Non-Interventional Final Study Report

PASS Information

Title	Nation-wide safety monitoring of Flixabi treatment in patients with Rheumatic diseases in Sweden
Version identifier of the final study report	1.0
Date of last version of the final study report	N/A
EU PAS register number	N/A
Active substance	Infliximab ATC code L04AB02
Medicinal product	Flixabi
Product reference	H0004020
Procedure number	EMA/VR/XXXXXXXXXX
Marketing authorisation	Samgsung Bioepis NL B.V.
Joint PASS	No
Research question and objectives	The objective of the analyses presented in this comparative safety report is to provide an assessment of pre-specified safety outcomes for Flixabi as used in the treatment of rheumatoid arthritis (RA), ankylosing spondylitis (AS) and other spondyloarthropathies (SpA), and psoriatic arthritis (PsA) in Sweden, using data from the Anti-Rheumatic Therapies In Sweden (ARTIS) system since 2019.
Country(-ies) of study	Sweden
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1 Abstract

Title

Nation-wide safety monitoring of Flixabi treatment in patients with Rheumatic diseases in Sweden

Keywords

Flixabi, Rheumatoid Arthritis (RA), Drug survival, Remission, Comparison

Rationale and background

The data used in the current report was extracted from Swedish registers in which information is prospectively collected (see section 9.5 Data sources and measurement). Patients treated with Flixabi entererd the study from January 1st 2019 (i.e. first year of availability of Flixabi for the treatment of RA in Sweden); Patients treated with another TNFi (excluding Flixabi), bionaive patients and general population comparators may enter the study from January 1st 2015, i.e. four years earlier (to optimize statistical power).

Research question and objectives

The objective of the analyses presented in this comparative safety report is to provide an assessment of pre-specified safety outcomes for Flixabi as used in the treatment of RA, AS and other spondyloarthropathies (SpA), and PsA in Sweden, using data from the ARTIS system since 2015.

Study design

The study design used in this comparative safety report is an active-comparator new-user cohort design. Patients who are treated with the drug of interest are compared to patients who are treated with alternative biological or targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs)(i.e., active-comparator) and all patients are followed up from treatment start (i.e., new-user). This design aims to be as close as possible to an RCT when working with observational data where no randomization was performed. Two additional cohorts were added for contextualisation purposes: a cohort of b/tsDMARD-naive patients, and a cohort of individuals from the general population.

Setting

The data used in the current report was extracted from Swedish registers in which information is prospectively collected (see section 9.5 Data sources and measurement). Patients treated with Flixabi entered the study from January 1st 2019 (i.e. first year of availability of Flixabi for the treatment of RA in Sweden); Patients treated with another TNFi (excluding infliximab), bionaive patients and general population comparators may entered the study from January 1st 2015, i.e. four years earlier (to optimize statistical power).

Subjects and study size, including dropouts

Flixabi has been available in Sweden for patients in RA since 2019. To maximise statistical precision, participants in comparator cohorts were allowed to enter from 2015.

Table 1. Subject

Cohort	Subject
Main exposure cohort	All patients with RA, AS-SpA, or PsA initiating their first ever treatment with Flixabi in 2019-2024.
Comparator cohorts	Patients with RA, AS-SpA, or PsA initiating originator-product Flixabi in 2015-2024
	Infliximab-naïve patients with RA, AS-SpA, or PsA starting any non-infliximab TNFi therapy 2015-2024
	b/tsDMARDs-naïve patients with RA, AS-SpA, or PsA
	The general Swedish population

Table 2. Participants of Each Indication

Indication	Participants	The Number of patients
Rheumatoid arthritis	Flixabi treatment (2019-2024	161
	Remicade treatment (2015-2024)	409
	other TNFis treatment (2015-2024)	13,026
	b/tsDMARDs-naïve patients	62,176
	General population	64,708
Ankylosing Spondylitis and Other Spondyloarthropathies	Flixabi treatment (2019-2024)	152
	Remicade treatment (2015-2024)	357
	other TNFis treatment (2015-2024)	7,529
	b/tsDMARDs-naïve patients	22,465
	General population	37,281
Psoriatic Arthritis	Flixabi treatment (2019-2024)	65
	Remicade treatment (2015-2024)	189
	other TNFis treatment (2015-2024)	6,904
	b/tsDMARDs-naïve patients	29,182

Indication	Participants	The Number of patients
	General population	33,311

Variables and data sources

The following 4 outcomes were analyzed:

1) All primary invasive cancers excluding non-melanoma skin cancers
2) Lymphoma
3) Tuberculosis (TB)
4) Demyelinating event/Multiple sclerosis (MS)

Outcome definitions, including ICD-codes and data source, are presented in Table 4. Individuals with a history of the event at start of follow-up were not excluded.

Results

This nationwide safety monitoring study identified 161 RA, 152 AS-SpA, and 65 PsA patients initiating Flixabi treatment in Sweden between 2019-2024. For all primary invasive cancers excluding non-melanoma skin cancers, standardized incidence rates were 11.3/1000 PYs (RA), 9.6/1000 PYs (AS-SpA), and 6.9/1000 PYs (PsA), which were comparable to originator-product infliximab and other TNFi cohorts . No tuberculosis or demyelinating events were observed in any Flixabi cohort across all indications, while one lymphoma event occurred in the AS-SpA cohort (3.2/1000 PYs) . Cox proportional hazards modeling was not performed due to insufficient events (<5 per cohort), limiting statistical comparisons between treatment groups.

Discussion

The short follow-up period (maximum 6 years) and limited Flixabi uptake in the study resulted in very few observed safety events, restricting definitive conclusions. Despite this limitation, incidence rates remained generally similar across all comparator cohorts for outcomes where events occurred, suggesting no apparent safety signal. Key strengths include the nationwide ARTIS registry approach with high coverage, prospectively collected longitudinal data, and multiple comparator cohorts including general population controls. However, residual confounding and channeling effects may remain, and generalizability to settings outside Western Europe and the US may be limited due to varying baseline risks and treatment patterns.

Marketing Authorisation Holder(s)

Samsung Bioepis NL B.V

Names and affiliations of principal investigators

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2 List of abbreviations

Abbreviation	Definition
AE	Adverse Event
ARTIS	AntiRheumatic Therapy In Sweden
AS	Ankylosing Spondylitis
AS-SpA	Ankylosing Spondylitis and other Spondyloarthropathies
ATC	Anatomical Therapeutic Chemical
COPD	Chronic Obstructive Pulmonary Disease
DAS28	Disease Activity Score based on 28 joints
DMARD	Disease-Modifying Anti-Rheumatic Drug
HAQ	Health Assessment Questionnaire
IBD	Inflammatory Bowel Disease
ICD	International Classification of Diseases
MI	Myocardial Infarction
MS	Multiple Sclerosis
NMSC	Non-Melanoma Skin Cancer
PsA	Psoriatic Arthritis
PY	Person-year
RA	Rheumatoid Arthritis
RCT	Randomized Control Trial
RF	Rheumatoid Factor
SOP	Standard Operating Procedures
SpA	Spondyloarthropathies
SRQ	Swedish Rheumatology Quality register
TNFi	Tumor Necrosis Factor inhibitor

3 Investigator

Name, Degree	Title	Affiliation
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4 parties

Not applicable

5 Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	N/A	2015	
End of data collection	Jul 30, 2025	Jul 30, 2025	Note: The end of data collection is Jul 30, 2025 however, the information on the outcomes were available only until Dec 31, 2024 for the national patient register, until Sep 30, 2024 for the tuberculosis register and until Dec 31, 2023 for the cancer register
Registration in the EU PAS register	N/A	N/A	Since the PASS is categorized as Category 3, it was not registered in the EU PAS register

6 Rationale and background

The treatment of chronic inflammatory rheumatic diseases including rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA) has been transformed by tumor necrosis factor inhibitors (TNFi) such as infliximab. RA affects approximately 0.5-1.0% of the adult population worldwide, while AS has a prevalence of 0.2-0.5% and PsA affects 0.1-0.3% of the general population.[1,2,3] However, Originator carry substantial costs, limiting patient access in many healthcare systems. Biosimilar infliximab products, including Flixabi, have been developed to reduce treatment costs and improve accessibility. Although biosimilars are highly similar to reference products, differences in manufacturing processes have raised concerns among clinicians and patients regarding potential safety differences, with surveys indicating variable confidence in biosimilars due to concerns about long-term safety .[4]

Randomized clinical trials(RCTs) have demonstrated comparable efficacy and short-term safety between infliximab biosimilars and reference products, but RCTs include selected populations with limited follow-up and are not powered to detect rare or long-term safety signals. Therefore, post-authorization safety studies (PASS) using real-world data from national registries are essential to monitor safety outcomes in routine clinical practice. This non-interventional study is designated as a Category 3 PASS and is a commitment to the EMA. The data used in the current report was extracted from Swedish registers in which information is prospectively collected. Patients treated with Flixabi entered the study from January 1st 2019 (i.e., first year of availability of Flixabi for the treatment of RA in Sweden); Patients treated with another TNFi (excluding Flixabi), bionaive patients and general population comparators may enter the study from January 1st 2015, i.e., four years earlier (to optimize statistical power). The following final report for Flixabi is based on ARTIS, which is built on the Swedish Rheumatology Quality Register (SRQ) that covers approximately 90% of all b/ts DMARD initiations in Swedish Rheumatology. Swedish health registers maintain greater than 95% completeness through mandatory reporting, enabling robust pharmacoepidemiological research. This study reports on predefined safety outcomes (malignancies, lymphoma, tuberculosis, and demyelinating events) in patients with RA, AS-SpA, and PsA initiating Flixabi compared to originator infliximab, other TNFi agents, b/tsDMARD-naïve patients, and the general Swedish population.

7 Research question and objectives

The objective of these analyses is to provide an assessment of pre-specified safety outcomes for Flixabi as used in the treatment of RA, AS and other spondyloarthropathies (SpA), and PsA in Sweden, using data from the ARTIS system from 2015.

8 Amendments and updates to the protocol

Version	Date	Section of study	Amendment or update	Reason
N/A				

9 Research methods

9.1 Study design

The study design used in this comparative safety report is an active-comparator new-user cohort design.[5] Patients who are treated with the drug of interest are compared to patients who are treated with alternative biological or targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs)(i.e., active-comparator) and all patients are followed up from treatment start (i.e., new-user). This design aims to be as close as possible to an RCT when working with observational data where no randomization was performed. Two additional cohorts were added for contextualisation purposes: a cohort of b/tsDMARD-naive patients, and a cohort of individuals from the general population.

9.2 Settings

The data used in the current report was extracted from Swedish registers in which information is prospectively collected (see section 9.5 Data sources and measurement). Patients treated with Flixabi entererd the study from January 1st 2019 (i.e. first year of availability of Flixabi for the treatment of RA in Sweden); Patients treated with another TNFi (excluding Flixabi), bionaive patients and general population comparators entered the study from January 1st 2015, i.e. four years earlier (to optimize statistical power).

9.2.1 Follow-up time and risk windows

For each cohort, follow-up time started at the date of entry (as specified above) and ended at the first of the following:

- outcome of interest (see below),
- first date of emigration from Sweden,
- date of death,
- December 31st 2024, (December 31st 2023 for cancer outcomes and September 30th 2024 for tuberculosis outcome)
- for the b/tsDMARD-naïve cohort only: date of first b/tsDMARD treatment start (where applicable)
- for the general population cohort only: date of RA diagnosis (where applicable).

In analyses of cancer incidence, the patients were considered “ever exposed” to their respective cohort membership. Follow-up of all other (non-cancer) outcomes employed an “on drug” approach, and thus also ended at the first occurrence of either:

- 90 days after discontinuing current biological (TNFi) treatment (where applicable) or
- when the patient transitioned to another cohort or treatment (for instance, when a member of cohort A or B switch b/tsDMARD treatment).

Examples of the last point include when a member of cohort A or B (as defined below) switch bDMARD treatment or when a member of cohort C (as defined below) starts a bDMARD treatment.

9.3 Subjects

9.3.1 Main exposure cohort

All patients with RA, AS, SpA, or PsA initiating their first ever treatment with Flixabi in 2019-2024.

This cohort was defined as all patients in ARTIS who started Flixabi as their first or later biological treatment. Entry was defined as date of first Flixabi treatment start. Note that the main cohort included Flixabi initiators both with and without prior use of TNFi therapy (including other infliximabs), to increase the statistical power.

9.3.2 Comparator cohorts

Although Flixabi was first available in 2019, statistical precision was increased by including data from 2015 and onwards for the comparator cohorts, as this substantially increased the number of patients without introducing any appreciable calendar period bias in the comparison to the Flixabi cohort.

For the comparator cohorts, treatments with one and the same biologic were counted as separate biological treatments if the previous treatment had been registered as discontinued, and more than 90 days had passed between discontinuation and the next initiation. Entry was defined as date of treatment start. For any biologic other than infliximab for which both the originator-product and biosimilars were available, no distinction was made between the originator-product and its biosimilar(s). For infliximab, Flixabi was considered as a different drug than the originator-product infliximab (Remicade) and any other infliximab biosimilar.

A) ***Patients with RA, AS, SpA, or PsA initiating originator-product infliximab in 2015-2024.*** This cohort was defined as all patients starting originator-product infliximab (Remicade) for the first time. This included patients with a history of other b/tsDMARDs, including other infliximabs.

B) ***Infliximab-naïve patients with RA, AS, SpA, or PsA starting any non-infliximab TNFi therapy 2015-2024.*** This cohort was defined as all patients starting treatment with any non-infliximab TNFi (adalimumab (originator or biosimilar), etanercept (originator or biosimilar), certolizumab pegol, or golimumab), and who had not at that date ever been treated with infliximab. Only the first treatment episode during the study period was included.

C) ***b/tsDMARD-naïve patients with RA, AS, SpA, or PsA.*** This cohort was defined as all patients with RA, AS, SpA or PsA identified as 2+ registrations of the corresponding ICD diagnosis codes (Table 3) in the Patient Register 1996 or later, one of which was recorded at a department of rheumatology or internal medicine, as has been used in previous ARTIS publications. Entry was defined as the first date when all inclusion criteria were fulfilled 2015-2024. Subjects were considered b/tsDMARD-naïve until start of first ever b/tsDMARD. The Prescribed Drug Register was used to supplement the Swedish Rheumatology Quality register (SRQ) and further ensure that this cohort was b/tsDMARD-naïve prior to entry, and to quality control the date of start of the first ever biologic.

D) ***The general Swedish population.*** The collective study population in the TNFi-treated cohorts was matched (1:5, by year of birth, sex, and vital status at the date of their first identification of arthritides 2001 and onwards) to the Swedish Population Register. Date of entry in the general population comparator cohorts was set to date of entry of their corresponding RA, AS, SpA or PsA patient.

9.3.3 Indications

The cohorts described above were all stratified by the indication for therapy. After inspecting the recorded indications in the SRQ, indications were grouped into Rheumatoid Arthritis (RA), Ankylosing Spondylitis and other spondyloarthropathies (AS-SpA), and Psoriatic Arthritis (PsA), as defined in Table 3.

Table 3. Indications

Indication	ICD10 codes	Data source
Rheumatoid Arthritis (RA)	M05, M06.0, M06.2, M06.3, M06.8, M06.9, M12.3	For main cohort and cohort A & B: the SRQ For cohort C: At least two separate visits with main or secondary diagnosis in the Patient

Indication	ICD10 codes	Data source
		register, in- or outpatient component, one of which at a department of rheumatology or internal medicine
Ankylosing Spondylitis and Other Spondylo-arthropathies (AS-SpA)	M45, M07.4, M07.5, M46.1, M46.8, M46.9	For main cohort and cohort A & B: the SRQ For cohort C: At least two separate visits with main or secondary diagnosis in the Patient register, in- or outpatient component, one of which at a department of rheumatology or internal medicine
Psoriatic arthritis (PsA)	L40.5, M07.0, M07.1, M07.3	For main cohort and cohort A & B: the SRQ For cohort C: At least two separate visits with main or secondary diagnosis in the Patient register, in- or outpatient component, one of which at a department of rheumatology or internal medicine

9.4 Variables

The following 4 outcomes were analyzed:

1) All primary invasive cancers excluding non-melanoma skin cancers
2) Lymphoma
3) Tuberculosis (TB)
4) Demyelinating event/Multiple sclerosis (MS)

Outcome definitions, including ICD-codes and data source, are presented in Table 4. The first event (per type) during follow-up was recorded. Individuals with a history of the event at start of follow-up were not excluded.

ICD codes to define disease history are summarized in Table 5.

Table 4. Outcome definitions

Outcome	ICD10 codes	Data sources
All primary invasive cancers excluding non-melanoma skin cancers	All non-benign tumors, except C44 and D04 (ICD7=191), and basal cell cancers	The Cancer Register, invasive only

Outcome	ICD10 codes	Data sources
Lymphoma	C81 – C86, C88, C91.1, C91.3, C91.4, C916	The Cancer Register
Tuberculosis	-	TB register at the Public Health Agency
Demyelinating event/MS	G04.8, G04.9, G35.9, G36.0, G36.8, G36.9, G37.1, G37.3, G37.5, G37.8, G37.9, H46, H48.1	Main or secondary diagnosis in the Patient register, in- or outpatient component.

Table 5. 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 or hip 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	J41-J44
Diabetes	The Patient Register	E10-E14, O24
Myocar dial infarction	The Patient Register	I21, I22

9.5 Data sources and measurement

9.5.1 Introduction

In Sweden, Flixabi (biosimilar Infliximab) was first made available for the treatment of RA in 2019. From the launch, it has been monitored by the Swedish b/tsDMARDs Register ARTIS (Anti-Rheumatic Treatment in Sweden) in collaboration with the Swedish Medical Products Agency. Built on the already existing SRQ (see below), ARTIS was initiated with the introduction of Enbrel (originator etanercept), the first biological Disease Modifying Anti-Rheumatic Drug (DMARD), in 1999, and serves as a national surveillance program for investigation of safety and effectiveness of new anti-rheumatic drugs. Figure 1 below depicts the accumulated number of patients.

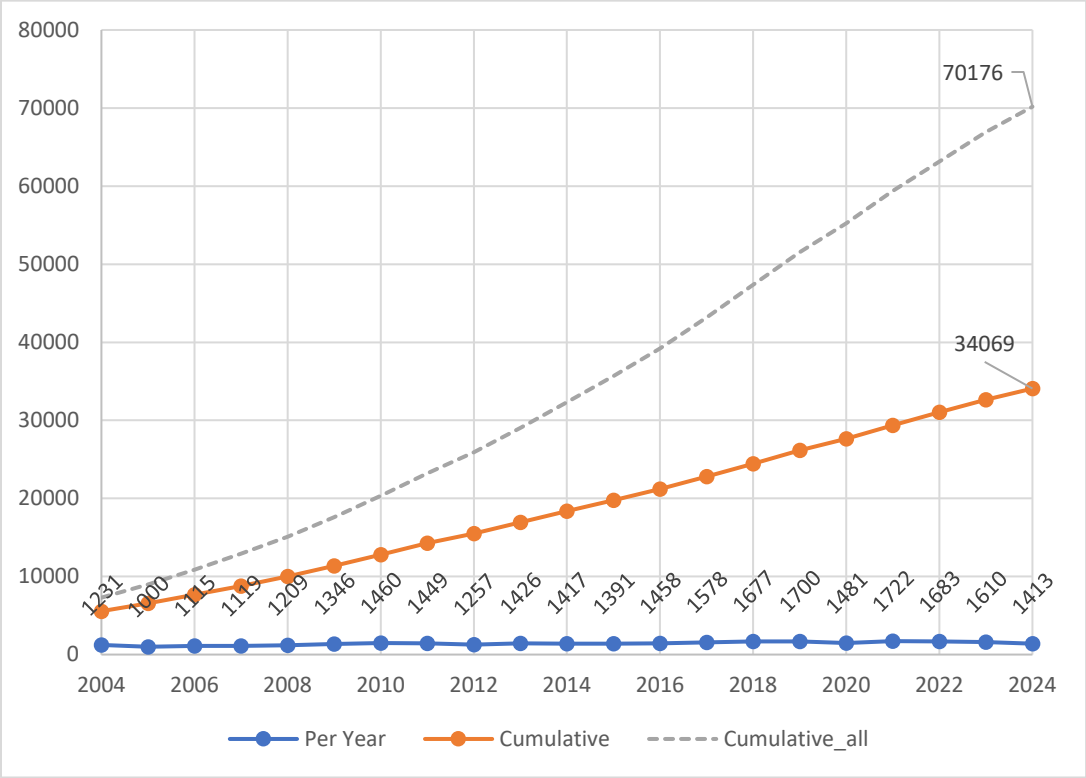
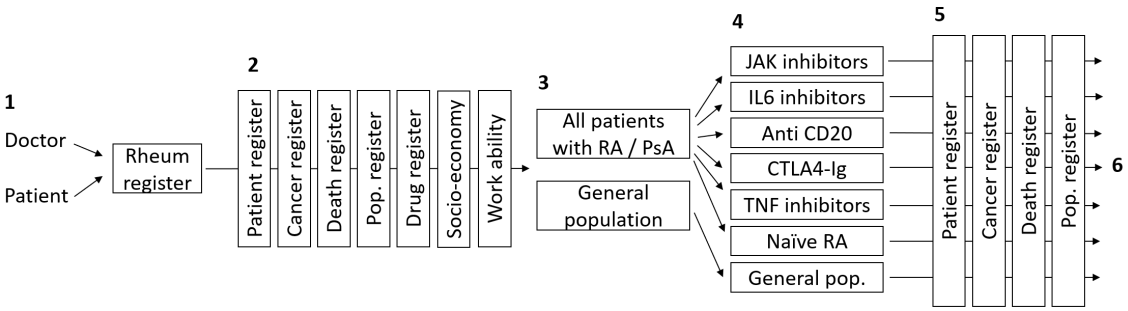


Figure 1. Accumulated number of first ever b/tsDMARD starts registers in the Swedish Rheumatology Quality Register (SRQ), specifically in its b/tsDMARD module (ARTIS). Dashed line = across all Rheumatology indications, bold lines = rheumatoid arthritis (RA) and polyarthritits (PA). Because of sequential discontinuations and switches to a second or third biologic, the total number of biologics treatment initiations is higher (>150,000 treatment starts for all indications).



1 Clinical data entry into the Rheumatology register, by the patient and by the rheumatologist
2 Linkage of the rheumatology registers to a series of other national population-based registers
3 Processing of the linked data to create a cohort of all patients with the rheum diagnosis in the country
4 Use of the data in **4** to define treatment-specific new-user cohorts, internal and external comparators, and covariates
5 Follow-up for defined or undefined safety outcomes through linkage to national population-based registers
6 Statistical analysis (pooling of data or results)

Figure 2. Schematic illustrating how different types of Swedish data may be linked to the data collected in the SRQ.

Since Flixabi entered the Swedish market, Samsung has had agreements with ARTIS via Karolinska Institutet regarding the safety monitoring of Flixabi as used in rheumatology in Sweden. In these agreements, safety data from the ARTIS program come from two sources:

(i) Spontaneous adverse drug reaction reporting to the Medical Products Agency. ARTIS has a reporting module that greatly facilitates this type of reporting. Once adjudicated and categorized, reported events are fed into the usual adverse drug reaction reporting system (Eudravigilance). The same adjudicated events also make up the biannual reports sent from ARTIS to Samsung, which has adhered to a pre-defined format ("the Manchester template").

(ii) Data from SRQ/ARTIS are (on a regular basis) linked to data from other national Swedish registers, as depicted in Figure 2 below and further described in the subjects and methods section. This report pertains entirely to events detected through this second route, i.e. register linkages.

The resulting linkage database is used for all scientific safety reports from ARTIS. Over the years, ARTIS has published on different aspects of safety of b/tsDMARD therapies, including reports on serious infections, TB, malignant lymphomas, other malignancies, cardiovascular risks, and on many other aspects.[6-58] In most of these reports, which all have used a study design, comparators, and analytic approach tailored so as to assess the outcome under study as optimally as possible.

Similar to other PASS studies, because of its mandated nature and focus on Flixabi since its launch, the current report takes a somewhat different approach compared to the published research reports. Whereas the latter focus on one safety outcome at a time, the former (and thus this report) use a singular design and a consistent analytical framework for the assessment of all safety outcomes under study. As a consequence, this report is both comprehensive (all pre-defined safety outcomes in one report) yet less detailed than the event-specific scientific reports, and also include exposure contrasts and time-frames that might not have been otherwise used for each specific outcome.

9.5.2 Swedish registers 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 is 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.[59] 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.

9.5.3 Data sources

Flixabi-treated patients were identified through the Swedish Rheumatology Quality Register (SRQ, www.srq.nu), with comparator cohorts identified through a combination of SRQ, the Swedish Patient Register, and the Total Population register. Baseline comorbidities and outcomes during follow-up were identified by linking individuals in these cohorts to the Swedish Patient Register, the Swedish Cancer Register, and the Cause of Death Register.

9.5.3.1 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). 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. SRQ is a profession-based register. It covers around 90% of all b/tsDMARD initiations in in Swedish Rheumatology after 1999.[60] Currently, some 34,000 patients with RA initiating over 70,000 b/tsDMARD treatments have been registered. 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.

9.5.3.2 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 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.[61] 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 the 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%.[62,63]

9.5.3.3 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%.[64,65]

9.5.3.4 The Tuberculosis Register.

The Tuberculosis (TB) Register started in 1969 on a national level and contains data on active TB diagnoses. Reporting incident TB cases to this register is done in parallel by both the microbiological laboratories and clinicians when a patient is culture-positive. In addition, any individual clinically diagnosed with TB is reported to the TB register's web-based reporting system by the clinician.

Completeness and quality of the data retrieved is monitored weekly, resulting in 100% coverage of all cases verified by culture.[66,67] Data until July 15th 2021 was available from the Tuberculosis Register for use in this report.

9.5.3.5 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 is 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. [68]

9.5.3.6 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 was used to identify the general population comparison cohorts, and to censor subjects who die or emigrate during follow-up.

9.6 Bias

Swedish registers data are prospectively collected, independently of both treatment exposure and outcomes, which reduces the risk of bias. However, we cannot rule out that surveillance bias may play a role, here: that patients on a given drug who are more closely monitored than others for a given outcome.

9.7 Study size

Flixabi has been available in Sweden for patients in RA since 2019. To maximise statistical precision, participants in comparator cohorts were allowed to enter from 2015.

9.8 Data transformation and groups

All continuous and numerical variables were used as such, without transformation with the following exception: the continuous variable RA/AS-SpA/PsA disease duration was dichotomized into less than five years vs. five years or more; the total number of days spent in hospital during the last five years was categorized into quartiles. The reason for this transformation was to handle highly skewed variables.

9.9 Statistical methods

9.9.1 Summary measures

Descriptive statistics for each of the five cohorts are presented for all covariates. Continuous variables are described with median, first and third quartiles, while categorical variables are reported with number and percentages. Descriptive statistics for the treated cohorts are additionally displayed after stratification on the number of previous b/tsDMARDs (0, 1-2, 3+).

9.9.2 Outcome Incidence Rates

Crude incidence and number of events are tabulated for each cohort and outcome. They are also presented by number of previous b/tsDMARDs for the three TNFi-exposed cohorts. Age/sex-standardized rates were calculated for each outcome, using the Flixabi cohort as standard. Rates were also stratified by the number of previous b/tsDMARDs (0, 1-2, 3+ previous b/tsDMARDs) at the time of treatment start. Note that the stratum of patients with no previous b/tsDMARD was thus free from patients switching between originator-product infliximab (Remicade) and Flixabi, while such patients were included in other strata (this choice was adopted since removing them was expected to substantially reduce the sample size in those strata).

A comparative analysis via Cox Proportional Hazards models was planned, but too few events were observed (<5 events per cohort), and thus no modelling was performed.

SAS version 9.4 was used for all analyses.

9.10 Quality control

ARTIS works mainly with data from the SRQ, a quality-of-care register with several regulations 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 the information on them.

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 guides the doctor in checking the quality of the registered information of their patients. Moreover, the data coordinator of SRQ periodically checks the quality of the data overall in the region.

The data warehouses of ARTIS reside on restricted, double backed-up, servers at the Clinical Epidemiology division at the Karolinska University Hospital Campus. All work with these data warehouses is performed by trained staff in adherence with local guidelines on good programming and data management practices and on archiving. Data, programs, and documents related to study reports will be maintained for a minimum of 10 years.

Quality control of specific reports is made in accordance with ARTIS SOPs through internal review by at least 2 members of staff: a statistician/epidemiologist responsible for assessing technical aspects and integrity of the results, and a clinical expert responsible for assessing the plausibility and consistency of observed rates and risks in relation to what is previously known on the topic. Any results that are marked as questionable or inconsistent are re-analysed/verified or rephrased until no more issues are identified.

10 Results

10.1 Participants

10.1.1 Rheumatoid arthritis

We identified a total of 161 patients with RA initiating Flixabi between 2019 and 2024, 409 patients initiating Remicade treatment (2015-2024), 13,026 patients initiating other TNFi's (2015-2024), 62,176 bionaive patients and 64,708 controls from the general population.

10.1.2 Ankylosing Spondylitis and Other Spondyloarthropathies

We identified a total of 152 patients with AS-SpA initiating Flixabi between 2019 and 2024, 357 patients initiating Remicade treatment (2015-2024), 7,529 patients initiating other TNFi's (2015-2024), 22,465 bionaive patients and 37,281 controls from the general population.

10.1.3 Psoriatic Arthritis

We identified a total of 65 patients with PsA initiating Flixabi between 2019 and 2024, 189 patients initiating Remicade treatment (2015-2024), 6,904 patients initiating other TNFi's (2015-2024), 29,182 bionaive patients and 33,311 controls from the general population.

10.2 Descriptive data

Baseline characteristics are displayed in Table 6 (a, b, c) and Table 7 (a, b, c). Table 6 describe the demographic and clinical characteristics of the cohort at baseline, disregarding the number of previous b/tsDMARDs to which patients had been exposed to. Table 7 present the same descriptive statistics when splitting the three TNFi-exposed cohorts (i.e., Fliaxbi, originator-product infliximab and other TNFi) into subcohorts defined by the number of previous b/tsDMARDs. The letters (a, b, c) refer to the indication, respectively RA, AS-SpA and PsA.

10.2.1 Rheumatoid arthritis

Table 6a describes the demographic and clinical characteristics of the Flixabi and comparator cohorts. We identified a total of 161 RA patients initiating Flixabi treatment between 2019 and 2024. The median age of first Flixabi initiation was 62 years, 73% were female, and 68% had RF-positive RA. Combination therapy with non-b/tsDMARD drugs was common, with 74% prescribed any conventional synthetic DMARDs, but less than half of all patients used concomitant oral steroids (35%) or NSAIDs (13%). Most patients had had RA for a relatively long time before initiating Flixabi treatment (median time since disease onset was 11.1 years), and disease activity was moderate at treatment start (median DAS28 4.2). Twenty-eight (28) percent of patients were b/ts-DMARD naïve at start of Flixabi and 44% had previously received Infliximab (other than Flixabi).

The Flixabi cohort was quite similar to the cohort of patients starting originator-product infliximab as well as to the cohort starting other TNFis, with the exception that the latter included patients who had a slightly shorter disease duration (with a median of 6.1 years) and were more often on their first TNFi (80%) compared to the Flixabi cohort. Twenty-one (21) percent of the originator-product infliximab cohort had been previously exposed to an infliximab biosimilar. By design, zero patients in the other-TNFi cohort had been exposed to infliximab (originator or biosimilar).

The b/tsDMARD-naïve RA cohort was slightly younger than the Flixabi cohort and patients had a similar rate of comorbidity for most investigated comorbid conditions, although surgeries and hospitalized infections were more common in the Flixabi cohort.

Compared to the Swedish general population cohort (age and sex matched to the cohorts defined by TNFi initiation), the Flixabi cohort had a higher rate of previous malignancies and myocardial infarctions, but a lower rate of all other comorbid conditions.

Table 7a presents the same descriptive statistics when splitting the three TNFi exposed cohorts (i.e., Flixabi, originator-product infliximab (Remicade) and other-TNFi) into subcohorts defined by the number of previous b/tsDMARDs. This table reveals that overall, and for all three (TNFi) cohorts, the disease duration and the rates of comorbidities are increasing with line of therapy.

10.2.2 Ankylosing Spondylitis and Other Spondyloarthropathies

Table 6b describes the demographic and clinical characteristics of the Flixabi and comparator cohorts in AS-SpA. We identified a total of 152 AS-SpA patients initiating Flixabi treatment between 2019 and 2024. The median age at first Flixabi initiation was 46 years and 47% were female. Combination therapy with non-b/tsDMARD drugs was less frequent than in RA, with 44% prescribed any conventional synthetic DMARDs and 8% prescribed concomitant oral steroids. However, 28% of patients were prescribed NSAIDs, which is higher than for RA patients. Most patients had had AS-SpA for a relatively long time before initiating Flixabi treatment (median time since disease onset was 15.3 years). Nineteen (19) percent of patients were b/tsDMARD naïve at start of Flixabi and 40% had previously received infliximab.

The Flixabi cohort was quite similar to the cohort of patients starting originator-product infliximab as well as to the cohort starting another TNFi, with the with the exceptions that they both had a higher proportion of patients who were bionaive prior to cohort entry (50% and 86%) than the Flixabi cohort

and that the other-TNFi cohort had a slightly shorter disease duration (median 8.9 years) than the other two. Twenty-one (21) percent of the originator-product infliximab cohort had been previously exposed to an infliximab biosimilar (Flixabi or another). By design, zero patients in the other-TNFi cohort had been exposed to infliximab (originator or biosimilar).

The b/tsDMARD-naïve AS-SpA cohort was slightly older than the Flixabi cohort and had similar rates of historical comorbid conditions.

Compared to the Swedish general population cohort (age and sex matched to the cohorts defined by TNFi initiation), the Flixabi cohort had higher rates of all comorbid conditions.

Table 7b presents the same descriptive statistics when splitting the three TNFi exposed cohorts (i.e., Flixabi, originator-product infliximab (Remicade) and other-TNFi) into subcohorts defined by the number of previous b/tsDMARDs. As for RA, this table shows that overall the disease duration and the rates of comorbidities are generally increasing with line of therapy, although this pattern is not as clear for the Flixabi cohort.

10.2.3 Psoriatic Arthritis

Table 6c describes the demographic and clinical characteristics of the Flixabi and comparator cohorts in PsA. We identified a total of 65 PsA patients initiating Flixabi treatment between 2019 and 2024. The median age of first Flixabi initiation was 55 years, and 49% were female. Combination therapy with non-b/tsDMARD drugs was not uncommon, with 69% prescribed any conventional synthetic DMARDs, 17% using oral steroids, and 20% using NSAIDs at Flixabi initiation. Most patients had had PsA for a relatively long time before initiating Flixabi treatment (median time since disease onset was 11.7 years), and disease activity was moderate at treatment start (DAS28 of 4.6). Twenty-two (22) percent of all patients initiating Flixabi treatment were b/tsDMARD naïve at that time point, and 35% had previously received infliximab.

The prevalence of comorbidities was on the whole similar comparing Flixabi to the other PsA cohorts exposed to originator-product infliximab or to another TNFi, although the Flixabi cohort had a higher rate of infections and the originator-product infliximab had a higher rate of surgeries. The originator product infliximab and other-TNFi cohorts included patients who were more likely to be on first line therapy (46% and 83%) than the Flixabi cohort. Twenty-four (24) percent of the originator-product infliximab cohort had been previously exposed to an infliximab biosimilar. By design, zero patients in the other-TNFi cohort had been exposed to infliximab (originator or biosimilar).

The b/tsDMARD-naïve PsA cohort had a slightly higher rate of comorbidity history for all investigated comorbid conditions, with the exception of joint replacement surgery).

Compared to the Swedish general population cohort (age and sex matched to the cohorts defined by TNFi initiation), the Flixabi cohort had slightly higher rates of comorbid conditions, with the exception of malignancies and surgeries, for which rates were slightly higher in the Flixabi cohort.

Table 7c presents the same descriptive statistics when splitting the three TNFi exposed cohorts (i.e., Flixabi, originator-product infliximab (Remicade) and other-TNFi) into subcohorts defined by the number of previous b/tsDMARDs. The pattern we observed in RA and AS-SpA, with overall increasing disease duration and rates of comorbidities with line of therapy, was not apparent for PsA.

Table 6. Baseline characteristics of Swedish patients initiating Flixabi, and comparator cohorts.

Table 6a. Baseline characteristics of Swedish RA patients initiating Flixabi, and comparator cohorts.

Status at entry	Main cohort	Comparator Cohorts			
	Flixabi	Originator-product infliximab (Remicade)	Other TNFi	b/ts-DMARD naïve	General population
N observations	161	409	13026	62176	64708
Demographics					
Age (median, IQR)	62 (53-71)	61 (51-69)	59 (48-69)	68 (57-77)	59 (48-69)
Gender (% females)	73%	73%	76%	69%	74%
Disease-related characteristics					
Rheumatoid factor positive (%)	68%	69%	71%	n/a	n/r
Disease duration (median, IQR)	11.1 (4.1-22.2)	9.6 (2.8-19.9)	6.1 (1.9-14.3)	n/a	n/r
Calendar year (median)	2022	2016	2020	2015	2020
DAS28 (median, IQR)	4.2 (3.2-4.9)	4.7 (3.6-5.6)	4.4 (3.5-5.2)	n/a	n/r
HAQ (median, IQR)	1.0 (0.4-1.6)	1.0 (0.6-1.5)	0.9 (0.4-1.3)	n/a	n/r
Concomitant DMARDs (%)	74%	84%	71%	n/a	n/r
Oral steroids (%)	35%	45%	38%	n/a	n/r
NSAIDs (%)	13%	28%	16%	n/a	n/r
Number of previous b/tsDMARDs					
0	28%	55%	80%	100%	100%
1-2	57%	31%	17%		
3+	15%	13%	3%		
Previous use of infliximab (%)	44%	21%	0%	0%	0%
Disease history					
Malignancy (%)	6.2%	5.9%	7%	13.7%	9.7%
Hosp infection, last 5 yrs (%)	11.8%	7.3%	6.4%	11%	3.6%
Joint replacement surgery (%)	23%	18.6%	15.5%	18.6%	6.1%

Status at entry	Main cohort	Comparator Cohorts			
	Flixabi	Originator-product infliximab (Remicade)	Other TNFi	b/ts-DMARD naïve	General population
COPD (%)	2.5%	3.2%	2.7%	5.1%	1.6%
Diabetes mellitus (%)	5%	5.9%	6.9%	9.7%	4.9%
MI (%)	0.6%	1.2%	1.3%	2.9%	1%
Total days in hosp (median, IQR)	0 (0-4)	0 (0-4)	0 (0-3)	0 (0-7)	0 (0-1)
Reason for discontinuing previous b/tsDMARD					
Safety, of those with info. (%)	10%	14%	13%	n/a	n/a
Inefficacy, of those with info. (%)	24%	42%	44%	n/a	n/a
Non-medical switch, of those with info. (%)	51%	18%	5%	n/a	n/a
Other, of those with info. (%)	14%	26%	38%	n/a	n/a
Missing, of total (%)	1%	1%	1%	n/a	n/a

b/tsDMARD= biological and targeted synthetic disease modifying anti-rheumatic drugs; csDMARDs= conventional synthetic disease-modifying antirheumatic drugs; COPD= chronic obstructive pulmonary disease; DAS28= disease activity score on 28 joints; HAQ= health assessment questionnaire; IQR= interquartile range (25th -75th percentile); MI= myocardial infarction; NSAID= non-steroidal anti-inflammatory drug; RA= rheumatoid arthritis; TNFi= Tumor Necrosis Factor inhibitor n/a= not available; n/r= not relevant

Table 6b. Baseline characteristics of Swedish AS-SpA patients initiating Flixabi, and comparator cohorts.

Status at entry	Main cohort	Comparator Cohorts			
	Flixabi	Originator-product infliximab (Remicade)	Other TNFi	b/ts-DMARD naïve	General population
N observations	152	357	7529	22465	37281
Demographics					
Age (median, IQR)	46 (34-58)	44 (34-55)	41 (31-52)	50 (37-63)	41 (31-53)
Gender (% females)	47%	46%	49%	46%	47%
Disease-related characteristics					
Disease duration (median, IQR)	15.3 (7.1-26.4)	14.6 (6.4-25.4)	8.9 (3.1-18.6)	n/a	n/r
Calendar year (median)	2022	2016	2019	2015	2019
HAQ (median, IQR)	0.8 (0.1-1.0)	0.8 (0.5-1.3)	0.6 (0.3-1.0)	n/a	n/r
Concomitant DMARDs (%)	44%	38%	19%	n/a	n/r
Oral steroids (%)	8%	13%	7%	n/a	n/r
NSAIDs (%)	42%	28%	30%	n/a	n/r
Number of previous b/tsDMARDs					
0	19%	50%	86%	100%	100%
1-2	57%	34%	13%		
3+	24%	16%	1%		
Previous use of infliximab (%)	40%	21%	0%	0%	0%
Disease history					
Malignancy (%)	7.2%	3.9%	2.3%	7.4%	3.5%
Hosp infection, last 5 yrs (%)	7.2%	7%	4.8%	7.4%	2.2%
Joint replacement surgery (%)	8.6%	5.6%	4.2%	7.1%	1.7%
COPD (%)	2%	0.6%	0.6%	2.1%	0.4%
Diabetes mellitus (%)	5.3%	3.9%	2.9%	5.8%	2.5%
MI (%)	1.3%	1.1%	0.8%	1.7%	0.4%
Total days in hosp (median, IQR)	0 (0-2)	0 (0-4)	0 (0-2)	0 (0-4)	0 (0-0)

Status at entry	Main cohort	Comparator Cohorts			
	Flixabi	Originator-product infliximab (Remicade)	Other TNFi	b/ts-DMARD naïve	General population
Reason for discontinuing previous b/tsDMARD					
Safety, of those with info. (%)	13%	11%	10%	n/a	n/r
Inefficacy, of those with info. (%)	39%	58%	44%	n/a	n/r
Non-medical switch, of those with info. (%)	40%	8%	7%	n/a	n/r
Other, of those with info. (%)	8%	23%	39%	n/a	n/r
Missing, of total (%)	1%	2%	1%	n/a	n/r

b/tsDMARD= biological and targeted synthetic disease modifying anti-rheumatic drugs; csDMARDs= conventional synthetic disease-modifying antirheumatic drugs; COPD= chronic obstructive pulmonary disease; DAS28= disease activity score on 28 joints; HAQ= health assessment questionnaire; IQR= interquartile range (25th -75th percentile); MI= myocardial infarction; NSAID= non-steroidal anti-inflammatory drug; AS-SpA= Ankylosing spondylitis and other Spondylo-arthropathies; TNFi= Tumor Necrosis Factor inhibitor n/a= not available; n/r= not relevant

Table 6c. Baseline characteristics of Swedish PsA patients initiating Flixabi, and comparator cohorts

Status at entry	Main cohort	Comparator Cohorts			
	Flixabi	Originator-product infliximab (Remicade)	Other TNFi	b/ts-DMARD naïve	General population
N observations	65	189	6904	29182	33311
Demographics					
Age (median, IQR)	55 (49-63)	52 (43-60)	51 (41-60)	58 (46-68)	51 (41-61)
Gender (% females)	49%	46%	53%	55%	51%
Disease-related characteristics					
Disease duration (median, IQR)	11.7 (4.7-23.1)	10.8 (5.7-17.7)	7.9 (3.1-15.6)	n/a	n/r
Calendar year (median)	2021	2016	2019	2015	2019
DAS28 (median, IQR)	4.6 (3.1-5.5)	3.9 (3.0-4.7)	3.9 (2.9-4.7)	n/a	n/r
HAQ (median, IQR)	0.9 (0.6-1.5)	0.9 (0.5-1.3)	0.8 (0.4-1.1)	n/a	n/r
Concomitant DMARDs (%)	69%	68%	49%	n/a	n/r
Oral steroids (%)	17%	18%	11%	n/a	n/r
NSAIDs (%)	20%	29%	21%	n/a	n/r
Number of previous b/tsDMARDs					
0	22%	46%	83%	100%	100%
1-2	60%	40%	15%		
3+	18%	15%	2%		
Previous use of infliximab (%)	35%	24%	0%	0%	0%
Disease history					
Malignancy (%)	7.7%	3.7%	4.9%	9.2%	5.9%
Hosp infection, last 5 yrs (%)	10.8%	7.9%	5.3%	7.3%	2.7%
Joint replacement surgery (%)	6.2%	11.6%	8.2%	10%	3.4%
COPD (%)	1.5%	2.1%	1.4%	2.9%	0.9%
Diabetes mellitus (%)	4.6%	6.9%	6.2%	8.6%	3.5%
MI (%)	0%	2.1%	1.1%	2.2%	0.7%

Status at entry	Main cohort	Comparator Cohorts			
	Flixabi	Originator-product infliximab (Remicade)	Other TNFi	b/ts-DMARD naïve	General population
Total days in hosp (median, IQR)	0 (0-3)	0 (0-4)	0 (0-2)	0 (0-3)	0 (0-0)
Reason for discontinuing previous b/tsDMARD					
Safety, of those with info. (%)	4%	21%	16%	n/a	n/r
Inefficacy, of those with info. (%)	43%	56%	52%	n/a	n/r
Non-medical switch, of those with info. (%)	37%	11%	4%	n/a	n/r
Other, of those with info. (%)	16%	13%	28%	n/a	n/r
Missing, of total (%)	0%	1%	2%	n/a	n/r

b/tsDMARD= biological and targeted synthetic disease modifying anti-rheumatic drugs; csDMARDs= conventional synthetic disease-modifying antirheumatic drugs; COPD= chronic obstructive pulmonary disease; DAS28= disease activity score on 28 joints; HAQ= health assessment questionnaire; IQR= interquartile range (25th -75th percentile); MI= myocardial infarction; NSAID= non-steroidal anti-inflammatory drug; PsA= psoriatic arthritis; TNFi= Tumor Necrosis Factor inhibitor n/a= not available; n/r= not relevant

Table 7. Baseline characteristics of Swedish patients initiating Flixabi or another TNFi, stratified by line of therapy

Table 8a. Baseline characteristics of Swedish RA patients initiating Flixabi or another TNFi, stratified by line of therapy

Status at entry	Exposed	Comparator Cohorts Starting another TNFi		Exposed	Comparator Cohorts Starting another TNFi		Exposed	Comparator Cohorts Starting another TNFi	
	Flixabi	Remicade	Other TNFi	Flixabi	Remicade	Other TNFi	Flixabi	Remicade	Other TNFi
	0 previous b/tsDMARD			1-2 previous b/tsDMARD			3+ previous b/tsDMARD		
N observations	45	226	10385	92	128	2215	24	55	426
Demographics									
Age (median, IQR)	57 (48-69)	60 (51-69)	58 (47-68)	65 (56-74)	62 (51-71)	62 (50-71)	57 (54-70)	64 (55-75)	62 (50-70)
Gender (% females)	82%	73%	75%	70%	75%	79%	71%	67%	85%
Disease characteristics									
Rheumatoid factor positive (%)	67%	69%	69%	65%	69%	76%	79%	67%	77%
Disease duration (median, IQR)	4.7 (2.3-10.3)	4.7 (1.5-12.8)	4.2 (1.4-11.0)	13.4 (4.9-25.4)	13.9 (7.2-24.3)	14.4 (8.9-23.0)	17.9 (11.3-23.3)	17.5 (10.6-25.5)	17.5 (11.3-26.3)
Calendar year (median)	2022	2015	2020	2022	2016.5	2018	2022	2017	2018
DAS28 (median, IQR)	4.4 (3.8-4.9)	4.8 (3.9-5.8)	4.4 (3.5-5.3)	3.3 (2.2-4.4)	4.3 (3.3-5.2)	4.2 (3.2-5.1)	5.3 (4.3-5.9)	4.5 (2.9-5.7)	4.6 (3.4-5.5)
HAQ (median, IQR)	0.8 (0.4-1.4)	1.0 (0.6-1.5)	0.9 (0.4-1.3)	1.0 (0.3-1.6)	1.0 (0.8-1.4)	1.0 (0.5-1.5)	1.6 (1.3-2.1)	1.4 (1.0-1.8)	1.3 (0.8-1.8)
Concomitant csDMARDs (%)	76%	90%	75%	66%	77%	59%	91%	66%	51%
Oral steroids (%)	38%	52%	38%	34%	27%	34%	27%	48%	53%
NSAIDs (%)	3%	24%	14%	16%	37%	26%	27%	31%	32%

Status at entry	Exposed	Comparator Cohorts Starting another TNFi		Exposed	Comparator Cohorts Starting another TNFi		Exposed	Comparator Cohorts Starting another TNFi	
	Flixabi	Remicade	Other TNFi	Flixabi	Remicade	Other TNFi	Flixabi	Remicade	Other TNFi
Previous use of infliximab (%)	0%	0%	0%	36%	7%	0%	45%	14%	0%
Disease history									
Malignancy (%)	0%	0%	0%	63%	47%	0%	54%	49%	0%
Hosp infection, last 5 yrs (%)	4.4%	4.9%	6.4%	6.5%	6.3%	9.8%	8.3%	9.1%	8.7%
Joint replacement surgery (%)	2.2%	6.6%	5.4%	15.2%	6.3%	9.6%	16.7%	12.7%	14.6%
COPD (%)	17.8%	12.4%	12.3%	22.8%	25%	26.2%	33.3%	29.1%	39.7%
Diabetes mellitus (%)	0%	4%	2.5%	3.3%	3.1%	3.5%	4.2%	0%	2.8%
MI (%)	2.2%	6.2%	6.8%	5.4%	7%	7.2%	8.3%	1.8%	8.5%
Total days in hosp (median, IQR)	0%	0.9%	1.2%	1.1%	2.3%	1.6%	0%	0%	1.9%
Reason for discontinuing previous b/tsDMARD									
Safety, of those with info. (%)	n/r	n/r	n/r	9%	15%	11%	17%	11%	21%
Inefficacy, of those with info. (%)	n/r	n/r	n/r	16%	40%	43%	57%	46%	47%
Non-medical switch, of those with info. (%)	n/r	n/r	n/r	60%	18%	6%	17%	19%	1%
Other, of those with info. (%)	n/r	n/r	n/r	15%	27%	39%	9%	24%	31%

Status at entry	Exposed	Comparator Cohorts Starting another TNFi		Exposed	Comparator Cohorts Starting another TNFi		Exposed	Comparator Cohorts Starting another TNFi	
	Flixabi	Remicade	Other TNFi	Flixabi	Remicade	Other TNFi	Flixabi	Remicade	Other TNFi
Missing, of total (%)	n/r	n/r	n/r	0%	1%	1%	4%	2%	2%

b/tsDMARD= biological and targeted synthetic disease modifying anti-rheumatic drugs; csDMARDs= conventional synthetic disease-modifying antirheumatic drugs; COPD= chronic obstructive pulmonary disease; DAS28= disease activity score on 28 joints; HAQ= health assessment questionnaire; IQR= interquartile range (25th -75th percentile); MI= myocardial infarction; NSAID= non-steroidal anti-inflammatory drug; RA= rheumatoid arthritis; TNFi= Tumor Necrosis Factor inhibitor
n/r= not relevant

Table 9b. Baseline characteristics of Swedish AS-SpA patients initiating Flixabi or another TNFi, stratified by line of therapy

Status at entry	Exposed	Comparator Cohorts Starting another TNFi		Exposed	Comparator Cohorts Starting another TNFi		Exposed	Comparator Cohorts Starting another TNFi	
	Flixabi	Remicade	Other TNFi	Flixabi	Remicade	Other TNFi	Flixabi	Remicade	Other TNFi
	0 previous b/tsDMARD			1-2 previous b/tsDMARD			3+ previous b/tsDMARD		
N observations	29	177	6455	87	123	983	36	57	91
Demographics									
Age (median, IQR)	38 (33-54)	42 (30-51)	40 (30-51)	47 (35-60)	48 (35-58)	46 (35-57)	48 (35-56)	47 (36-56)	49 (41-60)
Gender (% females)	34%	44%	49%	48%	47%	47%	56%	50%	60%
Disease characteristics									
Disease duration (median, IQR)	8.2 (4.7-19.4)	11.1 (3.4-22.0)	7.3 (2.6-16.8)	17.2 (8.0-29.2)	15.9 (8.7-27.7)	16.1 (9.7-25.4)	16.0 (10.0-31.6)	18.1 (12.8-27.6)	18.5 (11.8-27.6)
Calendar year (median)	2022	2015	2020	2021	2016	2018	2022	2017	2018
HAQ (median, IQR)	0.5 (0.0-0.9)	0.8 (0.6-1.1)	0.6 (0.3-1.0)	0.6 (0.1-0.9)	0.8 (0.5-1.1)	0.6 (0.4-1.0)	1.0 (0.9-1.3)	0.8 (0.0-1.6)	1.1 (0.8-1.4)
Concomitant csDMARDs (%)	38%	43%	18%	41%	37%	21%	64%	23%	28%
Oral steroids (%)	13%	12%	6%	5%	15%	9%	9%	13%	22%
NSAIDs (%)	38%	26%	29%	41%	23%	39%	55%	48%	35%
Previous use of infliximab (%)	0%	0%	0%	52%	41%	0%	44%	42%	0%
Disease history									
Malignancy (%)	3.4%	4%	2.1%	9.2%	4.9%	3.2%	5.6%	1.8%	6.6%

Status at entry	Exposed	Comparator Cohorts Starting another TNFi		Exposed	Comparator Cohorts Starting another TNFi		Exposed	Comparator Cohorts Starting another TNFi	
	Flixabi	Remicade	Other TNFi	Flixabi	Remicade	Other TNFi	Flixabi	Remicade	Other TNFi
Hosp infection, last 5 yrs (%)	6.9%	7.3%	4.4%	5.7%	6.5%	7%	11.1%	7%	8.8%
Joint replacement surgery (%)	6.9%	2.3%	3.5%	9.2%	8.1%	7.6%	8.3%	10.5%	16.5%
COPD (%)	0%	0.6%	0.5%	3.4%	0.8%	1.1%	0%	0%	1.1%
Diabetes mellitus (%)	3.4%	2.8%	2.7%	4.6%	2.4%	3.8%	8.3%	10.5%	4.4%
MI (%)	0%	0%	0.7%	1.1%	2.4%	1.1%	2.8%	1.8%	4.4%
Total days in hosp (median, IQR)	0 (0-4)	0 (0-3)	0 (0-1)	0 (0-1)	0 (0-4)	0 (0-3)	0 (0-4)	0 (0-6)	0 (0-7)
Reason for discontinuing previous b/tsDMARD									
Safety, of those with info. (%)	n/r	n/r	n/r	9%	8%	9%	23%	16%	16%
Inefficacy, of those with info. (%)	n/r	n/r	n/r	36%	59%	43%	46%	57%	49%
Non-medical switch, of those with info. (%)	n/r	n/r	n/r	47%	9%	7%	23%	7%	2%
Other, of those with info. (%)	n/r	n/r	n/r	8%	24%	40%	9%	20%	32%
Missing, of total (%)	n/r	n/r	n/r	0%	2%	1%	3%	2%	0%

Status at entry	Exposed	Comparator Cohorts Starting another TNFi		Exposed	Comparator Cohorts Starting another TNFi		Exposed	Comparator Cohorts Starting another TNFi	
	Flixabi	Remicade	Other TNFi	Flixabi	Remicade	Other TNFi	Flixabi	Remicade	Other TNFi
b/tsDMARD= biological and targeted synthetic disease modifying anti-rheumatic drugs; csDMARDs= conventional synthetic disease-modifying antirheumatic drugs; COPD= chronic obstructive pulmonary disease; DAS28= disease activity score on 28 joints; HAQ= health assessment questionnaire; IQR= interquartile range (25th -75th percentile); MI= myocardial infarction; NSAID= non-steroidal anti-inflammatory drug; RA= rheumatoid arthritis; TNFi= Tumor Necrosis Factor inhibitor n/r= not relevant									

Table 10c. Baseline characteristics of Swedish PsA patients initiating Flixabi or another TNFi, stratified by line of therapy

Status at entry	Exposed	Comparator Cohorts Starting another TNFi		Exposed	Comparator Cohorts Starting another TNFi		Exposed	Comparator Cohorts Starting another TNFi	
	Flixabi	Remicade	Other TNFi	Flixabi	Remicade	Other TNFi	Flixabi	Remicade	Other TNFi
	0 previous b/tsDMARD			1-2 previous b/tsDMARD			3+ previous b/tsDMARD		
N observations	14	86	5706	39	75	1054	12	28	144
Demographics									
Age (median, IQR)	57 (49-67)	52 (42-59)	51 (40-60)	55 (49-63)	51 (43-62)	53 (44-62)	57 (39-61)	52 (47-61)	54 (46-63)
Gender (% females)	71%	45%	53%	38%	46%	53%	58%	54%	66%
Disease characteristics									
Disease duration (median, IQR)	6.3 (2.7-10.6)	7.3 (2.7-14.6)	6.6 (2.5-13.5)	11.7 (4.4-25.3)	13.1 (6.7-20.8)	13.7 (8.1-21.7)	19.6 (11.9-28.0)	16.9 (11.7-22.9)	17.5 (11.9-23.8)
Calendar year (median)	2021	2015	2020	2021	2017	2018	2021	2017	2017
DAS28 (median, IQR)	4.7 (3.6-5.5)	4.1 (3.0-4.9)	3.9 (2.9-4.7)	4.5 (3.1-5.4)	3.8 (2.9-4.6)	3.8 (2.8-4.6)	4.2 (2.9-6.1)	3.3 (3.0-4.0)	4.3 (3.5-5.3)
HAQ (median, IQR)	0.8 (0.8-1.0)	0.8 (0.5-1.3)	0.8 (0.4-1.1)	1.1 (0.4-1.8)	0.9 (0.6-1.1)	1.0 (0.5-1.4)	0.9 (0.7-1.7)	1.1 (0.8-1.5)	1.1 (0.8-1.5)
Concomitant csDMARDs (%)	44%	81%	51%	75%	56%	42%	83%	38%	35%
Oral steroids (%)	11%	18%	10%	15%	15%	14%	33%	31%	18%
NSAIDs (%)	11%	21%	19%	15%	44%	31%	50%	31%	40%
Previous use of infliximab (%)	0%	0%	0%	38%	39%	0%	67%	57%	0%
Disease history									
Malignancy (%)	14.3%	3.5%	4.5%	5.1%	4%	6.5%	8.3%	3.6%	5.6%

Status at entry	Exposed	Comparator Cohorts Starting another TNFi		Exposed	Comparator Cohorts Starting another TNFi		Exposed	Comparator Cohorts Starting another TNFi	
	Flixabi	Remicade	Other TNFi	Flixabi	Remicade	Other TNFi	Flixabi	Remicade	Other TNFi
Hosp infection, last 5 yrs (%)	0%	5.8%	4.6%	12.8%	9.3%	8.1%	16.7%	10.7%	13.2%
Joint replacement surgery (%)	0%	7%	7.3%	7.7%	12%	12.4%	8.3%	25%	12.5%
COPD (%)	0%	2.3%	1.3%	2.6%	0%	1.7%	0%	7.1%	1.4%
Diabetes mellitus (%)	7.1%	5.8%	5.8%	2.6%	8%	7.7%	8.3%	7.1%	11.8%
MI (%)	0%	1.2%	1.1%	0%	2.7%	1.2%	0%	3.6%	0%
Total days in hosp (median, IQR)	0 (0-1)	0 (0-4)	0 (0-1)	0 (0-4)	1 (0-5)	0 (0-3)	2 (0-8)	3 (0-5)	1 (0-6)
Reason for discontinuing previous b/tsDMARD									
Safety, of those with info. (%)	n/r	n/r	n/r	3%	19%	16%	8%	26%	17%
Inefficacy, of those with info. (%)	n/r	n/r	n/r	44%	57%	51%	42%	52%	57%
Non-medical switch, of those with info. (%)	n/r	n/r	n/r	36%	11%	4%	42%	11%	
Other, of those with info. (%)	n/r	n/r	n/r	18%	13%	29%	8%	11%	25%
Missing, of total (%)	n/r	n/r	n/r	0%	0%	2%	0%	4%	1%

Status at entry	Exposed	Comparator Cohorts Starting another TNFi		Exposed	Comparator Cohorts Starting another TNFi		Exposed	Comparator Cohorts Starting another TNFi	
	Flixabi	Remicade	Other TNFi	Flixabi	Remicade	Other TNFi	Flixabi	Remicade	Other TNFi
b/tsDMARD= biological and targeted synthetic disease modifying anti-rheumatic drugs; csDMARDs= conventional synthetic disease-modifying antirheumatic drugs; COPD= chronic obstructive pulmonary disease; DAS28= disease activity score on 28 joints; HAQ= health assessment questionnaire; IQR= interquartile range (25th -75th percentile); MI= myocardial infarction; NSAID= non-steroidal anti-inflammatory drug; RA= rheumatoid arthritis; TNFi= Tumor Necrosis Factor inhibitor n/r= not relevant									

10.3 Outcome data

The number of participants for each of the oucomes analyses and in each cohort are reported in Tables 8a, 8b and 8c, respectively for RA, AS-SpA and PsA. In addition, for analyses related to cancer outcomes, the follow-up ended at 31st December 2023 (data availability from the Cancer Register), thereby excluding patients with a start of follow-up in 2024. For analyses related to tuberculosis, follow-up ended on the 30th of September 2024, which also restricted the analysis.

10.4 Main results

Table 8a-8c contain the results of the statistical analysis, with the number of patients, number of events, as well as crude and standardized incidence rates for all outcomes. For all tables, the letters (a, b, c) refer to the indication, respectively RA, AS-SpA and PsA. While Cox regressions were originally planned, they were not estimated due to the low number of events in the Flixabi cohort (<5).

10.4.1 All primary invasive cancers excluding non-melanoma skin cancers

During 266.42 person-years (PYs) of follow-up among 148 RA patients initiating treatment with Flixabi 2019-2024, we observed 3 individuals diagnosed with malignant tumors resulting in a standardized incidence rate of 11.3/1000 PYs, whereas the other cohorts had standardized incidence rates of 12.7/1000 PYs (originator-product infliximab cohort), 12.3/1000 PYs (other TNFi cohort), 13.5/1000 PYs (b/tsDMARD naïve cohort) and 12.0/1000 PYs (general population cohort).

During 311.96 person-years of follow-up amoing 145 AS-SpA patients initiating treatment with Flixabi 2019-2024, we observed 3 individuals who were diagnosed with malignancies, resulting in a standardized incidence rate of 9.6/1000 PYs, whereas the other cohorts had standardized incidence rates of 9.4/1000 PYs (originator-product infliximab cohort), 7.0/1000 PYs (other TNFi cohort), 8.2/1000 PYs (b/tsDMARD naïve cohort) and 6.7/1000 PYs (general population cohort).

During 145.62 person-years (PYs) of follow-up among 62 PsA patients initiating treatment with Flixabi 2019-2024, we observed one individual diagnosed with malignancies, resulting in an incidence rate of 6.9/1000 PYs (95% confidence interval: (0.001 – 0.049). For the originator-product cohort, the standardized incidence rate was 10.0/1000 PYs, for the other TNFi cohort it was 10.1/1000 PYs, for the b/tsDMARD-naïve cohort it was 12.5/1000 PYs and for the general population the standardized incidence rate was 9.8/1000 PYs.

10.4.2 Lymphoma

During 270.16 person-years (PYs) of follow-up among 148 RA patients initiating treatment with Flixabi 2019-2024, we did not observe any individual diagnosed with a lymphoma, whereas the standardized incidence rates in the other cohorts were 0.5/1000 PYs (originator-product infliximab), 0.9/1000 PYs (other-TNFi), 0.9 /1000 PYs (b/tsDMARD-naïve) and 0.6/1000 PYs (general population).

During 315.41 person-years (PYs) of follow-up among 145 As-SpA patients initiating treatment with Flixabi 2019-2024, we observed one (1) individual diagnosed with a lymphoma, resulting in an incidence rate of 3.2/1000 PYs. The standardized incidence rates in the other cohorts were 1.0/1000 PYs (originator-product infliximab), 0.4/1000 PYs (other-TNFi), 0.4/1000 PYs (b/tsDMARD-naïve) and 0.3/1000 PYs (general population).

During 148.20 person-years (PYs) of follow-up among 62 PsA patients initiating treatment with Flixabi 2019-2024, we did not observe any individuals diagnosed with lymphoma, whereas the standardized incidence rates in the other cohorts were 0.9/1000 PYs (with 1 event, in the originator-product infliximab), 0.6/1000 PYs (other-TNFi), 0.7/1000 PYs (b/tsDMARD-naïve) and 0.4/1000 PYs (general population).

10.4.3 Tuberculosis

During 192.46 person-years (PYs) of follow-up among 158 RA patients initiating treatment with Flixabi 2019-2024, we did not observe any individuals diagnosed with tuberculosis. This was also the case in the originator-product infliximab cohort, whereas the standardized incidence rates in the other cohorts were 0.3/1000 PYs (other-TNFi), 0.1/1000 PYs (with 14 events in the b/tsDMARD-naïve cohort) and 0.0/1000 PYs (with 8 events in the general population).

During 211.59 person-years (PYs) of follow-up among 151 As-SpA patients initiating treatment with Flixabi 2019-2024, we did not observe any individuals diagnosed with tuberculosis. The standardized incidence rates in the other cohorts were 0.0/1000 PYs for all except for the originator-product infliximab cohort (with one event and a standardized incidence rate of 2.2/1000 PYs). We observed two events in the other-TNFi cohort, 6 in the b/tsDMARD-naïve cohort and 3 in the general population cohort.

During 89.58 person-years (PYs) of follow-up among 65 PsA patients initiating treatment with Flixabi 2019-2024, we did not observe any individuals diagnosed with tuberculosis. This was similar in the originator-product infliximabcohort, whereas the standardized incidence rates in the other cohorts were 0.0/1000 PYs for all, with two events in the other-TNFi cohort, three events in the b/tsDMARD-naïve cohort and four events in the general population.

10.4.4 Demyelinating event/MS

During 202.25 person-years (PYs) of follow-up among 161 RA patients initiating treatment with Flixabi 2019-2024, we did not observe any individuals diagnosed with a demyelinating event, whereas the standardized incidence rates in the other cohorts were 0.8/1000 PYs (with 1 event in the originator-product infliximab), 0.3/1000 PYs (other-TNFi), 0.7/1000 PYs (b/tsDMARD-naïve) and 0.8/1000 PYs (general population).

During 218.70 person-years (PYs) of follow-up among 152 As-SpA patients initiating treatment with Flixabi 2019-2024, we did not observe any individuals diagnosed with a demyelinating event. This was also the case in the originator-product infliximab cohort, whereas the standardized incidence rates in the other cohorts were 0.8/1000 PYs (other-TNFi), 1.2/1000 PYs (b/tsDMARD-naïve) and 0.8/1000 PYs.

During 92.70 person-years (PYs) of follow-up among 65 PsA patients initiating treatment with Flixabi 2019-2024, we did not observe any individuals diagnosed with a demyelinating event. This was also the case in the originator-product infliximab cohort, whereas the standardized incidence rates in the other cohorts were 0.4/1000 PYs (other-TNFi), 0.8/1000 PYs (b/tsDMARD-naïve) and 0.7/1000 PYs.

Table 8. Total number of events, crude and standardized incidence rates

Table 8a. Total number of events, crude and standardized incidence rates (RA patients)

Cohort	Patients	Events	Person-Year	IR/PYs	95% CI	Std IR/PYs	Mean follow-up, years
All primary invasive cancers excluding non-melanoma skin cancers							
Flixabi	148	3	266.42	0.0113	(0.004-0.035)	0.0113	1.80
0 previous b/tsDMARD	44	2	80.38	0.0249	(0.006-0.099)		1.83
1-2 previous b/tsDMARDs	83	0	149.51	0.0000	(.-.)		1.80
3+ previous b/tsDMARDs	21	1	36.53	0.0274	(0.004-0.194)		1.74
Originator-product infliximab	407	30	2772.08	0.0108	(0.008-0.015)	0.0127	6.81
0 previous b/tsDMARD	226	18	1683.43	0.0107	(0.007-0.017)		7.45
1-2 previous b/tsDMARDs	127	8	791.08	0.0101	(0.005-0.020)		6.23
3+ previous b/tsDMARDs	54	4	297.58	0.0134	(0.005-0.036)		5.51
Other TNFi	11836	536	48993.15	0.0109	(0.010-0.012)	0.0123	4.14
0 previous b/tsDMARD	9366	409	37053.61	0.0110	(0.010-0.012)		3.96
1-2 previous b/tsDMARDs	2062	107	9956.47	0.0107	(0.009-0.013)		4.83
3+ previous b/tsDMARDs	408	20	1983.06	0.0101	(0.007-0.016)		4.86
B/tsDMARD naïve	59749	4614	289452.4	0.0159	(0.015-0.016)	0.0135	4.84

Cohort	Patients	Events	Person-Year	IR/PYs	95% CI	Std IR/PYs	Mean follow-up, years
General Population	59061	2672	247000.9	0.0108	(0.010-0.011)	0.0120	4.18
Lymphoma							
Flixabi	148	0	270.16	0.0000	(.-.)	0.0000	1.83
0 previous b/tsDMARD	44	0	81.44	0.0000	(.-.)		1.85
1-2 previous b/tsDMARDs	83	0	149.51	0.0000	(.-.)		1.80
3+ previous b/tsDMARDs	21	0	39.21	0.0000	(.-.)		1.87
Originator-product infliximab	407	1	2839.04	0.0004	(0.000-0.003)	0.0005	6.98
0 previous b/tsDMARD	226	0	1731.13	0.0000	(.-.)		7.66
1-2 previous b/tsDMARDs	127	1	801.61	0.0012	(0.000-0.009)		6.31
3+ previous b/tsDMARDs	54	0	306.30	0.0000	(.-.)		5.67
Other TNFi	11836	38	50070.30	0.0008	(0.001-0.001)	0.0009	4.23
0 previous b/tsDMARD	9366	28	37848.39	0.0007	(0.001-0.001)		4.04
1-2 previous b/tsDMARDs	2062	10	10197.60	0.0010	(0.001-0.002)		4.95
3+ previous b/tsDMARDs	408	0	2024.31	0.0000	(.-.)		4.96
b/tsDMARD naïve	59749	326	300733.2	0.0011	(0.001-0.001)	0.0009	5.03
General Population	59061	146	253096.6	0.0006	(0.000-0.001)	0.0006	4.29

Cohort	Patients	Events	Person-Year	IR/PYs	95% CI	Std IR/PYs	Mean follow-up, years
Tuberculosis							
Flixabi	158	0	192.46	0.0000	(.-.)	0.0000	1.22
0 previous b/tsDMARD	44	0	54.84	0.0000	(.-.)		1.25
1-2 previous b/tsDMARDs	92	0	105.70	0.0000	(.-.)		1.15
3+ previous b/tsDMARDs	22	0	31.93	0.0000	(.-.)		1.45
Originator-product infliximab	409	0	997.34	0.0000	(.-.)	0.0000	2.44
0 previous b/tsDMARD	226	0	494.04	0.0000	(.-.)		2.19
1-2 previous b/tsDMARDs	128	0	358.19	0.0000	(.-.)		2.80
3+ previous b/tsDMARDs	55	0	145.11	0.0000	(.-.)		2.64
Other TNFi	12814	9	34197.99	0.0003	(0.000-0.001)	0.0003	2.67
0 previous b/tsDMARD	10205	6	27386.36	0.0002	(0.000-0.000)		2.68
1-2 previous b/tsDMARDs	2187	3	5939.36	0.0005	(0.000-0.002)		2.72
3+ previous b/tsDMARDs	422	0	872.27	0.0000	(.-.)		2.07
B/tsDMARD naïve	61753	14	326142.6	0.0000	(0.000-0.000)	0.0001	5.28
General Population	63716	8	295813.6	0.0000	(0.000-0.000)	0.0000	4.64
Demyelinating events/MS							

Cohort	Patients	Events	Person-Year	IR/PYs	95% CI	Std IR/PYs	Mean follow-up, years
Flixabi	161	0	202.25	0.0000	(.-.)	0.0000	1.26
0 previous b/tsDMARD	45	0	57.35	0.0000	(.-.)		1.27
1-2 previous b/tsDMARDs	92	0	110.81	0.0000	(.-.)		1.20
3+ previous b/tsDMARDs	24	0	34.09	0.0000	(.-.)		1.42
Originator-product infliximab	409	1	1010.53	0.0010	(0.000-0.007)	0.0008	2.47
0 previous b/tsDMARD	226	0	497.06	0.0000	(.-.)		2.20
1-2 previous b/tsDMARDs	128	1	364.92	0.0027	(0.000-0.019)		2.85
3+ previous b/tsDMARDs	55	0	148.55	0.0000	(.-.)		2.70
Other TNFi	13026	10	35765.75	0.0003	(0.000-0.001)	0.0003	2.75
0 previous b/tsDMARD	10385	8	28708.40	0.0003	(0.000-0.001)		2.76
1-2 previous b/tsDMARDs	2215	2	6160.52	0.0003	(0.000-0.001)		2.78
3+ previous b/tsDMARDs	426	0	896.84	0.0000	(.-.)		2.11
B/tsDMARD naïve	62176	183	333701.1	0.0005	(0.000-0.001)	0.0007	5.37
General Population	64708	242	310066.2	0.0008	(0.001-0.001)	0.0008	4.79

b/tsDMARD= biological and targeted synthetic disease modifying anti-rheumatic drugs; CI= Confidence Interval; IR= Incidence Rate; MS= Multiple Sclerosis; PYs= Person-Years; RA= Rheumatoid Arthritis; Std IR= standardized to the age/sex distribution in the Flixabi cohort; TNFi= Tumor Necrosis Factor inhibitor

Table 8b. Total number of events, crude and standardized incidence rates (AS-SpA patients)

Cohort	Patients	Events	Person-Year	IR/PYs	95% CI	Std IR/PYs	Mean follow-up, years
All primary invasive cancers excluding non-melanoma skin cancers							
Flixabi	145	3	311.96	0.0096	(0.003-0.030)	0.0096	2.15
0 previous b/tsDMARD	28	1	58.47	0.0171	(0.002-0.121)		2.09
1-2 previous b/tsDMARDs	81	1	190.28	0.0053	(0.001-0.037)		2.35
3+ previous b/tsDMARDs	36	1	63.21	0.0158	(0.002-0.112)		1.76
Originator-product infliximab	356	17	2450.47	0.0069	(0.004-0.011)	0.0094	6.88
0 previous b/tsDMARD	177	8	1345.62	0.0059	(0.003-0.012)		7.60
1-2 previous b/tsDMARDs	123	9	749.41	0.0120	(0.006-0.023)		6.09
3+ previous b/tsDMARDs	56	0	355.44	0.0000	(.-.)		6.35
Other TNFi	6945	143	30529.77	0.0047	(0.004-0.006)	0.0070	4.40
0 previous b/tsDMARD	5944	114	24986.35	0.0046	(0.004-0.005)		4.20
1-2 previous b/tsDMARDs	915	21	5086.48	0.0041	(0.003-0.006)		5.56
3+ previous b/tsDMARDs	86	8	456.95	0.0175	(0.009-0.035)		5.31
B/tsDMARD naïve	21692	1142	116458.4	0.0098	(0.009-0.010)	0.0082	5.37
General Population	34574	684	154376.0	0.0044	(0.004-0.005)	0.0067	4.47

Cohort	Patients	Events	Person-Year	IR/PYs	95% CI	Std IR/PYs	Mean follow-up, years
Lymphoma							
Flixabi	145	1	315.41	0.0032	(0.000-0.023)	0.0032	2.18
0 previous b/tsDMARD	28	0	61.72	0.0000	(.-.)		2.20
1-2 previous b/tsDMARDs	81	1	190.28	0.0053	(0.001-0.037)		2.35
3+ previous b/tsDMARDs	36	0	63.41	0.0000	(.-.)		1.76
Originator-product infliximab	356	2	2497.41	0.0008	(0.000-0.003)	0.0010	7.02
0 previous b/tsDMARD	177	1	1364.37	0.0007	(0.000-0.005)		7.71
1-2 previous b/tsDMARDs	123	1	777.60	0.0013	(0.000-0.009)		6.32
3+ previous b/tsDMARDs	56	0	355.44	0.0000	(.-.)		6.35
Other TNFi	6945	8	30894.61	0.0003	(0.000-0.001)	0.0004	4.45
0 previous b/tsDMARD	5944	8	25270.66	0.0003	(0.000-0.001)		4.25
1-2 previous b/tsDMARDs	915	0	5140.89	0.0000	(.-.)		5.62
3+ previous b/tsDMARDs	86	0	483.07	0.0000	(.-.)		5.62
B/tsDMARD naïve	21692	52	119890.5	0.0004	(0.000-0.001)	0.0004	5.53
General Population	34574	31	155903.6	0.0002	(0.000-0.000)	0.0003	4.51
Tuberculosis							

Cohort	Patients	Events	Person-Year	IR/PYs	95% CI	Std IR/PYs	Mean follow-up, years
Flixabi	151	0	211.59	0.0000	(.-.)	0.0000	1.40
0 previous b/tsDMARD	28	0	44.59	0.0000	(.-.)		1.59
1-2 previous b/tsDMARDs	87	0	121.00	0.0000	(.-.)		1.39
3+ previous b/tsDMARDs	36	0	46.00	0.0000	(.-.)		1.28
Originator-product infliximab	356	1	855.43	0.0012	(0.000-0.008)	0.0022	2.40
0 previous b/tsDMARD	177	0	370.10	0.0000	(.-.)		2.09
1-2 previous b/tsDMARDs	123	0	313.64	0.0000	(.-.)		2.55
3+ previous b/tsDMARDs	56	1	171.70	0.0058	(0.001-0.041)		3.07
Other TNFi	7445	2	21800.33	0.0001	(0.000-0.000)	0.0000	2.93
0 previous b/tsDMARD	6381	2	18408.00	0.0001	(0.000-0.000)		2.88
1-2 previous b/tsDMARDs	973	0	3150.18	0.0000	(.-.)		3.24
3+ previous b/tsDMARDs	91	0	242.15	0.0000	(.-.)		2.66
B/tsDMARD naïve	22337	6	130518.1	0.0000	(0.000-0.000)	0.0000	5.84
General Population	36888	3	181418.0	0.0000	(0.000-0.000)	0.0000	4.92
Demyelinating events/MS							
Flixabi	152	0	218.70	0.0000	(.-.)	0.0000	1.44

Cohort	Patients	Events	Person-Year	IR/PYs	95% CI	Std IR/PYs	Mean follow-up, years
0 previous b/tsDMARD	29	0	46.30	0.0000	(.-.)		1.60
1-2 previous b/tsDMARDs	87	0	125.65	0.0000	(.-.)		1.44
3+ previous b/tsDMARDs	36	0	46.75	0.0000	(.-.)		1.30
Originator-product infliximab	357	0	869.31	0.0000	(.-.)	0.0000	2.44
0 previous b/tsDMARD	177	0	371.86	0.0000	(.-.)		2.10
1-2 previous b/tsDMARDs	123	0	320.77	0.0000	(.-.)		2.61
3+ previous b/tsDMARDs	57	0	176.67	0.0000	(.-.)		3.10
Other TNFi	7529	21	22730.69	0.0009	(0.001-0.001)	0.0008	3.02
0 previous b/tsDMARD	6455	16	19230.00	0.0008	(0.001-0.001)		2.98
1-2 previous b/tsDMARDs	983	4	3256.87	0.0012	(0.000-0.003)		3.31
3+ previous b/tsDMARDs	91	1	243.82	0.0041	(0.001-0.029)		2.68
B/tsDMARD naïve	22465	131	133403.5	0.0010	(0.001-0.001)	0.0012	5.94
General Population	37281	126	189872.9	0.0007	(0.001-0.001)	0.0008	5.09

b/tsDMARD= biological and targeted synthetic disease modifying anti-rheumatic drugs; CI= Confidence Interval; IR= Incidence Rate; MS= Multiple Sclerosis; PYs= Person-Years; RA= Rheumatoid Arthritis; Std IR= standardized to the age/sex distribution in the Flixabi cohort; TNFi= Tumor Necrosis Factor inhibitor

Table 8c. Total number of events, crude and standardized incidence rates (PsA patients)

Cohort	Patients	Events	Person-Year	IR/PYs	95% CI	Std IR/PYs	Mean follow-up, years
All primary invasive cancers excluding non-melanoma skin cancers							
Flixabi	62	1	145.62	0.0069	(0.001-0.049)	0.0069	2.35
0 previous b/tsDMARD	14	1	34.82	0.0287	(0.004-0.204)		2.49
1-2 previous b/tsDMARDs	37	0	84.05	0.0000	(.-.)		2.27
3+ previous b/tsDMARDs	11	0	26.75	0.0000	(.-.)		2.43
Originator-product infliximab	186	10	1302.41	0.0077	(0.004-0.014)	0.0100	7.00
0 previous b/tsDMARD	86	4	665.85	0.0060	(0.002-0.016)		7.74
1-2 previous b/tsDMARDs	73	4	491.27	0.0081	(0.003-0.022)		6.73
3+ previous b/tsDMARDs	27	2	145.28	0.0138	(0.003-0.055)		5.38
Other TNFi	6373	194	27618.73	0.0070	(0.006-0.008)	0.0101	4.33
0 previous b/tsDMARD	5253	152	21927.01	0.0069	(0.006-0.008)		4.17
1-2 previous b/tsDMARDs	979	35	4926.53	0.0071	(0.005-0.010)		5.03
3+ previous b/tsDMARDs	141	7	765.19	0.0091	(0.004-0.019)		5.43
B/tsDMARD naïve	28090	1980	150658.1	0.0131	(0.013-0.014)	0.0125	5.36

Cohort	Patients	Events	Person-Year	IR/PYs	95% CI	Std IR/PYs	Mean follow-up, years
General Population	30868	937	135331.4	0.0069	(0.006-0.007)	0.0098	4.38
Lymphoma							
Flixabi	62	0	148.20	0.0000	(.-.)	0.0000	2.39
0 previous b/tsDMARD	14	0	37.40	0.0000	(.-.)		2.67
1-2 previous b/tsDMARDs	37	0	84.05	0.0000	(.-.)		2.27
3+ previous b/tsDMARDs	11	0	26.75	0.0000	(.-.)		2.43
Originator-product infliximab	186	1	1333.04	0.0008	(0.000-0.005)	0.0009	7.17
0 previous b/tsDMARD	86	0	682.44	0.0000	(.-.)		7.94
1-2 previous b/tsDMARDs	73	1	493.90	0.0020	(0.000-0.014)		6.77
3+ previous b/tsDMARDs	27	0	156.69	0.0000	(.-.)		5.80
Other TNFi	6373	11	28057.43	0.0004	(0.000-0.001)	0.0006	4.40
0 previous b/tsDMARD	5253	9	22262.73	0.0004	(0.000-0.001)		4.24
1-2 previous b/tsDMARDs	979	2	5007.73	0.0004	(0.000-0.002)		5.12
3+ previous b/tsDMARDs	141	0	786.97	0.0000	(.-.)		5.58
B/tsDMARD naïve	28090	126	156284.6	0.0008	(0.001-0.001)	0.0007	5.56
General Population	30868	40	137374.7	0.0003	(0.000-0.000)	0.0004	4.45

Cohort	Patients	Events	Person-Year	IR/PYs	95% CI	Std IR/PYs	Mean follow-up, years
Tuberculosis							
Flixabi	65	0	89.58	0.0000	(.-.)	0.0000	1.38
0 previous b/tsDMARD	14	0	26.09	0.0000	(.-.)		1.86
1-2 previous b/tsDMARDs	39	0	50.79	0.0000	(.-.)		1.30
3+ previous b/tsDMARDs	12	0	12.70	0.0000	(.-.)		1.06
Originator-product infliximab	188	0	456.40	0.0000	(.-.)	0.0000	2.43
0 previous b/tsDMARD	86	0	168.51	0.0000	(.-.)		1.96
1-2 previous b/tsDMARDs	74	0	213.53	0.0000	(.-.)		2.89
3+ previous b/tsDMARDs	28	0	74.36	0.0000	(.-.)		2.66
Other TNFi	6811	2	18594.48	0.0001	(0.000-0.000)	0.0000	2.73
0 previous b/tsDMARD	5633	2	15427.26	0.0001	(0.000-0.001)		2.74
1-2 previous b/tsDMARDs	1034	0	2807.47	0.0000	(.-.)		2.72
3+ previous b/tsDMARDs	144	0	359.75	0.0000	(.-.)		2.50
B/tsDMARD naïve	28990	3	170011.9	0.0000	(0.000-0.000)	0.0000	5.86
General Population	32872	4	159910.5	0.0000	(0.000-0.000)	0.0000	4.86
Demyelinating events/MS							

Cohort	Patients	Events	Person-Year	IR/PYs	95% CI	Std IR/PYs	Mean follow-up, years
Flixabi	65	0	92.70	0.0000	(.-.)	0.0000	1.43
0 previous b/tsDMARD	14	0	27.35	0.0000	(.-.)		1.95
1-2 previous b/tsDMARDs	39	0	52.15	0.0000	(.-.)		1.34
3+ previous b/tsDMARDs	12	0	13.20	0.0000	(.-.)		1.10
Originator-product infliximab	189	0	462.40	0.0000	(.-.)	0.0000	2.45
0 previous b/tsDMARD	86	0	169.01	0.0000	(.-.)		1.97
1-2 previous b/tsDMARDs	75	0	217.01	0.0000	(.-.)		2.89
3+ previous b/tsDMARDs	28	0	76.38	0.0000	(.-.)		2.73
Other TNFi	6904	10	19388.16	0.0005	(0.000-0.001)	0.0004	2.81
0 previous b/tsDMARD	5706	8	16118.52	0.0005	(0.000-0.001)		2.82
1-2 previous b/tsDMARDs	1054	2	2900.35	0.0007	(0.000-0.003)		2.75
3+ previous b/tsDMARDs	144	0	369.29	0.0000	(.-.)		2.56
B/tsDMARD naïve	29182	124	173876.8	0.0007	(0.001-0.001)	0.0008	5.96
General Population	33311	125	167354.1	0.0007	(0.001-0.001)	0.0007	5.02

b/tsDMARD= biological and targeted synthetic disease modifying anti-rheumatic drugs; CI= Confidence Interval; IR= Incidence Rate; MS= Multiple Sclerosis; PYs= Person-Years; RA= Rheumatoid Arthritis; Std IR= standardized to the age/sex distribution in the Flixabi cohort; TNFi= Tumor Necrosis Factor inhibitor

10.5 Adverse events

Occurrence of adverse events in special interest within the treatment groups are described in section 10.4. The adverse events reported during Flixabi treatment in the study are presented by SOC and PT in Table 11. Overall, 9 AEs were reported during the ARTIS study for Flixabi.

Table 11 Summary of adverse events occuring under Flixabi

SOC Preferred Term(PT)	Seriousness		Total
	No	Yes	
Cardiac disorders	**1**	**0**	**1**
Palpitations	1	0	1
Eye disorders	**1**	**0**	**1**
Ocular hyperaemia	1	0	1
General disorders and administration site conditions	**2**	**0**	**2**
Chest discomfort	1	0	1
Hyperhidrosis	1	0	1
Injury, poisoning and procedural complications	**1**	**0**	**2**
Infusion related reaction	1	0	1
Investigations	**1**	**0**	**1**
Blood pressure increased	1	0	1
Respiratory, thoracic and mediastinal disorders	**1**	**0**	**1**
Pharyngeal swelling	1	0	1
Skin and subcutaneous tissue disorders	**2**	**0**	**2**
Erythema	2	0	2
Total	**9**	**0**	**9**

11 Discussion

11.1 Key results

This report describes the relative uptake of Flixabi in the treatment of RA, AS-SpA and PsA in Sweden since market approval, and presents a coherent analysis of key safety outcomes.

The short follow-up time and the low number of patients treated with Flixabi resulted in very low number of observed events. The low number of events limit the conclusions one may make based on the analyses, although we note that incidence rates remained similar overall across different cohorts for the outcomes that had events. For the same reason, it was not possible to perform statistical comparison between cohorts (Cox regression analysis).

11.2 Limitations

A series of limitations should be recognized: (a) While our design, comparators, and multitude of data allowed for examining multiple outcomes and disease, it is likely that residual confounding and channeling effects remain. This is especially true since the clinical decision-making process is multifactorial and based on – in addition to more easily estimable factors related to indication (e.g., DAS28) – an elusive mix of personal preferences, subjective estimates of "frailty" and perceived prognosis. (b) As Flixabi was launched in the Swedish market in 2019, and the cut-off date for data access was limited to end of 2024 (2023 for cancer) a maximum of only 6 years follow-up (5 years for cancer outcomes) was available. Also, the uptake of Flixabi in Sweden was somewhat limited, leading to a low number of patients who have been prescribed Flixabi.

11.3 Interpretation

This nationwide safety monitoring study assessed predefined safety outcomes for Flixabi in patients with RA, AS-SpA, and PsA using Swedish ARTIS register data from 2019-2024. Standardized

incidence rates for malignancies, lymphoma, tuberculosis, and demyelinating events were generally comparable between Flixabi and comparator cohorts (originator infliximab, other TNFi, b/tsDMARD-naïve, and general population). No tuberculosis or demyelinating events were observed in any Flixabi cohort across all indications, and one lymphoma event occurred in the AS-SpA cohort (3.2/1000 PYs). Although numerical differences in incidence rates were observed for some outcomes, no statistical comparisons were performed due to insufficient events (<5 per cohort), precluding definitive conclusions regarding relative risks. These findings are consistent with existing real-world evidence on infliximab biosimilars showing comparable safety profiles to reference products. Study limitations include short follow-up (maximum 6 years), limited Flixabi uptake in Sweden resulting in small sample sizes, and very few observed events restricting statistical power. Residual confounding and channeling effects inherent to observational designs cannot be ruled out. No new or unexpected safety signals were identified, and the observed safety profile aligns with the current Summary of Product Characteristics and Risk Management Plan of Flixabi. Despite limitations, the available evidence suggests Flixabi demonstrates a comparable safety profile to other infliximab products and TNFi agents.

11.4 Generalisability

The population-based setting in a public health care system acted to increase generalizability, although we acknowledge that baseline risks for the outcomes under study, the set-up of other risk factors, as well as the penetration of b/tsDMARD therapies may vary across countries, and thus that the generalizability to other settings (particularly outside of western Europe and the US) may be limited.

12 Other information

Not applicable

13 Conclusion

In summary, this report describes the occurrence of a series of predefined safety outcomes in Swedish patients with chronic inflammatory rheumatic disease treated with Flixabi, or with other anti-rheumatic treatments, compared to the general Swedish population. The overall pattern of risks that emerges is of no safety signal with few observed safety events, but the limited number of Flixabi-treated patients and short follow-up time prevents drawing definitive conclusions.

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