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 Swedish, Population based, Anti Rheumatic Treatment in Sweden (ARTIS) Register
Protocol number	B3281013
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EU Post Authorization Study (PAS)	EUPAS37694 HMA-EMA Study ID 41897
Active substance	PF-05280586 Rituximab
Medicinal product	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 in the ARTIS register who are treated with Ruxience? **Objectives:** To estimate incidence rates of infections, including serious infections, malignancies,

	cardiovascular events, and use during pregnancy among patients with rheumatoid arthritis in the ARTIS register who initiate Ruxience.
Country(-ies) of study	Sweden
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Not applicable

1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ARTIS	Anti-Rheumatic Treatment in Sweden
AS	ankylosing spondylitis
b/tsDMARD	biological or targeted synthetic disease modifying anti-rheumatic drug
csDMARD	conventional synthetic disease modifying anti-rheumatic drug
CLL	Chronic lymphocytic leukemia
CRP	C-reactive protein
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
GEP	Good Epidemiological Practice
GPA	Granulomatosis with polyangiitis
HAQ	health Assessment Questionnaire
ICD	International Classification of Diseases
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MA	Market Authorisation
MACE	Major acute cardiovascular event
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
NSAIDs	nonsteroidal anti-inflammatory drugs
PASS	Post-Authorization Safety Study

Abbreviation	Definition
PPV	positive predictive value
PV	Pemphigus Vulgaris
RA	rheumatoid arthritis
RMP	Risk Management Plan
SRQ	Swedish Rheumatology Quality Register
TNF	Tumor necrosis factor
VAS	visual analog scale

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
Cynthia de Luise, MPH, PhD	Senior Director, Safety Surveillance Research	Pfizer, Inc. Safety Surveillance Research Worldwide Medical and Safety
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4. OTHER RESPONSIBLE PARTIES

Not applicable

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Date of IEC approval		18 November 2015	
Registration in the HMA-EMA Catalogues of RWD Studies	Prior to the start of data collection	21 October 2020	
Start of data collection^	31 July 2021	31 July 2021	
End of data collection#	31 December 2023	31 December 2022	On **22 April 2024**, Karolinska Institute informed Pfizer that only data up to 31 December 2022 were available for analysis given that data linkage has been delayed by up to one year or longer by the Swedish National Board of Health and Welfare. They were unable to provide a date for when additional data would become available. Consequently, the end of data collection for this report is 31 December 2022.
Final report of study results	30 November 2024	17 July 2024	Final report is based on data through 31 December 2022

^ Start of data collection is the planned date for starting data extraction for the purposes of the study 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 study objective(s).

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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.[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 ARTIS and initiate treatment with Ruxience?

Objectives:

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

8. AMENDMENTS AND UPDATES

None

9. RESEARCH METHODS

9.1. Study design

This active surveillance study used anonymized secondary data from the established ARTIS register, an ongoing, prospective, disease based cohort started in 1999 with the primary aim of evaluating the safety of RA patients who are started on new biologic therapies for RA during routine post-marketing clinical use.

9.2. Setting

Swedish health-care is tax-funded and offers universal access. Hospital referral is based on geography rather than insurance-status. Patients with arthritides are typically treated by rheumatologists, the vast majority of whom work in public and hospital-based clinics. Health and demographic information are recorded in a series of registers with a very high degree of completeness resulting from the mandatory and semi-automated registration. Based on each Swedish resident's unique personal identification number, issued to all Swedish residents alive in 1947 or born thereafter, linkage of data from different registers is possible.[15] The registers are maintained by governmental bodies (the main registers used in this project are held by the National Board of Health and Welfare (Socialstyrelsen) and Statistics Sweden), who may perform data linkages and provide de-identified data for research purposes.

9.3. Subjects

All patients with RA who initiated Ruxience as their first or later biologic treatment and were enrolled in ARTIS through 31 December 2023 were included in this study with entry defined as the start of treatment with Ruxience. Note: Due to delays in data linkage, data up to 31 December 2022 were available for analysis for this final report.

9.4. Variables

Outcomes (safety events of special interest)

The following 6 outcomes were analysed:

1. Hospitalized infections
2. All primary invasive cancers excluding non-melanoma skin cancers and basal cell cancer
3. Non-melanoma skin cancer (NMSC)
4. Major adverse cardiovascular event (MACE)
5. Venous thromboetic events (VTE)
6. Cardiovascular event (CV), combined VTE and MACE outcomes

Outcome definitions, including ICD-codes and planned data source, are presented in **Table 1.** The first event (per type) during follow-up were recorded, and individuals with a history of the event at start of follow-up were not excluded.

Table 1. Outcome Definitions

Outcome	ICD10 codes	Data sources
Hospitalized Infections	A00-B99 (excluding A33 and A50), D73.3, E06.0, 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	Main diagnosis in the inpatient component of the Swedish Patient Register. If main diagnosis is RA, then contributory diagnoses are allowed.
All primary invasive cancers excluding non-melanoma skin cancers and basal cell cancers	All non-benign tumors, except C44, and basal cell cancers	The Swedish Cancer Register, The Swedish Basal Cell Cancer Register
Non-melanoma skin cancer (NMSC)	C44, non-benign records, plus basal cell cancers	The Swedish Cancer Register and the Basal Cell Cancer Register
Major adverse cardiovascular event (MACE)	Combines MI, stroke, and fatal cardiovascular events: I00-I99 as main cause of death, or I20.0, I21, I60-I64 as diagnosis	Main or secondary diagnosis in the Patient register, in- or out-patient component or the underlying (main) cause recorded in the Cause of Death Register
Venous thrombotic events (VTE)	I26, I80-I82 with a filled prescription of an anticoagulant (ATC = B01AA, B01AB (excluding B01AB01 and B01AB02), B01AE, B01AF, B01AX) within 30 days after the VTE ICD10 code record in the National patient register, unless any death from any cause occurred within 30 days.	Main diagnosis in the Patient Register (in- or outpatient component), plus I26.0 as main cause of death in the Cause of Death Register. Anti-coagulants identified using the prescribed drug register.
Cardiovascular event	Combines the MACE and VTE outcomes as described above.	

ICD= International Classification of Disease

Follow up Definitions

Follow-up time was defined as start of date of entry (as specified above) and ending at the first of the following for an “ever-exposed” analysis approach for malignancy outcomes.

- Outcome of interest,
- First date of emigration from Sweden,
- Date of death,
- 31 December 2021 (data for malignancy outcomes was only available to 31 December 2021)

For non-malignancy outcomes, an “on-drug” approach was applied where follow-up time was defined as starting at the date of entry (as specified above) and ending at the first of the following:

- Outcome of interest,
- End of treatment + 270 days,
- First date of emigration from Sweden,
- Date of death,
- 31 December 2023 (note that due to delays in data linkage, only data up to 31 December 2022 were available for analysis for this final report)

The following variables were selected from ARTIS to describe Ruxience initiators:

1. Seropositive disease (RF+/RF-)
2. RA disease duration
3. Calendar year of entry into cohort
4. DAS28
5. HAQ
6. C-reactive protein (CRP)
7. Erythrocyte sedimentation rate (ESR)
8. Swollen join count
9. Tender joint count
10. Pain on a visual analogue scale
11. Patient’s global assessment of disease
12. Doctor’s global assessment of disease
13. Concomitant conventional synthetic DMARD (csDMARD) use at time of cohort entry (Y/N)
14. Concomitant oral steroids at the time point of cohort entry (Y/N)
15. History of malignancy (Y/N)
16. History of hospitalization listing infection, last 5 years (Y/N)
17. History of knee/hip joint replacement surgery (Y/N)
18. History of chronic obstructive pulmonary disease (COPD), last 5 years (Y/N)
19. History of myocardial infarction (MI), last 5 years (Y/N)
20. History of diabetes (Y/N) last 5 years
21. Total number of days spent in hospital during the last 5 years
22. (Where applicable) Reason for discontinuation of most recent b/tsDMARD (safety/inefficacy/other)

ICD codes used to define disease history are summarized in Table 2.

Table 2. Definitions of Baseline Diseases Considered as Potential Confounders

Disease	Data source	ICD10
Malignancy	The Cancer register	All except benign malignancies
Infection	Main diagnoses from the Inpatient component of Patient Register.	A00-B99, D73.3, E06.0, 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, J38.3, 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, N10, N11, N12, 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
Knee, hip, foot or shoulder prosthesis	Operation codes from the Patient register	NGB, NFB, NBB, NHB, NHC, NHE, NHF, NHG, 8423, 8424, 8426, 8419, 8437, 8436, 8420, 8421, 8422, 8400-8415
Chronic obstructive pulmonary disease	The Patient Register (main or secondary diagnoses, in- and outpatient component)	J41-J44
Diabetes	The Patient Register (main or secondary diagnoses, in- and outpatient component)	E10-E14, O24
Myocardial infarction	The Patient Register (main or secondary diagnoses, in- and outpatient component)	I21, I22

9.5. Data sources and measurement

Ruxience-treated patients were selected through the Swedish Rheumatology Quality Register (SRQ, www.srq.nu) with additional drug data, baseline comorbidities and outcomes during follow-up identified by linking individuals in these cohorts (e.g. ARTIS) to the Swedish Patient Register, the Swedish Cancer Register, the Swedish Basal Cell Cancer Register, the Swedish Prescribed Drug Register, the Cause of Death Register, the Total Population Register and the Medical Birth Register. These registers are further described below.

9.5.1. The Swedish Rheumatology Quality Register (SRQ) and ARTIS

The Swedish Rheumatology Quality Register (SRQ) was started in 1995 by the Swedish Rheumatology Society to improve the healthcare and treatment for patients with rheumatoid arthritis (RA).[16] SRQ followed on regional registry initiatives, to enable a national real-world documentation of many different aspects of RA and developed over time into a harmonized national registry. SRQ was started mainly for patients with RA, but over time it has been expanded to cover several other rheumatic diseases including ankylosing spondylitis and psoriatic arthritis, myositis, systemic lupus erythematosus and additional conditions. Its

biologics component, ARTIS, is a profession-based register. It covers around 90% of all biologic initiations in Swedish Rheumatology after 1999.[17] Currently, about 25,000 patients with RA initiating over 75,000 biological treatments have been enrolled in ARTIS. The SRQ also contains early RA patients, and increasingly, RA patients can be followed from their first RA diagnosis and onwards. In conjunction with each patient visit, the treating rheumatologist enters data on disease activity and anti-rheumatic treatment.

9.5.2. The Swedish Patient Register

The Swedish Patient Register collects information on all hospitalized (inpatient treated) patients, and all visits to non-primary outpatient care (such as a visit to a rheumatologist). Diagnoses are assigned by the discharging physician, as well as date of discharge, discharging hospital and department. Diagnoses are coded according to the ICD, with version 8 used until 1986, version 9 from 1987 to 1996 and ICD10 since 1997. The inpatient component was originally initiated by several counties in 1964, had 85% country-wide coverage in 1983, and is considered complete since 1987. Validation against medical files have found an overall error rate in the main diagnoses of 4% at the ICD chapter level, and 12% at the three-digit level. The outpatient component of the Patient register was initiated with nationwide coverage in 2001. Overall, 13% of outpatient visits lack records, but coverage is higher for somatic public care (including most rheumatology care). Chart reviews and validation of RA diagnosis based on different algorithms applied to the register data indicate a positive predictive value for a register-based diagnosis of RA around 90%.[18,19]

9.5.3. The Swedish Cancer Register

The Swedish Cancer Register was established in 1958 and contains information on date of cancer (and some selected pre-cancers) onset, and type of cancer according to the ICD classification and morphology/histology. 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%.[20] This register is used to identify malignancy events in ARTIS, except for basal cell cancer, which are captured using the Basal Cell Cancer Register as described below. Note that information from the Swedish Cancer Register was only available to 31 December 2021 for this report.

9.5.4. The Swedish Basal Cell Cancer Register

The Swedish Basal Cell Cancer Register was established in 2004, and is linked to the Swedish Cancer Register.[21] Approximately 50,000 individuals are diagnosed with basal cell carcinoma each year in Sweden. Note that information from the Swedish Basal Cell Cancer Register was only available to 31 December 2021 for this report.

9.5.5. The Prescribed Drug Register

The Prescribed Drug Register was established in July 2005 and contains data with unique patient identifiers for all filled prescriptions to patients in ambulatory care for the whole population. All drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system. Measurement units for utilization of prescription medications are prescriptions and DDDs. Information on drugs administrated in hospitals or nursing homes, and drugs sold over-the counter is not captured.

9.5.6. The Cause of Death Register

The Cause of Death Register is a national register containing information on date and cause of death (underlying and contributory) for all deceased residents, including deaths among Swedish residents who died abroad. The register was started in 1952, and the data are considered complete since 1961. From that year and onward, cause of death is missing for less than 0.5% of deceased individuals, and in 2002, a validation study estimated that only 3.3% had any errors at the three-digit level of the ICD-coded underlying cause of death.[22]

9.5.7. The Total Population Register

The Total Population Register lists data on residency at a given point in time since it was founded in 1961, and dates of emigration/immigration for all subjects ever resident in Sweden since 1961. This register is used to identify subjects who die or emigrate during follow-up.

9.5.8. The Medical Birth Register

The Medical Birth Register contains prospectively collected data from antenatal, obstetric, and neonatal records since 1973, and covers all live and still births (but not all miscarriages) up to 22 weeks in Sweden.[23] Among the variables covered are maternal age, parity, smoking and family situation in early pregnancy, and the infant's birth weight and length, gestational age (primarily based on ultrasound dating), and Apgar score. Complications and mother's and infant's morbidities are coded according to the ICD, with version 8 used until 1986, version 9 from 1987 to 1996, and ICD10 since 1997. This register is used to identify use of Ruxience during pregnancy and was available until 31 December 2021.

9.6. Bias

This study was designed to monitor the safety of Ruxience in the clinical practice setting utilising the ARTIS Register, a well-established Swedish-based rheumatology register. Endpoint misclassification is of particular concern within the observational setting due to less stringent monitoring relative to clinical trials. While ARTIS has an established system to identify and capture endpoint data, all events cannot be fully verified via source documentation. Instead, linkage to national health care registers allows the register to obtain data on all safety events of interest (regardless of suspected causal relationship to the treatments).

9.7. Study Size

All eligible patients in ARTIS who initiated Ruxience during the study period were included, with no upper limit on the sample size. This was a descriptive study with no apriori hypotheses. **Table 3** presents 95% confidence intervals around the incidence proportions for safety events of interest reported in the Ruxience RMP.

Table 3. Precision Estimates Based on Incidence Proportions for Safety Events Reported in the Ruxience RMP*

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

NMSC, non-melanoma skin cancer; CV, cardiovascular; CI, confidence interval.
* Ruxience (rituximab) European Union Risk Management Plan Version 1.0 dated December 2019. ruxience-epar-risk-management-plan-summary_en.pdf (europa.eu)

9.8. Data transformation

None

9.9. Statistical methods

9.9.1. Main summary measures

The Ruxience cohort was analysed overall and stratified by previous biologics use. The general analytic approach was descriptive and included incidence rates of events of interest within the Ruxience cohort. Incidence rates were calculated by dividing the number of events by the person-time of exposure and included 95% confidence intervals. No comparative analyses with other treatment cohorts were planned. All statistical analyses were performed by ARTIS using SAS version 9.4 or later.

Crude incidence rates and number of events were tabulated for each outcome and by the number of previous b/tsDMARDs (0,1-2, 3+).

ICD-code-based algorithms were used to identify serious infections, malignancies and CV events (MACE), in the Swedish patient register as shown in Table 1.

9.9.2. Main statistical methods

Not applicable

9.9.3. Missing values

None

9.9.4. Sensitivity analyses

None

9.9.5. Amendments to the statistical analysis plan

None

9.10. Quality control

This study uses data existing within ARTIS. ARTIS works mainly with data from the SRQ, a quality of care register with several guidelines in place to monitor and maintain data quality. Physicians working with the SRQ have access to an online portal in which they can monitor all their patients and their information. Regional representatives encourage/remind the physicians to check the quality of the information by accessing the “Data Quality” section of the “Visit monitoring” tool: in this section a series of questions guide the doctor in checking the quality of the registered information of their patients. Moreover, the data coordinator of SRQ periodically check the quality of the data overall in the region. The data received by Pfizer for this study were structured, anonymized data and considered available for analysis.

9.11. Protection of human subjects

Subject information and consent

Patient consent is not required for this study as data already exist within ARTIS register.

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

The data assembly and analyses performed in this report were approved by the Ethics Committee in Stockholm (DNR: 2015/1844 31/2, and 2023-03804-01).

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, Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association, the Karolinska Institutet’s guidelines on Research Conduct and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).

10. RESULTS

10.1. Patients

Twenty-five (25) patients initiated Ruxience in ARTIS from the time of Ruxience availability in Sweden in 2020 up to 31 December 2022. Of these, 12 patients were observed prior to 31 December 2021, and were thus included in the analyses for malignancy outcomes (where data were available only up to the end of 2021).

10.2. Descriptive data

Table 4 describes demographic and clinical characteristics of the Ruxience cohort. The median age of Ruxience initiators was 66 years and the majority were female (68%). The majority had RA disease for a long period prior to Ruxience initiation with a median disease

duration of 17.5 years. The majority of initiators had received 1-2 previous b/tsDMARDs (60%). A fifth (20%) had a previous cancer diagnosis and 24% had a history of joint surgery.

Table 4. Baseline Characteristics of RA Patients in Sweden who Initiated Ruxience

Status at entry	**Ruxience**
N initiations	25
N patients	25
Demographics	
Age, median (IQR)	66 (57-74)
Sex (% females)	68%
Females child-bearing age (18-44 years)	8%
Disease-related characteristics	
Rheumatoid factor positive	79%
Disease duration, median (IQR)	17.5 (11.9-23.7)
Calendar year, median	2022
DAS28, median (IQR)	3.8 (2.9-4.5)
HAQ, median (IQR)	0.9 (0.4-1.4)
CRP, median (IQR)	5.5 (3.8-11.5)
ESR, median (IQR)	21.0 (10.0-49.0)
SJC, median (IQR)	2.0 (0.0-3.0)
TJC, median (IQR)	2.5 (0.0-11.0)
Pain VAS, median (IQR)	54.0 (41.0-70.0)
Patient's global assessment of disease, median (IQR)	53.5 (34.0-73.5)
Doctor's global assessment of disease, median (IQR)	1.0 (0.5-2.0)
Ever smoker	0%
Concomitant csDMARDs	38%
Oral steroids	46%
NSAIDs	23%
Number of previous b/tsDMARDs	
0	8%
1-2	60%
3+	32%
Comorbidities	
Malignancy	20%
Hospitalised infection	12%
Joint surgery	24%
COPD	0%
Diabetes	8%
MI	0%
Hospitalisation days, median (IQR)	0 (0-3)
Reason for discontinuing previous b/tsDMARD	
Safety, of those with information	26%
Inefficacy, of those with information	13%
Non-medical switch, of those with information	39%
Other, of those with information	22%
Missing, of total	0%

IQR= interquartile range; 25th-75th; DAS28= disease activity score on 28 joints; HAQ= health assessment questionnaire; CRP=c-reactive protein

Table 4. Baseline Characteristics of RA Patients in Sweden who Initiated Ruxience

Status at entry	Ruxience

ESR= Erythrocyte sedimentation rate; SJC= swollen joint count; TJC=tender joint count; VAS= visual analogue scale; csDMARD= conventional synthetic disease modifying anti-rheumatic drug; b/tsDMARD=biological or targeted synthetic disease modifying anti-rheumatic drug; NSAIDs=non-steroidal anti-inflammatory drug; COPD= chronic obstructive pulmonary disease; MI= myocardial infarction

Table 5 describes baseline characteristics of Ruxience initiators by line of therapy. Only 2 individuals initiated Ruxience without having received a previous b/tsDMARD. Descriptive statistics were not presented for this group due to too few observations. There were some dissimilarities between the Ruxience initiations with 1-2 previous b/tsDMARDs and 3+ previous b/tsDMARDs (CRP, TJC, comorbidities), but any differences should be interpreted in light of the low number of observations in each group.

Table 5. Baseline Characteristics of RA Patients in Sweden who Initiated Ruxience by line of therapy

Status at entry	0 previous b/tsDMARDs	1-2 previous b/tsDMARDs	3+ previous b/tsDMARDs
N initiations	2	15	8
N individuals	2	15	8
Demographics			
Age, median (IQR)	n/a	66 (60-75)	59 (54-71)
Sex (% females)	n/a	67%	75%
Females child-bearing age (18-44 years)	n/a	7%	13%
Disease-related characteristics			
Rheumatoid factor positive	n/a	80%	86%
Disease duration, median (IQR)	n/a	17.4 (11.3-23.9)	17.7 (14.5-23.5)
Calendar year, median	n/a	2022	2021
DAS28, median (IQR)	n/a	4.0 (3.2-5.1)	4.1 (3.1-4.5)
HAQ, median (IQR)	n/a	0.5 (0.2-0.8)	1.4 (1.0-1.5)
CRP, median (IQR)	n/a	9.0 (3.5-15.0)	4.0 (4.0-7.5)
ESR, median (IQR)	n/a	19.0 (11.0-34.0)	20.0 (9.0-48.0)
SJC, median (IQR)	n/a	2.5 (0.0-6.0)	2.5 (0.0-3.0)
TJC, median (IQR)	n/a	10.0 (2.0-15.0)	2.5 (0.0-3.0)
Pain VAS, median (IQR)	n/a	51.0 (48.0-57.0)	64.5 (45.0-77.0)
Patient's global assessment of disease, median (IQR)	n/a	50.0 (46.0-64.0)	63.5 (45.0-77.0)
Doctor's global assessment of disease, median (IQR)		n/a	
Ever smoker	n/a	0%	0%
Concomitant csDMARDs	n/a	33%	50%
Oral steroids	n/a	33%	50%
NSAIDs	n/a	0%	50%
Comorbidities			
Malignancy	n/a	20%	12.5%
Hospitalised infection	n/a	6.7%	0%
Surgery	n/a	26.7%	12.5%

Table 5. Baseline Characteristics of RA Patients in Sweden who Initiated Ruxience by line of therapy

Status at entry	0 previous b/tsDMARDs	1-2 previous b/tsDMARDs	3+ previous b/tsDMARDs
COPD	n/a	0%	0%
Diabetes	n/a	6.7%	12.5%
MI	n/a	0%	0%
Hospitalisation days, median (IQR)	n/a	2 (0-7)	0 (0-0)
Reason for discontinuing previous b/tsDMARD			
Safety, of those with information	n/r	27%	25%
Inefficacy, of those with information	n/r	7%	25%
Non-medical switch, of those with information	n/r	47%	25%
Other, of those with information	n/r	20%	25%
Missing, of total	n/r	0%	0%

n/a= result not presented due to too few individuals (n<5)
n/r= result not relevant
b/tsDMARD= biological or targeted synthetic disease modifying antirheumatic drug; IQR= interquartile range; 25th-75th; DAS28= disease activity score on 28 joints; HAQ= health assessment questionnaire; CRP=c-reactive protein; ESR= Erythrocyte sedimentation rate; SJC= swollen joint count; TJC=tender joint count; VAS= visual analogue scale; csDMARD= conventional synthetic disease modifying anti-rheumatic drug NSAIDs=non-steroidal anti-inflammatory drug; COPD= chronic obstructive pulmonary disease; MI= myocardial infarction

10.3. Outcome data

None

10.4. Main results

Table 6 presents the number of Ruxience initiators, events, person-years and incidence rates for each safety outcome of special interest overall, and by line of therapy. No safety events of special interest were recorded during the follow-up period for Ruxience initiators (up to 31 December 2021 for malignancy outcomes, and 31 December 2022 for non-malignancy outcomes). There were no deliveries recorded where Ruxience was started either before the delivery or where the drug was discontinued after the pregnancy was initiated.

Table 6. Patients, events, person-years and incidence rates of safety events of special interest for patients initiating Ruxience, overall and presented by line of therapy

Cohort	Patients	Events	Person-Years	IR/ PYs	95% CI	Mean follow-up, years
Hospitalised infections						

Table 6. Patients, events, person-years and incidence rates of safety events of special interest for patients initiating Ruxience, overall and presented by line of therapy

Cohort	Patients	Events	Person-Years	IR/ PYs	95% CI	Mean follow-up, years
Ruxience overall	25	0	25.78	0	-	1.03
0 previous b/tsDMARD	2	0	0.55	0	-	0.28
1-2 previous b/tsDMARDs	15	0	16.48	0	-	1.10
3+ previous b/tsDMARDs	8	0	8.74	0	-	1.09
All primary invasive cancers excluding non-melanoma skin cancers and basal cell cancer*						
Ruxience overall	12	0	8.58	0	-	0.71
0 previous b/tsDMARD	0	0	0	-	-	-
1-2 previous b/tsDMARDs	7	0	6.37	0	-	0.91
3+ previous b/tsDMARDs	5	0	2.20	0	-	0.44
NMSC*#						
Ruxience overall	12	0	8.58	0	-	0.71
0 previous b/tsDMARD	0	0	0	-	-	-
1-2 previous b/tsDMARDs	7	0	6.37	0	-	0.91
3+ previous b/tsDMARDs	5	0	2.20	0	-	0.44
MACE						
Ruxience overall	25	0	25.78	0	-	1.03
0 previous b/tsDMARD	2	0	0.55	0	-	0.28
1-2 previous b/tsDMARDs	15	0	16.48	0	-	1.10
3+ previous b/tsDMARDs	8	0	8.74	0	-	1.09
VTE						
Ruxience overall	25	0	25.78	0	-	1.03
0 previous b/tsDMARD	2	0	0.55	0	-	0.28
1-2 previous b/tsDMARDs	15	0	16.48	0	-	1.10
3+ previous b/tsDMARDs	8	0	8.74	0	-	1.09

Table 6. Patients, events, person-years and incidence rates of safety events of special interest for patients initiating Ruxience, overall and presented by line of therapy

Cohort	Patients	Events	Person-Years	IR/ PYs	95% CI	Mean follow-up, years
CV events						
Ruxience overall	25	0	25.78	0	-	1.03
0 previous b/tsDMARD	2	0	0.55	0	-	0.28
1-2 previous b/tsDMARDs	15	0	16.48	0	-	1.10
3+ previous b/tsDMARDs	8	0	8.74	0	-	1.09

*Note that entry to the Ruxience cohort was limited to 2021, due to the end of follow-up at 31 December 2021 for malignancy outcomes
NMSC includes squamous cell skin cancer and basal cell skin cancer
- not estimated due to too few exposed patients in the subcohort
IR=incidence rate; PYs=person-years; CI= confidence interval; b/tsDMARD=biological or targeted synthetic disease modifying antirheumatic drug; NMSC=non-melanoma skin cancer; MACE= major adverse cardiovascular events; VTE= veneous thromboetic event; CV= cardiovascular

10.5. Other analyses

None

10.6. Adverse events / adverse reactions

For this study, Pfizer received data from ARTIS 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

Only 25 persons initiated Ruxience in ARTIS from the time of Ruxience availability in Sweden in 2020 up to 31 December 2022. No safety events of special interest were reported during follow-up among the Ruxience initiators. Due to the small number of persons exposed to Ruxience, no conclusions can be drawn from the data.

11.2. Limitations

Endpoint misclassification is of particular concern within the observational setting due to less stringent monitoring relative to clinical trials. While ARTIS has an established system to identify and capture endpoint data, all events cannot be fully verified via source documentation. Instead, linkage to national health care registers allows the register to obtain data on all safety events of interest (regardless of suspected causal relationship to the treatments).The specific algorithms for defining those endpoints have not been validated, though the Swedish patient register has been validated several times.[24] The overall positive predictive value (PPV) of the inpatient diagnoses generally ranged from 85% to 95%. A regional validation study of hospitalised acute MI and stroke (components of the MACE

endpoint) found PPVs of 96% and 94%, respectively, in the period 1977 to 1987.[25] While the ICD algorithms used by ARTIS to define the endpoints of interest may not be validated, their use can be justified given the importance to contextualise the study results with historical findings. ARTIS has previously conducted and published studies of serious infections [26,27,28,29] and MACE [30,31,32,33] events in RA patients.

As a new therapy in the RA treatment armamentarium, it is possible that patients treated with Ruxience represented those with the most severe cases of disease, longer disease duration, history of multiple failed RA therapies and physical comorbidities that place patients at risk for safety events of special interest. Biases resulting from channeling may present as increased rates of safety events of special interest in the early phases of the study. Stratification on key indicators of disease severity, patient characteristics and past therapies can be done for contextualisation.

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

Another limitation of this study design is the absence of a control group, which does not allow for comparative analysis of incidence rates with other treatments. This study followed patients for a period of approximately 2 years. This period of follow-up may not be sufficient to adequately evaluate all safety events of interest, specifically malignancies. Conclusions may not be generalisable outside of the approximate 2-year period since initiation of therapy.

11.3. Interpretation

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

11.4. Generalizability

Given the population-based nature of ARTIS and the linked registers used in this study, the data generated are generalizable to the underling Swedish population, however, generalizability of these data beyond this geographic region cannot be determined.

12. OTHER INFORMATION

Not applicable

13. CONCLUSIONS

This report describes the uptake of Ruxience in the treatment of RA since its availability in 2020 and any recorded safety events of special interest up to 31 December 2022 (2021 for malignancy outcomes) as recorded in ARTIS. No safety events of special interest were reported during follow-up among the Ruxience initiators. However, due to the very limited uptake of Ruxience in Sweden (n=25), no conclusions can be drawn from these data.

14. REFERENCES

[1] Alamanos Y, Drosos AA. Epidemiology of adult rheumatoid arthritis. AutoimmunRev 2005;4 (3):130-6

[2] Michaud K, Wolfe F. Comorbidities in rheumatoid arthritis. Best Pract and Res Clin Rheumatol. 2007 Oct;21(5):885-906.

[3] Carmona L, Descalzo MA, Perez-Pampin E, et al. All-cause and cause-specific mortality in rheumatoid arthritis are not greater than expected when treated with tumour necrosis factor antagonists. Ann Rheum Dis 2007; 66(7):880-5.

[4] Salliot C, Gossec L, Ruyssen-Witrand A, et al. Infections during tumour necrosis factor alpha blocker therapy for rheumatic diseases in daily practice: a systematic retrospective study of 709 patients. Rheumatology 2007; 46:327-334.

[5] Askling J, Fored CM, Brandt L, et al. Time-dependent increase in risk of hospitalisation with infection among Swedish RA patients treated with TNF antagonists. Annals of the rheumatic diseases 2007;66(10):1339-44.

[6] Strangfeld A, Eveslage M, Schneider M, et al. Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? Ann Rheum Dis 2011; 70(11):1914-20.

[7] Smitten AL, Simon TA, Hochberg MC, et al. A meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis. Arthritis Res and Ther 2008, 10:R45 (doi:10.1186/ar2404).

[8] Parikh-Patel A, Allen M, Cress R, White RH. Risk of cancer among rheumatoid arthritis patients in California. Cancer Causes Control: CCC. 2009;20(6):1001-1010. doi:10.1007/s10552-009-9298-y.

[9] Mercer LK, Galloway JB, Lunt M, et al. Risk of lymphoma in patients exposed to antitumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis Ann Rheum Dis 2017;76:497–503.

[10] Wadström H, Frisell T, Askling J, et al. Malignant neoplasms in patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors, tocilizumab, abatacept, or rituximab in clinical practice. JAMA Intern Med. 2017;177(1):1605 1612.

[11] Peters MJ, Nielen MM, Raterman HG, et al. Increased cardiovascular disease in patients with inflammatory arthritis in primary care: a cross sectional observation. J Rheumatol 2009; 36(9):1866-8.

[12] MabThera SmPC July 2019: MabThera, INN-rituximab (europa.eu).

[13] Rituxan (rituximab) - First New Drug for Non-Hodgkin's Lymphoma in a Decade Receives FDA Clearance for Marketing. https://www.drugs.com/newdrugs/rituxan-rituximab-first-new-non-hodgkin-s-lymphoma-decade-receives-fda-clearance-marketing-4823.html#moreResources. Posted November 1997.

[14] Ruxience (rituximab) European Union Risk Management Plan Version 1.0 dated December 2019. ruxience-epar-risk-management-plan-summary_en.pdf (europa.eu)

[15] Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, et al. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. European journal of epidemiology 2009;24(11):659-67.

[16] Eriksson JK, Askling J, Arkema EV. The Swedish Rheumatology Quality Register: optimisation of rheumatic disease assessments using register-enriched data. Clinical and experimental rheumatology 2014;32(5 Suppl 85):S-147-9

[17] Wadstrom H, Eriksson J, Neovius M, et al. How good is the coverage and how accurate are exposure data in the Swedish Biologics Register (ARTIS)? Scand J Rheumatol 2015;44(1):22-8

[18] Knight A, Sandin S, Askling J. Risks and relative risks of Wegener's granulomatosis among close relatives of patients with the disease. Arthritis Rheum-Us. Jan 2008;58(1):302-307.

[19] Eriksson JK, Neovius M, Ernestam S, Lindblad S, Simard JF, Askling J. Incidence of Rheumatoid Arthritis in Sweden: A Nationwide Population-Based Assessment of Incidence, Its Determinants, and Treatment Penetration. Arthrit Care Res. Jun 2013;65(6):870-878.

[20] Barlow L, Westergren K, Holmberg L, et al. The completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta oncologica 2009;48(1):27-33.

[21] Socialstyrelsen. Registret över basalcellscancer. https://www.socialstyrelsen.se/statistik-och-data/register/alla-register/cancerregistret/basalcellscancer/. Accessed February 4th 2022.

[22] Socialstyrelsen. Bortfall och Kvalitet. 2014; http://www.socialstyrelsen.se/register/dodsorsaksregistret/bortfallochkvalitet. Accessed August 28th 2014.

[23] Centre for Epidemiology. The Swedish Medical Birth Register - A Summary of Content and Quality. In: National Board of Health and Welfare, ed., 2003. http://www.socialstyrelsen.se/register/halsodataregister/medicinskafodelseregistret/inenglish (accessed 15 May 2018).

[24] Ludvigsson JF, Andersson E, et al. External review and validation of the Swedish national inpatient register. BMC Public Health 2011;11:450.

[25] Lindblad U, Råstam L, Ranstam J, et al. Validity of register data on acute myocardial infarction and acute stroke: the Skaraborg Hypertension Project. Scand J Soc Med 1993;21(1):3-9.

[26] Grøn KL, Arkema EV, Glintborg B, The ARTIS Study Group, et al. Risk of serious infections in patients with rheumatoid arthritis treated in routine care with abatacept, rituximab and tocilizumab in Denmark and Sweden. Annals of the Rheumatic Diseases 2019;78:320-27.

[27] Askling J, Fored CM, Brandt L, et al. Time dependent increase in risk of hospitalization with infection among Swedish RA patients treated with TNF antagonists. Annals of the Rheumatic Diseases 2007;66:1339-1344

[28] Askling J, Fored CM, Brandt L, et al. TNF antagonist treatment and risk of hospitalization for infection. Results from the National Swedish Monitoring Program for Biologics in Askling J, Fored CM, Brandt L, et al. Risk of hospitalization for infections following TNF blockade. Preliminary results of an ongoing Swedish monitoring programme of biologics in RA. Annals of the Rheumatic Diseases 2005;64:449-449. RA (ARTIS). Abstract 973. Arthritis Rheum 2006;54(9) Suppl:S420-S421.

[29] Askling J, Fored CM, Brandt L, et al. Risk of hospitalization for infections following TNF blockade. Preliminary results of an ongoing Swedish monitoring programme of biologics in RA. Annals of the Rheumatic Diseases 2005;64:449-449.

[30] Ljung L, Askling J, Rantapää-Dahlqvist S, et al. The risk of acute coronary syndrome in rheumatoid arthritis in relation to tumour necrosis factor inhibitors and the risk in the general population: a national cohort study. Arthritis Res Ther 2014;16:R127. doi: 10.1186/ar4584.

[31] Jacobsson LT, Rantapää-Dahlqvist SB, Nilsson JA, et al. Anti-TNF therapy in RA and the risk of acute myocardial infarction (AMI), stroke and any cardiovascular (CVD) events up to 7 years after treatment start. Arthritis Rheum 2008;58(9) Suppl:S900-S900.

[32] Askling J, Fored M, Brandt J, et al. TNF antagonist treatment and risk of hospitalization for cardiovascular disease. Results from the National Swedish Monitoring Program for Biologics in RA (ARTIS). Arthritis Rheum 2006;54(9) Suppl:S421-S421.

[33] Askling J, Fored M, Brandt J, et al. Risk of cardiovascular morbidity and mortality following TNF-blockade. Preliminary results of an ongoing Swedish monitoring programme of biologics in RA. Annals of the Rheumatic Diseases. 2005;64:448-449.

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