatic drug
EEIG	European Economic Interest Grouping
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ETA	etanercept
EU	European Union
GPA	Granulomatosis polyangiitis
HRQoL	Health-related Quality of Life
ICD	International Classification of Diseases
IEC	Independent Ethics Committee
INF	infliximab
IRB	Institutional Review Board
MA	Market Authorisation
MACE	Major acute cardiovascular events
MAH	Market Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MPA	Microscopic polyangiitis

Abbreviation	Definition
NHL	Non-Hodgkin's lymphoma
NI	Non-Interventional
NICE	National Institute for Health and Clinical Excellence
NMSC	non-melanoma skin cancer
NSAIDs	non-steroidal anti-inflammatory drugs
PAS	Post-Authorisation Study
PASS	Post-Authorization Safety Study
PV	Pemphigus Vulgaris
RA	Rheumatoid Arthritis
QALY	Quality-adjusted Life Year
RMP	Risk management plan
SAP	Statistical Analysis Plan
SMQ	Standarised MedDRA Queries
TNF	tumor necrosis factor
TNFi	tumor necrosis factor inhibitor
UK	United Kingdom

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

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

Not applicable

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Registration in EU PAS register	21-Oct-2020	21-Oct-2020	
Start of data collection	31-May-2021	31-May-2021	
Date of first annual report	31-Jul-2021	Report not prepared	Insufficient patients enrolled
Date of second annual report	31-Jul-2022	Report not prepared	Insufficient patients enrolled
Date of third annual report	31-Jul-2023	Report not prepared	Insufficient patients enrolled
End of data collection	31-Jul-2023	31-Jul-2023	
Final report of study results	31-Dec-2023	19-Feb-2024	

6. 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.(1) 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.(2) Compared with the general population, RA patients are at a higher risk of infections, CV disease (CVD) and malignancies (including lymphoma).(3-11) 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).(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 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.(14) The EMA approved two rituximab biosimilars from 2 MAHs including Rixathon (Sandoz) in June 2017, and Truxima (Celltrion) in November 2018. PF-05280586 (Ruxience) was developed by the Market Authorisation Holder (MAH - Pfizer) as a proposed biosimilar to the licensed reference product MabThera and was approved by the EMA on 1 April 2020.

The MAH proposed the assessment of safety events of special interest based on the Ruxience RMP v. 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).

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

7. RESEARCH QUESTION AND OBJECTIVES

What are incidence rates of safety events of special interest in patients with RA who are enrolled in the BSRBR-RA and initiate treatment with Ruxience?

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 BSRBR-RA who initiate Ruxience.

8. AMENDMENTS AND UPDATES

None

9. RESEARCH METHODS

9.1. Study design

This was an active surveillance descriptive study using existing data within the BSRBR-RA, 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-marketed clinical use in the UK.

9.2. Setting

The BSRBR-RA was established in 2001 to study the safety of biologic therapies in RA patients living in the UK. For the first 7-8 years the main focus was on the study of the safety profile of the first three tumor necrosis factor inhibitor (TNFi) agents (ie, adalimumab (ADA), etanercept (ETA) and infliximab (INF) as a class and as individual therapies. At the time the register was established, the most appropriate comparison group for these three TNFi agents was patients with active RA receiving treatment with csDMARDs. The register remains a relevant resource for studying the safety profile of new biologic, biosimilar and other targeted therapies as they receive National Institute for Health and Clinical Excellence (NICE) approval and are used in real world practice where patients have more diverse clinical background and comorbidities than a typical clinical trial population.

Unique features of BSRBR-RA include recruitment and collection of data from parallel comparison groups of patients consisting of (i) those with active RA who were treated with csDMARDs, and (ii) those with active RA who are biologic naïve treated with TNFi, a high proportion of recruited patients in the UK (>80%), and linkage with national mortality and malignancy registries.(15) Several studies have been conducted using data from the BSRBR-RA including work regarding risks of infections(16) and malignancies.(17)

External validity, ie, generalisability to RA patients who are not enrolled in the register, is maximised by encouraging physicians to enrol each and every patient meeting inclusion criteria, regardless of their baseline demographic or clinical characteristics or treatment history.

9.2.1. Inclusion Criteria

Patients in this study were included if they satisfied the following criteria:

1. Eligible for inclusion in BSRBR-RA (18);
2. Newly initiated treatment with Ruxience for RA;
3. Age >16 years at the initiation of Ruxience treatment.

9.2.2. Exclusion Criteria

There were no exclusion criteria for this study.

9.3. Variables

This study focused on specific variables routinely captured in the BSRBR-RA 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, CV events, and events associated with use during pregnancy.

9.3.1. Baseline Data

Baseline data were derived from BSRBR-RA reported by the recruiting clinician (or patient where noted), using a standardised form:

1. Diagnosis (including the presence or absence of those features listed in 1987 American College of Rheumatology (ACR) criteria for RA);
2. Age at treatment start, gender, year of recalled symptom onset, year of diagnosis;
3. Ethnicity (patient form);
4. Previous drug history of immunosuppressive csDMARDs and biologics, biosimilar or other new advanced therapy, including duration of therapy recorded as start month/year;
5. Comorbidities;
6. Al current therapy for all illnesses.

9.3.2. Endpoints

The BSRBR-RA is an existing, efficient data collection system for evaluating a range of safety outcomes associated with therapies used to treat RA including cancers,(17) cardiovascular events(19) and serious infections.(16) The endpoints collected in BSRBR-RA are events associated with RA itself and therapies used to treat moderate to severe disease.

The following events of interest were pre-specified for this study:

1. Hospitalised infections overall;

2. Non-melanoma skin cancer (NMSC);

3. Cardiac disorders, including but not limited to heart failure, coronary artery disease, myocardial infarction, and other cardiac disorders;

4. Malignancies, excluding NMSC;

5. Events associated with use during pregnancy.

9.4. Data sources and measurement

BSRBR is the source of core baseline data, including patient demographics and disease characteristics collected by the recruiting clinician, using a standardised form.

Follow up

BSRBR data are the source of information on anti-rheumatic treatment, updated every 6-12 months depending on how long a patient has been in the register (6 monthly for the first 3 years and 12 monthly thereafter). This change is to reduce the burden of data capture on study sites, but the same data are collected at each follow-up. As patients starting Ruxience will have been enrolled previously when they started Mabthera, follow up may only be every 12 months. Some patients starting Ruxience as their first anti B cell therapy will provide data more often as per the BSRBR protocol and some trusts may decide themselves to reconsent patients each time they switch drugs and send data every 6 months for 3 years again. Data captured includes continuation on drug and dates and reasons for stopping, with details of any change in dose and commencement of any new co therapy. Clinical information to permit calculation of the Disease Activity Score in 28 joints (DAS 28) is also collected.

Endpoints

BSRBR data include reports of serious morbidity reported directly by the rheumatology team at each scheduled follow-up date. For serious events additional data are captured, either against a pre-specified set of questions for certain events of special interest or using an open request for additional data. All events included in this protocol are considered events of special interest. All serious morbidities reported to BSRBR are coded by a trained nurse using the Medical Dictionary for Regulatory Activities (MedDRA).

BSRBR is linked to the UK national death and cancer registers which allow the “flagging” of individuals such that if they die or are entered in a cancer register, the BSRBR-RA learns of the event and obtains death certificate details or cancer register details. These data are held in a separate secure data safe haven at the University of Manchester. On average deaths are usually reported within 1 week to the national register although cancers can take much longer due to the structure of national reporting. BSRBR-RA received a download of death and cancer on average once/year. Table 1 provides a list of 10th revision of International

Classification of Diseases and MedDRA codes for select safety endpoints in the BSRBR-RA and other RA registries in Europe and elsewhere.

Table 1. ICD and MedDRA Codes for Select Safety Endpoints

	ARTIS		BIOBADASER, BSRBR, RABBIT
Event	**Operationalisation**	**Validation ICD**	**Operationalisation (Final list TBD based on reported endpoints)**
Serious infections	Hospitalisations in the Patient Register listing as main diagnosis ICD10-codes below. If main diagnosis is RA, contributory diagnoses are also considered. A00-B99 (excluding A33 and A50), D73.3, E32.1, G00-G02, G04.2, G05-G07, H00.0, H44.0, H60.0-H60.3, H66-H67, H70, I30.1, I40.0, J00-J22, J32, J34.0, J36, J39.0-J39.1, J44.0, J85, J86, K04.4, K04.6, K04.7, K10.2, K11.3, K12.2, K14.0, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.1, K65.2, K65.9, L00-L08, L30.3, M00-M01, M46.2-M46.5, M60.0, M65.0, M71.0, M71.1, M72.6, M86, N13.6, N15.1, N15.9, N30.0 N30.8, N34.0, N41.2, N43.1, N45.2, N45.3, N45.4, N48.2, N61, N70, N73, N75.1.	This algorithm has not been specifically validated in ARTIS, but the register itself is subject to strict quality assurance routines and has been validated several times. References: Ludvigsson et al. External Review and Validation of the Swedish National Inpatient Register, BMC Public Health, 2011 (11):450. http://www.socialstyrelsen.se/register/halsodataregister/patientregistret/inenglish.	Hospitalisation and/or use of parenteral antibiotics + MedDRA Infections and Infestations SOC 10021881.
CV risk	Major Acute Cardiovascular Events (MACE), combines MI, stroke, and fatal cardiovascular events: I00-I99 as main cause of death, or I20.0, I21, I60-I64 as diagnosis in in- or outpatient care.	See Serious Infections 'Outcome' was defined as any first-ever acute coronary syndrome (ACS) event, which in turn was defined as a primary discharge diagnosis of acute myocardial infarction or unstable angina pectoris, or as acute myocardial infarction being the underlying cause of death. For discharge diagnoses, the date of admission to hospital was considered the event date. This outcome definition has previously been validated in a Swedish early RA cohort, with a positive predictive value of 95%. In addition, a regional validation study of hospitalised acute MI and stroke found positive	Fatal and non-fatal 10000891 Acute myocardial infarction; 10006147Brain 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

Table 1. ICD and MedDRA Codes for Select Safety Endpoints

	ARTIS		BIOBADASER, BSRBR, RABBIT
Event	**Operationalisation**	**Validation ICD**	**Operationalisation (Final list TBD based on reported endpoints)**
		predictive values of 96% and 94% respectively, in the period 1977 to 1987. References: https://onlinelibrary.wiley.com/doi/epdf/10.1002/art.39267 Mantel et al. Risk Factors for the Rapid Increase in Risk of Acute Coronary Events in Patients With New-Onset Rheumatoid Arthritis. A Nested Case-Control Study. Arthritis & Rheumatology. 2015; 67(11):2845-2854. Lindblad et al. Validity of register data on acute myocardial infarction and acute stroke. Scandinavian Journal of Public health 1993; 21 (1):3-9.	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;

Table 1. ICD and MedDRA Codes for Select Safety Endpoints

	ARTIS		BIOBADASER, BSRBR, RABBIT
Event	**Operationalisation**	**Validation ICD**	**Operationalisation (Final list TBD based on reported endpoints)**
			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.

Table 1. ICD and MedDRA Codes for Select Safety Endpoints

	ARTIS		BIOBADASER, BSRBR, RABBIT
Event	**Operationalisation**	**Validation ICD**	**Operationalisation (Final list TBD based on reported endpoints)**
NMSC	Identified through the Cancer register as all malignancies with ICD-O/2 code C44, and all basal cell cancers recoded in the register's subcomponent on basal cell cancers Alt: all invasive NMSC, identified as non-benign ICD-O/2 code C44, and no basal cell cancers.	About 99% of cancers have been morphologically verified. Reporting of incident cancers (including invasive malignancies as well as cancer in situ) is mandatory and semi automated, resulting in an estimated coverage greater than 95%.	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.
Malignancy	All invasive malignancies recorded in the cancer register, excluding NMSC.	See NMSC.	Malignant or unspecified tumours (SMQ).

9.5. Bias

Not applicable.

9.6. Study Size

This was a descriptive study without pre specified hypotheses, therefore there was no minimum sample size requirement. All Ruxience-treated patients with data in the BSRBR-RA during the study period were included in this study. Table 1 displays precision estimates included in the study protocol for reported incidence proportions of safety events in Ruxience RMP.

Table 2. Precision Estimates for Reported Incidence Proportions of Safety Events in Ruxience RMP[12]

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
Malignancy (excluding NMSC)	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

NMSC, non-melanoma skin cancer; CV, cardiovascular; CI, confidence interval.

9.7. Data transformation

All data are submitted by the local hospital sites to the University of Manchester via a secure online web portal. The BSRBR-RA data capture system is a web-based (https://bsrbr.org/database/), access managed, secure system hosted on the University of Manchester virtual secure servers, which is accessed by 160 NHS clinical sites across the UK. NHS clinical staff use the web interface to log into their restricted area, enter and submit clinical data and efficiently communicate with study staff. The system uses encryption in transit and at rest and secure web authentication.

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

9.8. Statistical methods

9.8.1. Main summary measures

See section 9.8.2.

9.8.2. Main statistical methods

All statistical analyses were performed by BSRBR using Stata.

The general analytic approach was descriptive and included rates of events of interest among Ruxience-treated patients. Data were presented as number of events, incidence rates and 95 % confidence intervals. Such analyses were performed by and at the direction of BSRBR based on an a priori statistical analysis plan (SAP) maintained by University of Manchester

and shared with the Sponsor. The codes were harmonised with other registers conducting similar analysis.

Index Date

The Index Date is the date of Ruxience initiation. Patients who switch from another therapy to Ruxience while they are enrolled in BSRBR-RA are eligible for enrollment, and the index date will be the date of Ruxience initiation.

Risk Window

Patients were evaluated for safety events of interest while exposed to Ruxience and accrued person-time from Index Date until the first occurrence of the event of interest, death, date of last scheduled clinical data provision to the register, lost to follow up, exit from the register or completion of approximately 2 years of follow up. The final report censored all patients at 2 years after Date of Study Start.

Some outcomes of interest in this study are thought to potentially occur at a higher rate while on the drug, but that increased risk subsides after the drug is discontinued (ie, serious infections, CV events). In these situations, these events are calculated using a risk window from Ruxience initiation until 270 days (eg, 9 months) after last infusion based on Ruxience's half-life and mechanism of action. This does not apply to patients who were lost to follow-up, have exited the registry, completed 3 years of follow-up or for whom the most recent date of clinical data provision to the register is within the 270 day window, in which case data will be censored on that date instead. Based on The National Institute for Care and Health Excellence (NICE) guidelines on the use of rituximab treatment, most patients will not be considered for further treatment with Ruxience until at least 6 months from the date of last infusion.

For non-melanoma skin cancer (NMSC) and other malignancies, the manifestation of which is expected to be delayed relative to the time of exposure, the outcomes were evaluated from drug initiation until the first event, loss to follow up or completion of 2 years of follow up, reflecting a once exposed always at risk paradigm.

Because of the very low number of patients exposed to Ruxience in this study, annual reports were not prepared and only this final report has been prepared. Furthermore, due to the very small number of Ruxience-exposed patient (n=3), data protection practices prohibited the presentation of any demographic or clinical characteristic for these 3 patients.

9.8.3. Missing values

Not applicable

9.8.4. Sensitivity analyses

None

9.8.5. Amendments to the statistical analysis plan

None

9.9. Quality control

BSRBR-RA have guidelines in place to monitor and maintain the quality of the data received. All information received on serious adverse events are reviewed by 1 of 2 trained registered nurses prior to coding. Reports can be sent from hospitals treating the patient, the patients themselves, or the national registers. Reporting malignancies to the national cancer registries is mandatory by law in the UK. To allow serious adverse events to be processed, the following information is required as a minimum:

- A legible and recognised disorder/sign/symptom;
- The date of event;
- Which targeted therapy drug(s) the patient was on at the time of the event.

Where information is missing, the BSRBR-RA pharmacovigilance team contacts the hospital to validate and confirm the details around the serious adverse event. Where a serious adverse event is reported by a patient, a request for information is sent to the hospital for validation. Events that do not fall under the definition of a serious adverse event are not subject to such validation. The data undergo regular validation checks both manually and automatically.

9.10. Protection of human subjects

Subject information and consent

Not applicable.

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

The analyses for the Ruxience PASS were completed using fully anonymised data. The data do not contain any patient identification information (eg, name), except for a unique number assigned for the purpose of linking files.

The BSRBR-RA protocols are approved by the Northwest 5 Research Ethics Committee (REC 00/8/053 with most recent approval amendment (#27) approval date of 06 Dec 2018).

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 Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), EMA, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology.

10. RESULTS

10.1. Participants

During the study period, a total of 3 patients with RA initiated Ruxience in the BSRBR-RA. Patients were recruited from 3 hospitals across the UK prescribing this treatment for RA. In terms of comparison cohorts, 2160 anti-TNF treated patients and 3694 csDMARD treated patients were also recruited to the BSRBR-RA at any time since establishment of the registry.

10.2. Descriptive data

The baseline characteristics of the cohorts are presented in **Table 3** and **Table 4**. Due to data protection practices, data on patients starting Ruxience have not been stratified by gender, age or baseline characteristics.

Table 3. Baseline demographic details of patients registered in the csDMARD and anti-TNF cohorts, and those initiating Ruxience

		csDMARD Cohort	Anti-TNF Cohort	Ruxience Cohort
Cumulative number of registrations		3694	2160	3
Cumulative number by gender	**Male**	1018 (27.6%)	521 (24.1%)	-
	Female	2676 (72.4%)	1639 (75.9%)	-
Cumulative number by age at registration	**16-18**	2 (<1%)	2 (<1%)	-
	19-34	122 (3.3%)	140 (6.5%)	-
	35-44	326 (8.8%)	207 (9.6%)	-
	45-54	676 (18.3%)	517 (23.9%)	-
	55-64	1192 (32.3%)	634 (29.4%)	-
	65-74	969 (26.2%)	525 (24.3%)	-
	75 +	407 (11.0%)	135 (6.3%)	-

Table 4. Baseline characteristics of patients registered in the csDMARD and anti-TNF cohorts, and those initiating Ruxience

		csDMARD Patients [N = 3694]			Anti-TNF Patients [N = 2160]			Ruxience Patients [N = 3]		
		N	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Age in Years	Male	1018	61.4	11.9	521	58.7	11.4	-	-	-
	Female	2676	59.6	12.6	1639	56.7	13.3	-	-	-
	Total	**3694**	**60.1**	**12.4**	**2160**	**57.2**	**12.9**	**3**	**73.8**	**4.4**
Years since diagnosis	Male	1010	8.6	9.4	503	56.7	13.3	-	-	-
	Female	2661	10.0	10.7	1604	9.3	9.7	-	-	-
	Total	**3671**	**9.6**	**10.4**	**2107**	**9.0**	**9.4**	**3**	**29.0**	**11.5**
HAQ	Male	794	1.3	0.8	400	1.3	0.8	-	-	-
	Female	2163	1.6	0.7	1260	1.6	0.7	-	-	-
	Total	**2957**	**1.5**	**0.8**	**1660**	**1.5**	**0.8**	**-**	**-**	**-**
DAS28	Male	996	4.9	1.4	520	5.9	1.1	-	-	-
	Female	2643	5.2	1.3	1635	6.0	1.0	-	-	-
	Total	**3639**	**5.1**	**1.3**	**2155**	**5.9**	**1.1**	**-**	**-**	**-**
Tender Joint Count	Male	996	7.9	6.9	489	14.3	7.5	-	-	-
	Female	2628	8.7	6.6	1557	14.5	7.1	-	-	-
	Total	**3624**	**8.4**	**6.7**	**2046**	**14.5**	**7.2**	**-**	**-**	**-**
Swollen Joint Count	Male	995	5.8	5.3	489	9.0	5.3	-	-	-
	Female	2626	5.8	4.8	1554	8.4	4.9	-	-	-
	Total	**3621**	**5.8**	**4.9**	**2043**	**8.5**	**5.0**	**-**	**-**	**-**
ESR	Male	910	33.4	24.8	382	31.0	27.2	-	-	-

	Female	2389	35.0	24.4	1221	30.1	24.0	-	-	-
	Total	**3299**	**34.6**	**24.5**	**1603**	**30.3**	**24.8**	**-**	**-**	**-**
CRP	Male	318	35.8	39.5	291	26.0	32.0	-	-	-
	Female	816	30.8	36.4	919	20.5	26.4	-	-	-
	Total	**1134**	**32.2**	**37.4**	**1210**	**21.8**	**27.9**	**-**	**-**	**-**
Global Health VAS	Male	997	52.3	24.3	477	71.5	20.3	-	-	-
	Female	2633	56.1	23.9	1512	73.9	19.9	-	-	-
	Total	**3630**	**55.1**	**24.1**	**1989**	**73.3**	**20.0**	**-**	**-**	**-**

10.3. Outcome data

See section 10.2.

10.4. Main results

See section 10.2.

10.5. Other analyses

During the study period there were no safety events of special interest reported among the 3 patients who initiated Ruxience.

10.5.1. Adverse events / adverse reactions

This study involves data that exists as structured data by the time of study start of 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 (i.e. identify a potential associated between) a particular medicine and medical event for any individual. Thus, the minimum criteria for reporting an AE (i.e. identifiable patient, identifiable reporter, a suspect product and event) cannot be met.

11. DISCUSSION

11.1. Key results

During the study period, only 3 patients with RA initiated Ruxience in the BSRBR-RA. Patients were recruited from 3 hospitals across the UK prescribing this treatment for RA.

11.2. Limitations

This study was designed to assess the safety of Ruxience within the clinical practice setting utilising the BSRBR-RA, a well-established UK based rheumatology register. However, only 3 patients with RA identified in the BSRBR-RA were exposed to Ruxience during the 2 year period of enrollment, making the assessment of the safety of Ruxience for the treatment of RA unfeasible.

The RA treatment landscape has evolved over time with the introduction of new therapies, treatment recommendations, and approaches to managing potential safety events associated with these treatments. The rates of events of interest and their distribution among patient types may have changed over time.

A possible reason for the extremely low enrollment of Ruxience-exposed patients with RA in the BSRBR-RA is that Ruxience launched approximately 2-3 years after two other rituximab biosimilar competitors in the UK (Rixathon in June 2017, and Truxima in November 2018). By the time Ruxience launched in the UK, rheumatologists may have already acquired experience

using available biosimilars for RA and may have had little reason to switch to another biosimilar. Identification of the precise reasons for the low number of Ruxience exposed patients with RA in the BSRBR-RA is beyond the scope of this study.

Endpoint misclassification is of particular concern within the observational setting due to less stringent monitoring relative to clinical trials. While the BSRBR-RA 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. It is also possible that some events will be missed as all reporting is done via the rheumatology departments. If rheumatologists are not aware of an event, they cannot report it and could result in underestimation of the incidence rate. For the serious events included in this analysis this is of low probability.

This study was planned to continue for a period of 2 years after study start. This period of time may not be sufficient to assess some events, particularly malignancies which may have a longer latency period. Another limitation is that this study of Ruxience was designed to be purely descriptive with no comparative analysis of Ruxience-exposed patients to another RA treatment group.

11.3. Interpretation

Given the results of this study, Ruxience was very rarely prescribed for RA during the study period based on information from the BSRBR-RA.

11.4. Generalizability

Given the limited information from this study, generalizability is not applicable.

12. OTHER INFORMATION

Not applicable

13. CONCLUSIONS

Results of this study demonstrate that during the study period, Ruxience was very rarely prescribed for RA based on data from the BSRBR-RA. Due to this, no conclusions can be drawn about these data.

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15. LIST OF SOURCE TABLES AND FIGURES

Not applicable