PASS Information

Title	Final Report on Flixabi Data of cohort 2 of the German biologics register Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT)
Version identifier of the final study report	1.0
Date of last version of the final study report	N/A
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Active substance	Infliximab ATC code L04AB02
Medicinal product	Flixabi®
Product reference	H0004020
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Marketing authorisation	Samsung Bioepis NL B.V.
Joint PASS	No
Research question and objectives	Investigating relevant safety outcomes in patients with rheumatoid arthritis by: - Evaluating and comparing unadjusted incidence rates (IR) of pre-defined outcomes in patients exposed to Flixabi (index drug group), and patients treated with infliximab (biologic original (BO) and biosimilar (BS)) except Flixabi (comparator group). - Estimating and comparing the risk of pre-defined outcomes in patients exposed to the index drug in comparison to patients exposed to drugs from the comparator group by applying multivariable adjusted analyses.
Country(-ies) of study	Germany
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1 Abstract

Title

Final Safety Report on Flixabi
Based on Data from the German Biologics Register RABBIT (Rheumatoide Arthritis: Beobachtung der Biologika-Therapie)

Keywords

Rheumatoid arthritis
Observational long-term cohort study
Janus kinase inhibitors
Pharmacovigilance
Drug safety

Rationale and background

Biologic agents are innovative treatments for patients with rheumatoid arthritis (RA). However, randomized controlled trials include only a limited spectrum of patients and are not designed to detect long-term safety signals. Data from long-term cohort studies are needed to investigate new substances after approval when used in daily rheumatologic practice. Flixabi contains the active compound infliximab, an inhibitor of the tumour necrosis factor alpha. This post-marketing study investigated safety aspects of Flixabi in daily rheumatologic care.

Research question and objectives

The objectives were to compare patients exposed to Flixabi (index group) and patients treated with any other infliximab except Flixabi (comparator group). The pre-defined outcomes comprised tuberculosis, serious infections (excluding tuberculosis) / sepsis, congestive heart failure, myocardial infarction, central demyelination / demyelinating disorders, serious hematologic disorders, neoplasms / malignancies, death, serious systemic hypersensitivity reactions / serious infusion reactions, hepatic failure, serious gastrointestinal ulcer / perforation, stroke, venous thromboembolism, pregnancy and pregnancy outcomes, and immunogenicity. Events are classified as serious or non-serious by the reporting physician.

Study design and methods

This is an ongoing non-interventional prospective observational cohort study using existing data within the German register “Rheumatoide Arthritis: Beobachtung der Biologika-Therapie” (RABBIT). Patients are included when they start treatment with a biologic, a targeted synthetic or a conventional synthetic (cs) disease-modifying anti-rheumatic drug (DMARD) after at least one prior csDMARD failure. Data are collected nationwide from approximately 300 rheumatologists working in specialised outpatient clinics or private practices.

Crude incidence rates (IR) of the pre-defined outcomes were calculated per 1,000 patient years (PY). The results are based on the on-drug approach with a three-month risk window. Additionally, neoplasms / malignancies were analysed with a once-exposed always at risk (ever-exposed) approach, using a latency period of 6 months. Relative risks for outcomes in the Flixabi compared to the comparator group were calculated by Cox regression models.

Setting

Patients with RA enrolled and observed in RABBIT between 01 January 2017 and 30 June 2025 were analysed according to their exposure groups and described both at the time of enrolment and at each start of therapy using summary measures.

Subjects and study size, including dropouts

The study population includes eligible RA patients who initiate treatment with either Flixabi or another infliximab compound as comparator cohort. To be eligible, all patients must have a diagnosis of RA (confirmed by a rheumatologist) and be at least 18 years of age at initiation of the treatment. Patients must additionally have at least one follow-up visit recorded after index date. There are no exclusion criteria.

Variables and data sources

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

Results

A total of 215 treatment episodes were eligible for the analyses, including 32 episodes based on 32 patients for Flixabi and 183 episodes based on 174 patients for the comparator group. Mean age at index date was 56.7 years in the Flixabi versus 57.0 years in the comparator group. Most patient characteristics were comparable for both groups.No events occurred in the Flixabi group for several pre-defined safety outcomes where events were observed in the comparator group, including serious infections/sepsis, myocardial infarction, neoplasms/malignancies, serious hematologic disorders, demyelinating disorders, serious gastrointestinal ulcer/perforation, stroke, and death.One case of venous thromboembolism (VTE) was observed in the Flixabi treatment group. No VTE events were recorded in the comparator group. The unadjusted IR of VTE in the Flixabi group was 34.75 (95% CI: 0.44–97.63). For immunogenicity, five events were observed in the Flixabi group, corresponding to an unadjusted IR of 96.65 (95% CI: 31.38–225.54). In the comparator group, 14 events were observed, resulting in an unadjusted IR of 57.9 (95% CI: 31.65–97.14).The fully adjusted Cox regression model for immunogenicity shows a numerically increased, but statistically not significant risk in the Flixabi group compared with the comparator group (HR: 2.16, 95% CI: 0.59–7.87).

Discussion

Within the RABBIT register, use of Flixabi in patients with RA was limited, resulting in small numbers of exposed patients and few events for the outcomes of interest. Adjusted risk estimates could be calculated only for immunogenicity events, irrespective of seriousness. One single VTE event was reported for Flixabi, leading to a numerically elevated incidence rate; however, given the limited exposure, it should be interpreted with caution. No new or unexpected safety signals were identified, and no increased risk was detected versus the comparator group during the follow-up period. However, the limited sample size and event numbers restrict the interpretation of these findings.

Marketing Authorisation Holder(s)

Samsung Bioepis NL B.V

Names and affiliations of principal investigators

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2 List of abbreviation

Abbreviation	Definition
AE	Adverse event
ACPA	Anti-citrullinated protein antibodies
bDMARD	Biologic disease-modifying anti-rheumatic drug
BMI	Body mass index
BO	Biologic original
BS	biosimilar
CI	Confidence interval
CNS	Central nervous system
COX-II	Cyclooxygenase II
CRF	Case report form
CRP	C-reactive protein
csDMARD	Conventional synthetic disease-modifying anti-rheumatic drug
CVD	Cardiovascular Disease
DAS28	Disease activity score based on 28 tender and swollen joints
DMARD	Disease-modifying anti-rheumatic drug
ESR	Erythrocyte sedimentation rate
FFbH	Hanover Functional Status Questionnaire
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
IPW	Inverse probability weights
IR	Incidence rate
JAKi	Janus kinase inhibitor
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	Non-steroidal anti-inflammatory drug
PASS	Post-Authorization Safety Study
PS	Propensity score
PT	Preferred term
PY	Patient years
RA	Rheumatoid arthritis
RABBIT	Rheumatoide Arthritis - Beobachtung der Biologika-Therapie
RCT	Randomised controlled trial
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SD	Standard deviation
SMD	Standardised mean difference
SMQ	Standardized MedDRA query
SOC	System organ class
TNF	Tumour necrosis factor
tsDMARD	Targeted synthetic disease-modifying anti-rheumatic drug
UCL	Upper confidence limit
vs.	Versus
VTE	Venous thromboembolism

3 Investigator

Name, Degree	Title	Affiliation
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Martin Schäfer, PhD	Lead Statistician RABBIT register	Epidemiology and Health Services Research, German Rheumatology Research Center; Berlin

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5 Milestones

The RABBIT register is an independent study that enrols patients treated with biologic (b)-, conventional synthetic (cs)- and targeted synthetic (ts) disease-modifying anti-rheumatic drugs (DMARDs). Enrolment thus goes far beyond the patients included in this study. The milestones in Table 1 therefore include dates that are relevant to the register but that precede the start of the current study.

Table 1: Enrolment dates of the RABBIT register cohort 2

Milestone	**Planned date**	**Comments**
Study progress reports for index drug	Semi-annually	No comments
Start of enrolment and data collection for this report	1 January 2017	No comments
End of enrolment and data collection for this report	30 June 2025	No comments
Database closing data for this report	30 June 2025	No comments
Final SAP for the report	24 November 2025	No comments
Final report of Flixabi	10 June 2026	No comments

6 Rationale and background

The treatment of rheumatoid arthritis (RA) has significantly improved over the last two decades with the introduction of biological disease-modifying antirheumatic drugs (bDMARDs), including the tumor necrosis factor inhibitor (TNFi) infliximab. However, the biologic originals are expensive, and biosimilar drugs have been developed over the last decade, helping to reduce costs and to increase patient access. As biosimilars are highly analogous but not identical to their originals and may vary in tri-dimensional structure and exact formulation, clinicians and patients have been concerned about differences between biologic originals (BO) and biosimilars (BS) regarding safety (1).

Recently performed meta-analyses from randomized clinical trials (RCTs) showed evidence of equivalence for infliximab biosimilars compared to their reference biologic originals for the outcome efficacy, measured by American College of Rheumatology 20% response criteria, and no difference regarding safety and immunogenicity was found (2, 3). Since RCTs include only a limited spectrum of patients and are not powered and designed to detect long-term safety signals, data from long-term cohort studies are needed to investigate new substances after approval when used in daily rheumatologic practice. Evidence from studies on real-world data is now slowly becoming available, showing similar safety profiles and similar effectiveness using disease activity scores (4). However, real-world evidence on safety outcomes for infliximab biosimilars compared to the infliximab original is based on one study with low quality, highlighting the need for future research using advanced statistics (4, 5).

The German biologics register RABBIT provides safety and effectiveness data on licenced b- and tsDMARDs available for the treatment of RA in daily routine care. For the active substance infliximab, four BS are available in RABBIT including Zessly®, Remsima®, Inflectra™ and Flixabi®. This post-authorization safety study(PASS) reports on characteristics of patients who received Flixabi compared to patients treated with the infliximab original (Remicade®) or infliximab BS except Flixabi.

7 Research question and objectives

The primary objective of this analysis is the investigation of relevant safety outcomes in patients with rheumatoid arthritis (RA) by:

- Evaluating and comparing crude, unadjusted IR of pre-defined outcomes in patients exposed to Flixabi (index drug group), and patients treated with any other infliximab (BO and BS) except Flixabi (comparator group).
- Estimating and comparing the risk of pre-defined outcomes in patients exposed to the index drug in comparison to patients exposed to drugs from the comparator group by applying multivariable adjusted analyses.

8 Amendments and updates to the protocol

No amendments and updates were added to the protocol. Information on updates to the statistical analysis plan is given in Section 9.9.5.

9 Research methods

9.1 Study design

This is a prospective non-interventional post-authorisation safety study using data collected by the RABBIT register. The final report includes therapy and safety data from patients with RA initiating treatment with infliximab and observed in the RABBIT register from 01 January 2017 until 30 June 2025.

9.2 Settings

The final report is based on data from the German biologics register RABBIT. RABBIT is a prospective observational, longitudinal cohort study to assess the short- and long-term safety and effectiveness of bDMARDs and tsDMARDs licensed for the treatment of patients with RA. A control cohort of patients treated with csDMARDs is followed-up in parallel. RABBIT was established in May 2001 in Germany as an independent nationwide ongoing cohort study.

Patients with RA are enrolled in RABBIT and observed in routine clinical care by the treating rheumatologists. The following inclusion criteria must be fulfilled at enrolment:

- Age at enrolment >17 years
- Age at onset of RA >15 years
- Rheumatologist confirmed diagnosis of RA and indication of the number of fulfilled 1987 classification criteria of the American College of Rheumatology (ACR) [6]. Until 2016, patients had to fulfil at least four of the seven 1987 ACR criteria
- Initiating treatment with a bDMARD (BO or BS), with a tsDMARD, or with a csDMARD (without concomitant b/tsDMARD therapy) after at least one prior DMARD treatment (see Table 3 below for drug class)

Due to the inclusion criteria, patients can be enrolled at different stages of the RA disease, and they are not assigned to specific treatments through randomization. Data is reported by physicians and patients at predefined time points of follow-up (enrolment, at three and six months, thereafter every six months). Once enrolled, patients are followed regardless of treatment changes, treatment cessation or treatment initiation. The type of the treatment administered, and the conduct of individual therapy, including dosages, is solely determined by the treating physician in agreement with the patient. Consequently, there is no influence on any treatment decision by the principal investigators, the scientific advisory board, or the pharmaceutical companies sponsoring the study. After five years of observation, follow-up may be extended for another five years, subject to the patient's consent. Patients provide written informed consent before study entry. The original study protocol was approved on 1 March 2001 by the ethics committee of the Charité University Medicine, Berlin, Germany (Protocol number 1508/2001). A revised and updated study protocol received approval on 5 July 2021 (Protocol number EA4/123/21).

RABBIT encompasses two cohorts reflecting different enrolment periods: From 1 May 2001 until 31 December 2006 patients starting a treatment with adalimumab (Humira), anakinra (Kineret), etanercept (Enbrel), or infliximab (Remicade), or with a csDMARD, were recruited into the RABBIT cohort 1. The originally planned recruitment period of five years for the tumour necrosis factor inhibitors (TNFi) and anakinra was reached by the end of 2006. Enrolment in RABBIT cohort 1 was stopped, and follow-up ended after an additional five years on 31 December 2011. For the newly licensed bDMARDs rituximab (MabThera) and abatacept (Orencia), a new cohort (cohort 2) was established starting on 1 January 2007, in which only patients initiating a treatment with MabThera or Orencia were eligible to be enrolled. During this second enrolment period, control patients starting on a csDMARD were not included. To overcome the disadvantage of comparing patients on a newly licenced drug with historical controls, in 2009 RABBIT cohort 2 was opened for the enrolment of patients starting a treatment with csDMARD as well as for patients starting any of the available bDMARDs licenced for the treatment of RA. As of 2017, enrolments under tsDMARDs were possible.

The final report only included therapies and safety data from patients with RA initiating Flixabi or a drug from the comparator group from 01 January 2017 onward as the treatment landscape has evolved in the last decades with the introduction of new therapies, treatment recommendations and approaches to manage adverse events. This approach allows fair comparison.

All enrolment therapies of RABBIT cohort 2 are depicted in Table 2. Enrolment in the RABBIT cohort 2 is ongoing.

Table 2: Enrolment therapies of the RABBIT register cohort 2

Trade name	Active substance	Start of enrolment	Trade name	Active substance	Start of enrolment
bDMARDs			**tsDMARDs**		
Humira	Adalimumab	1.1.2009	Olumiant	Baricitinib	1.5.2017
Hyrimoz	Adalimumab	1.1.2019	Xeljanz	Tofacitinib	1.5.2017
Amgevita	Adalimumab	1.1.2019	Rinvoq	Upadacitinib	1.1.2020
Imraldi	Adalimumab	1.4.2019	Jyseleca	Filgotinib	1.1.2021
Hulio	Adalimumab	1.7.2019			
Idacio	Adalimumab	1.7.2019			
Yuflyma	Adalimumab	1.7.2021	**csDMARDs**		
Hukyndra	Adalimumab	1.2.2023	Several names	Azathioprine	1.1.2009
Enbrel	Etanercept	1.1.2009	Several names	Cyclophosphamide	1.1.2009
Benepali	Etanercept	1.4.2016	Several names	Cyclosporine A	1.1.2009
Erelzi	Etanercept	1.8.2017	Several names	D-penicillamine	1.1.2009
Nepexto	Etanercept	1.7.2020	Several names	Gold	1.1.2009
Remicade	**Infliximab**	**1.1.2009**	Several names	Hydroxychloroquine/ Chloroquine	1.1.2009
Remsima i.v./s.c.*	**Infliximab**	**1.4.2015**			
Inflectra	**Infliximab**	**2.4.2015**	Several names	Leflunomide	1.1.2009
Flixabi	**Infliximab**	**1.3.2017**	Several names	Methotrexate	1.1.2009
Zessly	**Infliximab**	**1.1.2019**	Several names	Sulfasalazine	1.1.2009
Cimzia	Certolizumab	1.9.2009	**Enrolment with Remsima s.c. started from 1.7.2020 onwards.*		
Simponi	Golimumab	1.1.2009			
Orencia	Abatacept	1.7.2007	*Abbreviations: bDMARD, biologic disease-modifying anti-rheumatic drug; csDMARD, conventional-synthetic disease-modifying anti-rheumatic drug; i.v., intravenous; RABBIT, Rheumatoide Arthritis: Beobachtung der Biologika-Therapie; s.c., subcutaneous; tsDMARD, targeted-synthetic disease-modifying anti-rheumatic drug*		
Kevzara	Sarilumab	1.1.2018			
MabThera	Rituximab	1.1.2007			
Rixathon	Rituximab	1.8.2017			
Ruxience	Rituximab	1.7.2020			
RoActemra	Tocilizimab	1.1.2009			

9.2.1. Assessments

In RABBIT, outcome parameters and covariates are assessed by physicians and/or patients as applicable, on pre-defined case report forms (CRF) at study enrolment and follow-up visits. Apart from socio-demographic characteristics including school education, occupation and smoking habits, data on disease duration, comorbid conditions and anti-rheumatic co-medications are assessed. The main outcome measures are the occurrence of adverse events, the course of disease activity assessed by physician- and patient-reported measures, the impairment in daily life activities reported by patients, the medical treatment adherence determined by physician-reported treatment duration and medical indications for initiation of therapy, therapy change or therapy discontinuation. Treatment starts, stops and switches are recorded as the dates on which they occurred.

Patients have study visits at enrolment directly prior to the onset of a new medical treatment (t0), after three (t1) and six months (t2), and then every six months up to month 120 (t3 to t21). Assessments

performed at each of the respective study visits during the 120-month observation period are presented in Table 3.

Table 3: Assessments at study enrolment (t0) and follow-up visits (t1 to t21) in the RABBIT cohort

Follow-up visits (t)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Month of follow-up	0	3	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96	102	108	114	120
Date of visit	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Patient characteristics																						
Year of birth, sex, height	x																					
Rheumatoid factor, Erosive joint alterations, Rheumatoid nodules	x																					
Date of symptom onset	x																					
Comorbidities	x						x					x					x					x
Smoking habits (patient), weight	x			x		x		x		x		x		x		x		x		x		x
Treatment																						
Start/end of DMARDs	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Reasons for treatment change		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Anti-rheumatic comedications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pregnancy including outcome				x		x		x		x		x		x		x		x		x		x
Side effects (patient)		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Disease activity																						
ESR, CRP	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
28 Swollen/tender joint counts	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Morning stiffness	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Disease activity, NRS scale (physician)*	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Functional capacity (FFbH) (patient)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pain severity, NRS scale (patient)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Fatigue severity, NRS scale (patient)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
General health state, NRS scale (patient)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

X = measured variable at the indicated visit. All measurements are reported by the physician unless otherwise indicated.
**Physician reported disease activity was added to the questionnaires in 2013.*
Abbreviations: CRP = C-reactive protein; DMARD = disease-modifying anti-rheumatic drug; ESR = erythrocyte sedimentation rate; FFbH = Hanover Functional Status Questionnaire; NRS = numeric rating scale; RABBIT = Rheumatoide Arthritis - Beobachtung der Biologika-Therapie.

9.2.2. Ascertainment of adverse events

All adverse events reported to the RABBIT register are recorded following the International Conference of Harmonization guideline on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95/E2A) [7]. Accordingly, any untoward medical occurrence observed in a patient is reported as adverse event, regardless of a relationship between event and current medication. Physicians assign onset of symptoms, duration, intensity, the assumed causal relationship with DMARDs and the outcome of each reported adverse event. Any adverse event resulting in death or persistent or significant disability, being life-threatening, requiring hospitalisation or prolongation of hospitalisation, or being a congenital anomaly or birth defect is reported as a serious adverse event (SAE). SAEs with missing assignment of the causal relationship are considered as possibly related. All reported adverse events are registered continuously in a separate database; diagnoses are coded using the Medical Dictionary for Regulatory Activities (MedDRA) on the preferred term (pt) level [8]; the coding is updated with every MedDRA update.

Events of interest were defined in the RABBIT study protocol and comprise outcomes of tuberculosis (incident and reactivated), other serious infections, myocardial infarction, heart failure, stroke, venous thromboembolism, central demyelination, hepatic failure, serious systemic hypersensitivity reactions/serious infusion reactions, serious gastrointestinal ulcer/perforation, serious hematologic disorders, malignancies and deaths. In case of an event of interest or in case of an SAE which had been assigned to be possibly related to a DMARD, the treating physician is asked to complete a query for additional information. For all events of interest, as well as for pregnancies and pregnancy-related outcomes, additional event-specific queries are used. For SAEs with a possible relation to DMARD use, a general additional query is used without event-specific questions. All additional queries comprise details for greater specification of the event, related diagnostic and therapeutic procedures, as well as the course of DMARD therapy. In addition, all other medications the patient had been treated with at the time of the event are reported.

9.2.3. Quality control

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

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

Standardised procedures to obtain and report adverse event information are described in Section 9.2.2.

9.3 Subjects

The study population consists of patients enrolled in RABBIT that started a treatment with Flixabi or a drug from the comparator group from 01 January 2017 until 30 June 2025. General inclusion criteria of patients enrolled into the RABBIT register are given in Section 9.2.

The following patients are included in the final report:

- Index drug group: Patients who initiated Flixabi.
- Comparator group: Patients who initiated infliximab BO or infliximab BS except Flixabi.

Patients must additionally have at least one follow-up visit recorded after index date. There are no exclusion criteria.

Patients in the comparator group are eligible for inclusion when the start of a new Infiximab treatment line starting on or after 01 January 2017 (Figure 1).

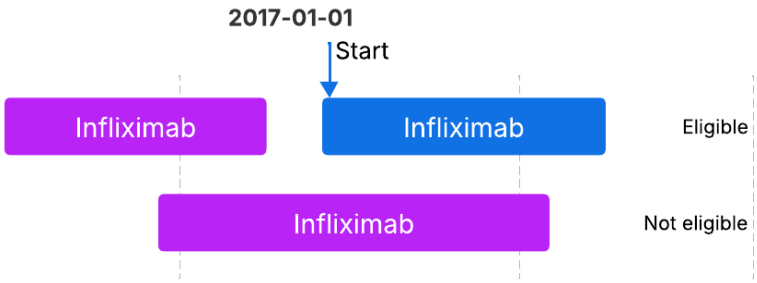

Figure 1: Illustrative examples of eligibility for inclusion in infliximab cohort (comparator) and start of follow-up

The following treatments were not investigated in the final report, and therefore episodes of patients initiating one of these treatments were excluded:

- Anakinra
- Janus kinase inhibitor (JAKi)
- bDMARDs other than infliximab (etanercept, adalimumab, certolizumab, golimumab, rituximab, sarilumab, tocilizumab and abatacept)
- csDMARD as monotherapy

9.4 Variables

9.4.2. Treatment exposure

Treatment exposure is categorized into the following two groups:

- **Index drug group**: patients initiating a treatment with the index drug (Flixabi). This group includes both bio/ts-naïve and bio/ts-experienced patients.
- **Comparator group**: patients initiating a drug with the active compound infliximab approved for the treatment of RA except Flixabi. This group includes both bio/ts-naïve and bio/ts-experienced patients. The following drugs are eligible: Remicade, Zessly, Remsima and Inflectra.

A patient was assigned to a treatment exposure group when initiating treatment with one of the drugs from the respective treatment exposure group.

Patients who received concomitant treatment with csDMARD(s) were still assigned to the index drug group or the comparator group.

Patients could contribute to several exposure groups during the time of observation, and also several times to one exposure group.

Different definitions for the time at risk (patient years, PY) were applied.

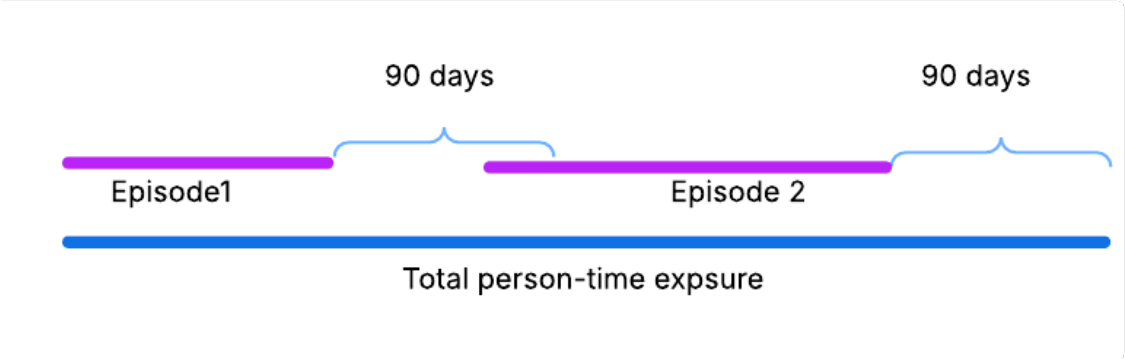

Figure 2: Total person-time exposure using the 90-days risk window, calculated from several treatment episodes

– On-drug approach: Time at risk was calculated from drug initiation until the occurrence of the event of interest, the stop of treatment, death, end of follow-up, or end of data collection, whichever occurs first. An additional three months of exposure (risk window) was added after discontinuation [9]. A switch from one drug to another in the comparator group does not count as stopping treatment, i.e., if another medication from the comparator group is given within three months, the time at risk continues. Index date is defined as drug initiation date, except that there is no new index date if another drug from the comparator group is initiated within the 90-days risk window. In the case that a new treatment from the other exposure group is started within the 90-days risk window, and an event occurs within that time, it was assigned to both groups as was the corresponding PY since index date to the respective group (Figure 2). A limitation of this approach is that effects of the drugs that may need longer time to develop may not be captured, due to censoring 90-days after drug discontinuation.

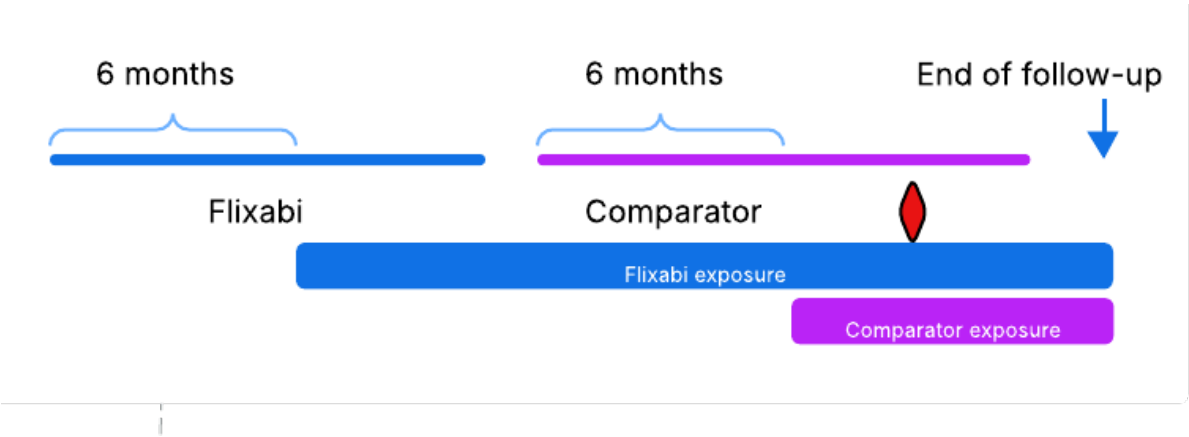

Figure 3: Assigning events in the "Ever-exposed" risk window with 6 months latency period

- Ever-exposed approach: Time at risk was calculated from the index date until the occurrence of the event of interest, death, end of follow-up, or end of data collection, whichever occurs first. A patient is considered as once exposed, always at risk, despite switching to another drug. To calculate the index date, a latency period of 6 months after drug initiation is applied to account for the slow development of events, as well as to deal with reverse causation and detection bias. In the case that a new treatment from the other exposure group is started and an event occurs at least six months after the start of the new treatment, for the calculation of incidence rates it was assigned to both groups as was the corresponding PY since index date to the respective group (Figure 3). For regression models, a patient can be assigned to only one of the two groups, namely the group that is used first during the observation period. A limitation of this approach is that the time between measurement of the adjustment variables and occurrence of events may be considerable.

Events were allocated to a treatment exposure group if the event occurs during the time at risk of the respective exposure group.

Depending on the outcome of interest, different approaches were applied:

- On-drug approach: applies to all outcomes
- Ever-exposed approach: applies only to malignancy / neoplasms

9.4.1. Outcomes

Safety outcomes are primarily based on the safety concerns in the index drug risk management plan that are indicated to be addressed by the RABBIT register study as an additional pharmacovigilance activity. The outcomes to be investigated in the final report are given in Table 4. The definition of outcomes was based on the semi-annual reports provided to the marketing authorisation holder using the Manchester template (a template in use since 2003 and endorsed by the EMA) if not otherwise indicated. In case the outcomes were not defined by the Manchester template, relevant MedDRA PT based on the HLGT, SMQ and SOC were provided by the Samsung Bioepis search strategy for safety concerns. Outcomes derived from the semi-annual reports are presented only for SAEs, while the seriousness of other outcomes is provided in detail.

Table 4: Outcomes of interest

Outcome	Outcome definition
Safety endpoints as listed in the study protocol:	
Tuberculosis	Not applicable
Other serious infections (e.g. pneumonia, infections of the CNS, septicemia, bone or joint infections, opportunistic infections)	Not applicable
Congestive heart failure	Not applicable
Myocardial infarction	Not applicable
Central demyelination	Not applicable
Serious hematologic disorders (e.g. bone marrow depression, hypoplastic anemia**)**	Not applicable
Neoplasms (lymphomas, solid malignancies, other	Not applicable

neoplasms)	
Deaths	Not applicable
Serious systemic hypersensitivity reactions / serious infusion reactions	Not applicable
Hepatic failure	Not applicable
Serious gastrointestinal ulcer/perforation	Not applicable
Stroke	Not applicable
Venous thromboembolism (VTE, including deep vein thrombosis (DVT), DVT postoperative, pulmonary embolism (PE), postprocedural PE, venous thrombosis limb)	Not applicable
Pregnancies and their outcomes	Not applicable
Safety concerns as listed in the risk management plan:	
Serious infections/sepsis	SOC Infections and infestations
Demyelinating disorders (including Multiple Sclerosis, Guillain-Barré Syndrom, Optic Neuritis)	HLGT Demyelinating disorders, PT Chronic inflammatory demyelinating polyradiculoneuropathy, Demyelinating polyneuropathy, Guillain-Barre syndrome, Miller Fisher syndrome, Multifocal motor neuropathy, Optic neuritis, Anti-myelin-associated glycoprotein associated polyneuropathy
BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure	SOC Pregnancy, puerperium and perinatal conditions
Malignancy	SMQ (Narrow) Malignant or unspecified tumours
Immunogenicity	SMQ (Broad) Hypersensitivity, SMQ (Narrow) Hypersensitivity

9.4.3. Confounders

Table 5 provides the possible confounders adjusted for if Cox regression analysis can be applied. They were pre-defined, in agreement with recommendations from the RABBIT scientific advisory board (and aligned with previous publications from RABBIT). Models were calculated with three different sets of covariables (A, B and C).

Table 5: Confounders for the Cox regression analysis.

	Infections	Malignancies / Neoplasms	All outcomes but infections and malignancies
Model A	None (crude/ unadjusted)	None (crude/ unadjusted)	None (crude/ unadjusted)
Model B	Age[a] Sex (male vs. female)	Age Sex (male vs. female)	Age Sex (male vs. female)
Model C	PS based IPW *General covariates:* Age Sex (male vs. female) RA disease duration RF/ ACPA (no vs. yes) Year of treatment start (until 2020 vs. after 2020) DAS28 FFbH prior b/tsDMARDs (0 vs. ≥ 1) Glucocorticoid dosage (<5 vs. 5-<10 / ≥ 10 mg/d) Smoking (never vs. ever) *Outcome-specific covariates:* COPD (no vs. yes) Chronic renal disease (no vs. yes)	PS based IPW *General covariates:* Age Sex (male vs. female) RA disease duration RF/ ACPA (no vs. yes) Year of treatment start (until 2020 vs. after 2020) DAS28 FFbH prior b/tsDMARDs (0 vs. ≥ 1) Glucocorticoid dosage (<5 vs. 5-<10 / ≥ 10 mg/d) Smoking (never vs. ever) *Outcome-specific covariates:* None	PS based IPW *General covariates:* Age Sex (male vs. female) RA disease duration RF/ ACPA (no vs. yes) Year of treatment start (until 2020 vs. after 2020) DAS28 FFbH prior b/tsDMARDs (0 vs. ≥ 1) Glucocorticoid dosage (<5 vs. 5-<10 / ≥ 10 mg/d) Smoking (never vs. ever) *Outcome-specific covariates:* None

All covariates without further specification of categories are captured in a continuous way.
[a]Age was considered as a categorical variable instead of a continuous one to take into account the nonlinear influence of age on the risk of AEs (≤ 50, > 50 – 60, > 60 – 70, > 70 years).Abbreviations: ACPA = anti-citrullinated protein antibodies; COPD = chronic obstructive pulmonary disease; DAS28 = disease activity score based on 28 joints; FFbH = functional capacity measured by Hannover Functional Status Questionnaire; IPW = inverse probability weights; PS = propensity score; RF = rheumatoid factor.

9.5 Data sources and measurement

The RABBT register served as the only data source for this final report. Details are given in Section 9.2.

9.6 Bias

A common problem of observational studies is the lack of randomisation of patients to treatment arms resulting in effect measures being possibly confounded by indication to a therapy [10]. Treatment decision and therefore exposure to a DMARD are usually based on the availability of drugs, the physician's experience to treat patients and on patients' characteristics such as age, severity of symptoms, the individual disease course and specific comorbidities. On the other hand, patients are individually susceptible to developing a particular adverse event depending on characteristics such as age, inflammatory activity of the RA, smoking habits, comorbid conditions or concomitant medication.

9.7 Study size

All patients enrolled in the RABBIT cohort or starting treatment after a switch between 1 January 2017 until 30 June 2025 were included in the analyses, except for the patients who were not eligible due to fulfilment of exclusion criteria (see Section 9.3). This active surveillance study was not intended to test a pre-specified statistical hypothesis. The size of the active surveillance population depends on use of Flixabi for RA in Germany.

9.8 Data transformation and groups

The Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. Obesity was defined according to the definition of the World Health Organization as BMI ≥30 kg/m^2. The Disease Activity Score based on 28 tender and swollen joints (DAS28), erythrocyte sedimentation rate (ESR) and patient's global health assessment was calculated [11]. Disability was assessed using the Hanover Functional Status Questionnaire (FFbH), which is highly correlated to the Health Assessment Questionnaire [12].

9.9 Statistical methods

9.9.1 Main summary measures

Baseline characteristics:

Depending on the treatment a patient receives, he/she was assigned to the respective treatment exposure group. The treatment exposure groups were described a) at the time of enrolment into the study (every patient counts only once) and b) at the time of the start of a new treatment either at enrolment or during follow-up observation. In the latter case, every new index date was considered as baseline, as this time defines the starting point of the time at risk for the respective group. As summary measures, mean with standard deviation and median with interquartile range (for continuous variables) or numbers and their according proportion (for categorical variables) were calculated.

Incidence rates:

For calculating crude, unadjusted IRs, the first event per patient per treatment was taken into account.

Pre-defined safety outcomes were listed as cumulative number of incident events during the time of observation, total PY, IR per 1,000 PY, and 95% confidence interval. The calculation of PY was based on the sum of the months at risk per patient and exposure group divided by twelve. To calculate confidence intervals, a Poisson distribution was assumed [13]. No statistical testing was used for these analyses.

9.9.2 Main statistical methods

Relative risk:

The relative risk for an outcome in the index drug group compared to the comparator group was calculated by Cox regression models with a robust variance estimator capable of handling dependencies between observations as well as some potential deviations from model assumptions, applying propensity score (PS) based inverse probability weights (IPW) methods to control for confounding by indication

when estimating the average treatment effect (ATE). The PS for each patient was estimated using multivariable logistic regression analysis, in which the assigned treatment was set as outcome. The PS was calculated as the predicted probability of initiating the exposure of interest. PS were calculated for each outcome separately. Confounders added to the PS are presented in Table 5. For treatments starting at enrolment, data for covariates of the PS was taken from the enrolment visit. For treatments starting during follow-up, data for time-varying covariates of the PS was taken from the visit date occurring most recently prior to the treatment start date. This means that to adjust for confounding, only covariates measured before or at the time of the new treatment start were included as covariates to estimate the IPW. This allowed to control for factors that are proximally related to the treatment switch. Covariates affected by the exposure and assumed to be in the causal path from exposure to outcome (intermediate variables) were not included in the model as the total causal effect could not be estimated otherwise. Models were calculated with three different sets of covariables (A, B and C). PS weights were stabilized and winsorized below the 1st percentile and above the 99th percentile. Stabilized weights were used to reduce variability induced by subjects with large weights and calculated by multiplying the IPW by the proportion of treated or untreated patients depending on the treatment status of the patient. Histograms were produced to visually depict the overlap in PS in the two treatment groups being compared. Standardized mean differences (SMD) were employed to compare the balance in baseline covariates between treatment exposure groups. The cut-off SMD value indicating relevant imbalance was chosen as 0.1 (10%). Variables for which this imbalance criterion is not met were set to be added as additional covariables to the Cox model. Generally, models were only calculated if the amount of overfitting was acceptable. The amount of overfitting was deemed as acceptable if the number of covariables in the model was less than m/10, where m is the number of events for the considered outcome (Harrell, F.E. (2015), Regression Modeling Strategies, Springer, 2nd edition, page 72), and if additionally, there were at least 4 events in the index drug group.

On-drug approach: The PS was calculated at the time of each new treatment initiation to model the treatment decision. Treatment episodes were handled in the regression analysis by applying extended Cox models (Andersen-Gill).

Ever-exposed approach: In the ever-exposed approach, PS was set to be calculated per patient (and not per treatment episode as it is done for the on-drug approach). A Cox proportional hazard regression analysis was set to be applied.

Unadjusted and adjusted Hazard ratios (HR) and 95% confidence intervals were provided. Confounders for the Cox regression analyses are given in Table 5. No unadjusted/adjusted Cox analyses were done for safety outcomes with <4 events in the index drug group.

Data cleaning and the creation of baseline tables were performed using R (version 4.4.2). Single imputation and Cox regression analyses were carried out in SAS (version 9.4).

Missing values

Absolute numbers and proportions of missing data were reported for the main baseline variables. To estimate relative risks using the IPW method, missing information was addressed by single imputation. The single imputation was performed by regression with fully conditional specification, including the covariates from Table 5 model C and the outcome [14]. Statistical analyses were then preformed as in Section 9.9.2. The robust variance estimator used for Cox model is expected to mitigate any undesired impact of the additional variance by the imputation method on the estimates.

9.9.3 Sensitivity analysis

The following subgroup analyses for IRs were performed.

- Excluding patients with prior use of infliximab (i.e. patients must be molecule-naive): all outcomes

- Excluding patients with prior use of b/tsDMARDs (i.e. patients must be b/tsDMARD naive): all outcomes

9.9.4 Amendments to the statistical analysis plan

- Some limited modifications were made to Table 5 compared to the statistical analysis plan: Age was considered as a categorical variable instead of a continuous one to take into account the nonlinear influence of age on the risk of AEs (≤ 50, > 50 – 60, > 60 – 70, > 70 years).
- Average daily glucocorticoid dose in the last 6 months prior to index date was considered with categories 0, > 0 - 5, > 5 - 10, > 10 mg/d instead of < 5, 5 - < 10, ≥ 10 mg/d.

9.10 Quality control

Details on quality control of the data used in the RABBIT register are specified in Section 9.2.2 and 9.2.3 Data presented in the final report were cross checked.

10 Results

10.1 Participants

From 01 January 2017 until 30 June 2025, a total of 7,998 patients with RA were enrolled in RABBIT cohort 2. Of those, 42 patients could be assigned to one of the two pre-defined exposure groups at enrolment: 10 patients initiated a treatment with Flixabi, 32 started a drug from the comparator group (Figure 4). The number of patients whose treatment initiation was documented at enrolment but did not have any visit after treatment initiation were zero in the Flixabi and 3 in the comparator group (9.4 %). Considering only patients with at least one visit after treatment initiation, 10 patients were enrolled with Flixabi and 29 patients were enrolled using a drug from the comparator group (Table 6). In the comparator group, the following treatments were initiated at index date: 0 on Remicade, 2 on Zessly, 21 on Remsima and 6 on Inflectra.

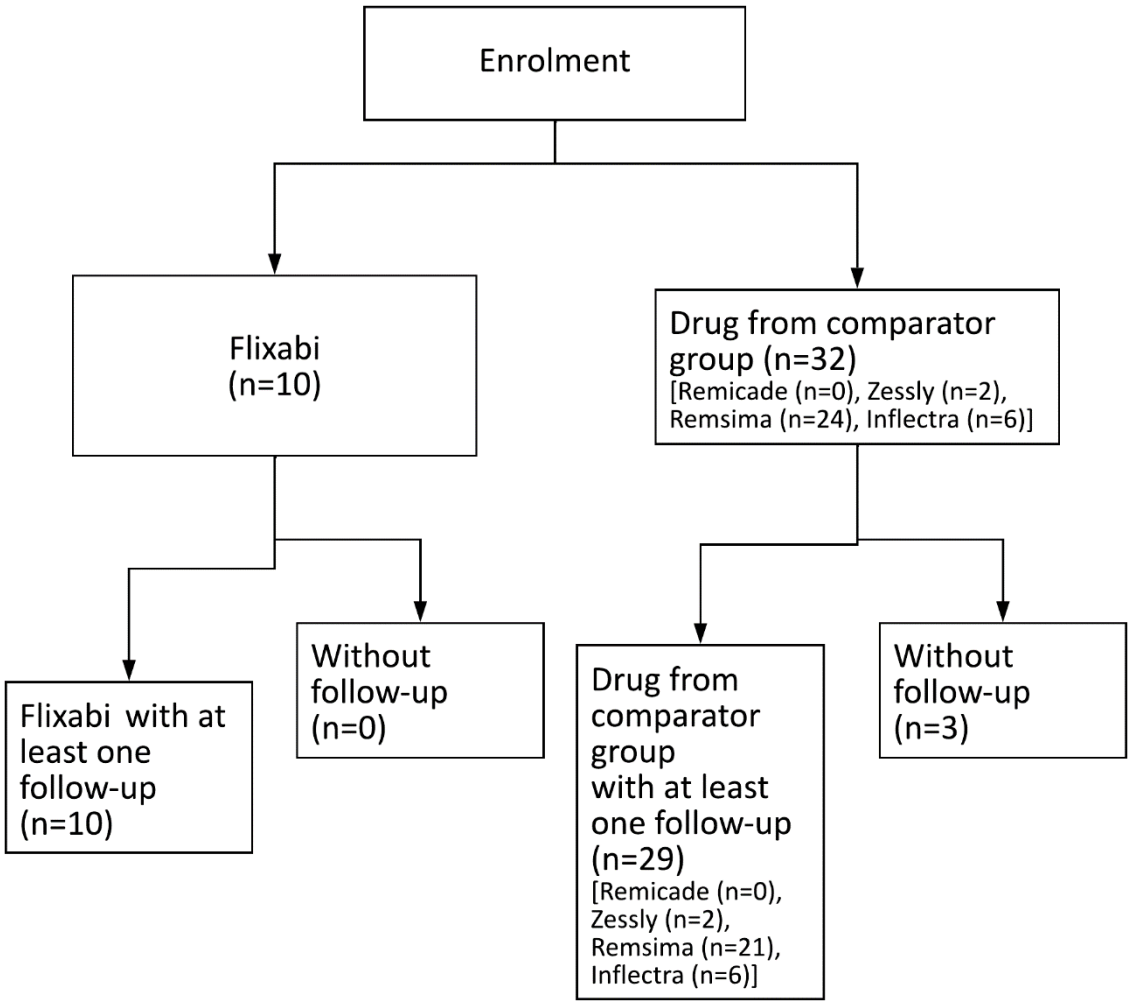

Figure 4: Flow chart with patients who started a new treatment with Flixabi or a comparator drug at enrolment.

Taking treatment initiations at enrolment and during follow-up (Figure 5) into account and considering only patients with at least one visit after treatment inititation, there were 32 episodes based on 32 patients for Flixabi and 183 episodes based on 174 patients for the comparator group (Table 7). In the comparator group, the following treatment episodes were initiated at enrolment or during follow-up (including drugs who were switched to within the 90 days risk window): 20 on Remicade, 18 on Zessly, 124 on Remsima and 30 on Inflectra. Because comparator episodes may involve more than one substance, the aggregate count across substances exceeds the total number of episodes.

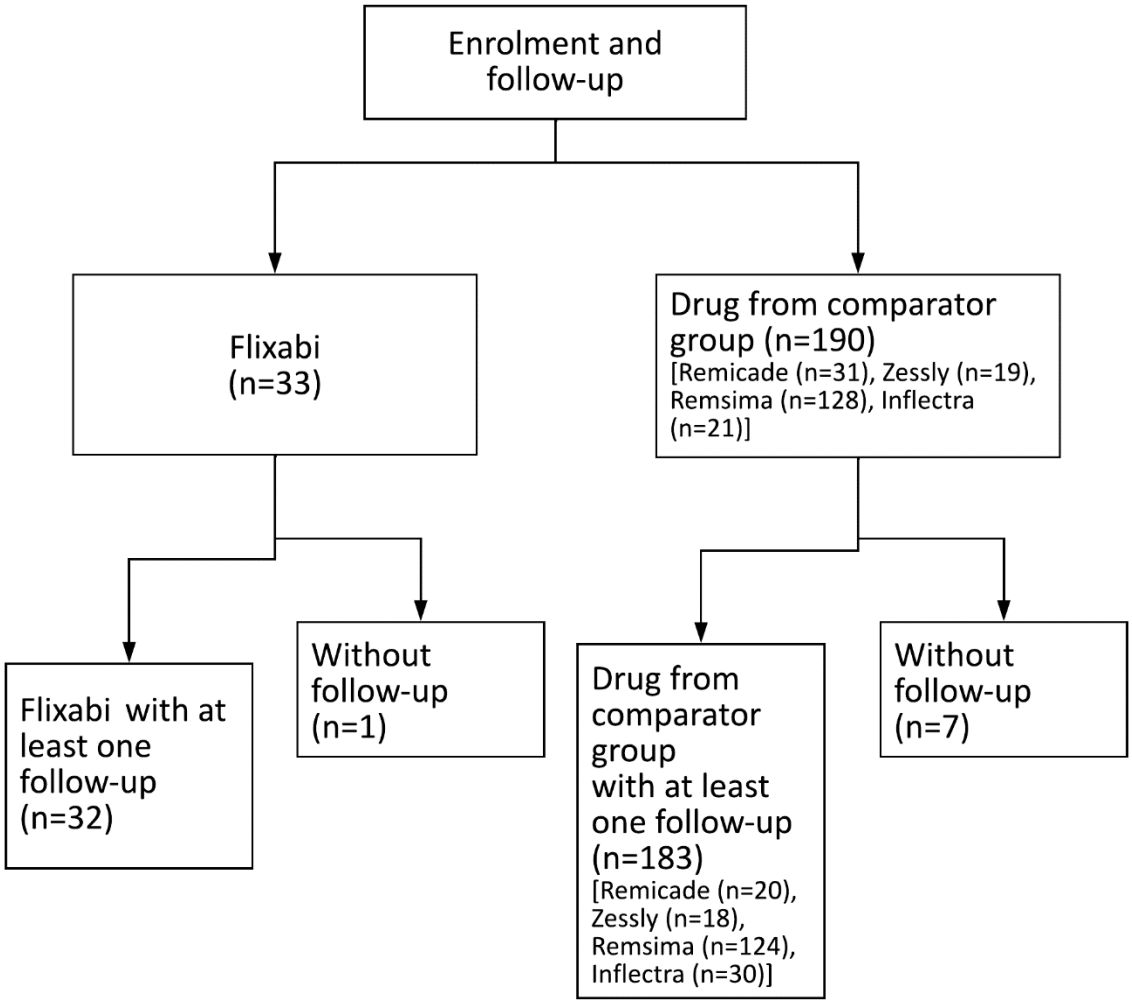

Figure 5: Flowchart of episodes initiating a new treatment with Flixabi or comparator drug(s) at enrolment or during follow-up

10.2 Descriptive data

Continuous variables are summarized using the mean, standard deviation (SD), median, 25th and 75th percentiles, minimum and maximum values, and the number of missing values. Binary and categorical variables are presented as frequency, percentage, and number of missing values, with percentages calculated based on non-missing data. Baseline characteristics are described using these descriptive analyses.

Characteristics of patients in the groups of Flixabi and comparator at the time of enrolment are given in Table 6. Only 10 patients were enrolled with Flixabi compared to 29 patients in the comparator group.

Table 6: Characteristics of patients in the Flixabi and comparator group at enrolment

Variables	Comparator group N = 29	Flixabi N = 10
Sex, n (%)		
Male	12 (41.4%)	5 (50.0%)
Female	17 (58.6%)	5 (50.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Age, years		
Mean (SD)	55.9 (15.7)	54.0 (13.1)
Median [Q1, Q3]	61.8 [42.1, 68.0]	57.6 [42.7, 64.3]
Min, Max	23.4, 77.3	27.6, 70.1
Missing, n (%)	0 (0.0%)	0 (0.0%)
Age categories 1, n (%)		
<= 50 years	9 (31.0%)	3 (30.0%)
> 50 and <= 60 years	5 (17.2%)	4 (40.0%)
> 60 and <= 70 years	9 (31.0%)	2 (20.0%)
> 70 years	6 (20.7%)	1 (10.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Education level, n (%)		
No school diploma	1 (4.3%)	0 (0.0%)
<= 10 years	15 (65.2%)	4 (44.4%)
> 10 years	7 (30.4%)	5 (55.6%)
Missing, n (%)	6 (20.7%)	1 (10.0%)
Enrolling institution, n (%)		
Rheumatology practice	24 (82.8%)	9 (90.0%)
Rheumatology clinic	5 (17.2%)	1 (10.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Average daily glucocorticoid dosis since last visit, n (%)		
No GC	17 (58.6%)	8 (80.0%)
GC > 0 - 5 mg/d	5 (17.2%)	1 (10.0%)
GC > 5 - 10 mg/d	3 (10.3%)	0 (0.0%)
GC > 10 mg/d	4 (13.8%)	1 (10.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Actual average daily glucocorticoid dosis, n (%)		
No GC	7 (24.1%)	4 (40.0%)
GC > 0 - 5 mg/d	10 (34.5%)	3 (30.0%)
GC > 5 - 10 mg/d	5 (17.2%)	2 (20.0%)
GC > 10 mg/d	7 (24.1%)	1 (10.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
% of full physical function		
Mean (SD)	62.8 (22.1)	83.6 (20.1)
Median [Q1, Q3]	68.1 [47.1, 80.6]	88.9 [72.2, 100.0]
Min, Max	13.9, 94.4	36.1, 100.0

Missing, n (%)	1 (3.4%)	0 (0.0%)
Employment status, n (%)		
Employed	15 (53.6%)	6 (60.0%)
Pension	10 (35.7%)	3 (30.0%)
Unemployed	3 (10.7%)	1 (10.0%)
Missing, n (%)	1 (3.4%)	0 (0.0%)
BMI, categorical, n (%)		
Underweight - under 18.5kg/m²	0 (0.0%)	0 (0.0%)
Normal weight - greater than or equal to 18.5kg/m² to 24.9 kg/m²	6 (20.7%)	6 (60.0%)
Overweight - greater than or equal to 25.0 kg/m² to 29.9 kg/m²	12 (41.4%)	2 (20.0%)
Obesity - greater than or equal to 30 kg/m²	11 (37.9%)	2 (20.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Smoking status, n (%)		
Current smoking	8 (29.6%)	2 (20.0%)
Past smoking	7 (25.9%)	4 (40.0%)
Non-smoking	12 (44.4%)	4 (40.0%)
Missing, n (%)	2 (6.9%)	0 (0.0%)
Smoking status binary, n (%)		
Ever smoked	15 (55.6%)	6 (60.0%)
Never smoked	12 (44.4%)	4 (40.0%)
Missing, n (%)	2 (6.9%)	0 (0.0%)
Year of cohort entry, n (%)		
2017	9 (31.0%)	0 (0.0%)
2018	4 (13.8%)	1 (10.0%)
2019	3 (10.3%)	2 (20.0%)
2020	1 (3.4%)	6 (60.0%)
2021	1 (3.4%)	0 (0.0%)
2022	3 (10.3%)	1 (10.0%)
2023	4 (13.8%)	0 (0.0%)
2024	4 (13.8%)	0 (0.0%)
2025	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Year of treatment start (until 2020 vs. after 2020), n (%)		
Before 2020	16 (55.2%)	3 (30.0%)
2020 or later	13 (44.8%)	7 (70.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
RA disease duration, years		
Mean (SD)	10.5 (10.6)	12.9 (8.6)
Median [Q1, Q3]	8.7 [3.3, 12.3]	12.3 [3.5, 21.9]
Min, Max	0.1, 41.0	1.6, 23.9
Missing, n (%)	0 (0.0%)	0 (0.0%)
DAS28-ESR		

Mean (SD)	4.5 (1.5)	3.8 (1.9)
Median [Q1, Q3]	4.5 [3.4, 4.9]	3.2 [2.0, 6.1]
Min, Max	2.3, 7.8	1.8, 6.3
Missing, n (%)	14 (48.3%)	0 (0.0%)
DAS28-ESR categories, n (%)		
Remission <2.6	1 (6.7%)	4 (40.0%)
Low activity 2.6-3.0	1 (6.7%)	1 (10.0%)
Active disease 3.1-5.0	10 (66.7%)	1 (10.0%)
Very active disease >5.0	3 (20.0%)	4 (40.0%)
Missing, n (%)	14 (48.3%)	0 (0.0%)
ESR, mm/h		
Mean (SD)	21.5 (21.2)	28.9 (34.0)
Median [Q1, Q3]	10.5 [6.5, 40.5]	11.0 [10.0, 36.0]
Min, Max	2.0, 65.0	5.0, 98.0
Missing, n (%)	13 (44.8%)	0 (0.0%)
C-reactive protein, mg/l		
Mean (SD)	19.7 (22.5)	30.1 (43.1)
Median [Q1, Q3]	15.0 [3.2, 26.5]	2.9 [1.6, 48.4]
Min, Max	1.0, 86.0	0.6, 116.7
Missing, n (%)	4 (13.8%)	1 (10.0%)
28 swollen joint count		
Mean (SD)	5.8 (5.3)	4.1 (4.3)
Median [Q1, Q3]	5.0 [2.0, 8.0]	3.5 [0.0, 6.0]
Min, Max	0.0, 24.0	0.0, 13.0
Missing, n (%)	1 (3.4%)	0 (0.0%)
28 tender joint count		
Mean (SD)	7.8 (6.0)	3.8 (4.8)
Median [Q1, Q3]	6.0 [4.0, 10.0]	1.0 [0.0, 8.0]
Min, Max	0.0, 24.0	0.0, 13.0
Missing, n (%)	0 (0.0%)	0 (0.0%)
Rheumatoid factor / ACPA status, n (%)		
Negative	12 (41.4%)	5 (50.0%)
Positive	17 (58.6%)	5 (50.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Patient reported pain, NRS (0-10)		
Mean (SD)	6.8 (1.8)	4.4 (2.8)
Median [Q1, Q3]	7.0 [6.0, 8.0]	5.0 [3.0, 7.0]
Min, Max	3.0, 10.0	0.0, 8.0
Missing, n (%)	0 (0.0%)	0 (0.0%)
Patient global health assessment, NRS (0-10)		
Mean (SD)	6.0 (2.0)	4.4 (2.5)
Median [Q1, Q3]	6.0 [4.0, 8.0]	4.0 [3.0, 7.0]
Min, Max	2.0, 9.0	1.0, 8.0
Missing, n (%)	0 (0.0%)	0 (0.0%)

Patient reported fatigue, NRS (0-10)		
Mean (SD)	5.5 (2.6)	3.2 (2.3)
Median [Q1, Q3]	6.0 [4.0, 7.0]	2.5 [2.0, 6.0]
Min, Max	0.0, 9.0	0.0, 7.0
Missing, n (%)	0 (0.0%)	0 (0.0%)
Joint erosions, n (%)		
No	0 (0.0%)	0 (0.0%)
Yes	13 (100.0%)	4 (100.0%)
Missing, n (%)	16 (55.2%)	6 (60.0%)
NSAIDs, n (%)		
No	18 (62.1%)	5 (50.0%)
Yes	11 (37.9%)	5 (50.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Analgetics, n (%)		
No	26 (89.7%)	10 (100.0%)
Yes	3 (10.3%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Coxibe, n (%)		
No	28 (96.6%)	8 (80.0%)
Yes	1 (3.4%)	2 (20.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Concomitant csDMARD therapy at treatment start, n (%)		
No	20 (69.0%)	5 (50.0%)
Yes	9 (31.0%)	5 (50.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Number of prior csDMARDs, n (%)		
<= 1	5 (17.2%)	0 (0.0%)
2	10 (34.5%)	4 (40.0%)
3+	14 (48.3%)	6 (60.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Number of prior b/tsDMARDs, n (%)		
0	12 (41.4%)	5 (50.0%)
1	7 (24.1%)	3 (30.0%)
2	2 (6.9%)	2 (20.0%)
3+	8 (27.6%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Ever Exposed to Infliximab, n (%)		
No	28 (96.6%)	10 (100.0%)
Yes	1 (3.4%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Comorbidities		
Malignancy, n (%)		

No	28 (96.6%)	10 (100.0%)
Yes	1 (3.4%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Lymphoma, n (%)		
No	29 (100.0%)	10 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Tuberculosis, n (%)		
No	29 (100.0%)	10 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Chronic hepatitis B or C, n (%)		
No	29 (100.0%)	10 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
HIV, n (%)		
No	29 (100.0%)	10 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
CVD, n (%)		
No	27 (93.1%)	10 (100.0%)
Yes	2 (6.9%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Coronary heart disease, n (%)		
No	27 (93.1%)	10 (100.0%)
Yes	2 (6.9%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Heart failure, n (%)		
No	29 (100.0%)	10 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Hyperlipidemia, n (%)		
No	24 (82.8%)	9 (90.0%)
Yes	5 (17.2%)	1 (10.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Hypertension, n (%)		
No	15 (51.7%)	8 (80.0%)
Yes	14 (48.3%)	2 (20.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Stroke, n (%)		
No	29 (100.0%)	10 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Diabetes, n (%)		
No	25 (86.2%)	10 (100.0%)
Yes	4 (13.8%)	0 (0.0%)

Missing, n (%)	0 (0.0%)	0 (0.0%)
Chronic obstructive pulmonary disease, n (%)		
No	29 (100.0%)	10 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Chronic kidney disease, n (%)		
No	29 (100.0%)	10 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Gastroduodenal ulcer, n (%)		
No	29 (100.0%)	10 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Osteoporosis, n (%)		
No	26 (89.7%)	10 (100.0%)
Yes	3 (10.3%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Crohn's disease or ulcerative colitis, n (%)		
No	28 (96.6%)	10 (100.0%)
Yes	1 (3.4%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
History of total joint replacement, n (%)		
No	23 (79.3%)	9 (90.0%)
Yes	6 (20.7%)	1 (10.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)

Table 7 (main baseline table) summarizes patient characteristics for episodes in which treatment starts either at enrolment or during follow-up. The table depicts a total of 215 treatment episodes, including 32 with Flixabi, and 183 with therapies of the comparator group.

Table 7: Characteristics of episodes in the groups of Flixabi and comparator at enrolment and during follow-up

Variables	**Comparator group N = 183**	**Flixabi N = 32**
Sex, n (%)		
Male	54 (29.5%)	9 (28.1%)
Female	129 (70.5%)	23 (71.9%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Age, years		
Mean (SD)	57.0 (12.9)	56.7 (12.3)
Median [Q1, Q3]	57.8 [47.9, 67.2]	57.7 [47.5, 64.2]
Min, Max	23.4, 82.9	27.6, 81.9

Missing, n (%)	0 (0.0%)	0 (0.0%)
Age categories 1, n (%)		
<= 50 years	50 (27.3%)	9 (28.1%)
> 50 and <= 60 years	49 (26.8%)	11 (34.4%)
> 60 and <= 70 years	53 (29.0%)	7 (21.9%)
> 70 years	31 (16.9%)	5 (15.6%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Education level, n (%)		
No school diploma	2 (1.3%)	0 (0.0%)
<= 10 years	104 (66.2%)	20 (71.4%)
> 10 years	51 (32.5%)	8 (28.6%)
Missing, n (%)	26 (14.2%)	4 (12.5%)
Enrolling institution, n (%)		
Rheumatology practice	139 (76.0%)	23 (71.9%)
Rheumatology clinic	44 (24.0%)	9 (28.1%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Average daily glucocorticoid dosis since last visit, n (%)		
No GC	91 (50.8%)	22 (68.8%)
GC > 0 - 5 mg/d	54 (30.2%)	8 (25.0%)
GC > 5 - 10 mg/d	21 (11.7%)	0 (0.0%)
GC > 10 mg/d	13 (7.3%)	2 (6.3%)
Missing, n (%)	4 (2.2%)	0 (0.0%)
Actual average daily glucocorticoid dosis, n (%)		
No GC	68 (37.2%)	11 (34.4%)
GC > 0 - 5 mg/d	66 (36.1%)	14 (43.8%)
GC > 5 - 10 mg/d	33 (18.0%)	5 (15.6%)
GC > 10 mg/d	16 (8.7%)	2 (6.3%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
% of full physical function		
Mean (SD)	64.4 (23.6)	69.5 (23.7)
Median [Q1, Q3]	69.4 [47.2, 82.4]	75.0 [47.2, 88.9]
Min, Max	2.8, 100.0	22.2, 100.0
Missing, n (%)	10 (5.5%)	1 (3.1%)
Employment status, n (%)		
Employed	93 (51.4%)	15 (46.9%)
Pension	65 (35.9%)	12 (37.5%)
Unemployed	23 (12.7%)	5 (15.6%)
Missing, n (%)	2 (1.1%)	0 (0.0%)
BMI, categorical, n (%)		
Underweight - under 18.5kg/m²	8 (4.4%)	2 (6.3%)
Normal weight - greater than or equal to 18.5kg/m² to 24.9 kg/m²	57 (31.3%)	13 (40.6%)
Overweight - greater than or equal to 25.0 kg/m² to 29.9 kg/m²	75 (41.2%)	12 (37.5%)

Obesity - greater than or equal to 30 kg/m²	42 (23.1%)	5 (15.6%)
Missing, n (%)	1 (0.5%)	0 (0.0%)
Smoking status, n (%)		
Current smoking	57 (31.5%)	9 (28.1%)
Past smoking	62 (34.3%)	12 (37.5%)
Non-smoking	62 (34.3%)	11 (34.4%)
Missing, n (%)	2 (1.1%)	0 (0.0%)
Smoking status binary, n (%)		
Ever smoked	119 (65.7%)	21 (65.6%)
Never smoked	62 (34.3%)	11 (34.4%)
Missing, n (%)	2 (1.1%)	0 (0.0%)
Year of cohort entry, n (%)		
2017	22 (12.0%)	2 (6.3%)
2018	11 (6.0%)	5 (15.6%)
2019	18 (9.8%)	8 (25.0%)
2020	20 (10.9%)	11 (34.4%)
2021	16 (8.7%)	4 (12.5%)
2022	19 (10.4%)	2 (6.3%)
2023	41 (22.4%)	0 (0.0%)
2024	35 (19.1%)	0 (0.0%)
2025	1 (0.5%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Year of treatment start (until 2020 vs. after 2020), n (%)		
Before 2020	51 (27.9%)	15 (46.9%)
2020 or later	132 (72.1%)	17 (53.1%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
RA disease duration, years		
Mean (SD)	13.4 (9.8)	15.3 (8.9)
Median [Q1, Q3]	10.7 [5.9, 20.6]	14.4 [8.3, 21.9]
Min, Max	0.1, 45.7	1.6, 33.5
Missing, n (%)	0 (0.0%)	0 (0.0%)
DAS28-ESR		
Mean (SD)	4.1 (1.4)	3.7 (1.6)
Median [Q1, Q3]	4.1 [3.1, 4.9]	3.4 [2.2, 5.1]
Min, Max	1.2, 7.8	0.9, 6.3
Missing, n (%)	52 (28.4%)	5 (15.6%)
DAS28-ESR categories, n (%)		
Remission <2.6	26 (19.8%)	7 (25.9%)
Low activity 2.6-3.0	4 (3.1%)	4 (14.8%)
Active disease 3.1-5.0	69 (52.7%)	9 (33.3%)
Very active disease >5.0	32 (24.4%)	7 (25.9%)
Missing, n (%)	52 (28.4%)	5 (15.6%)
ESR, mm/h		
Mean (SD)	22.4 (21.5)	23.0 (25.3)

Median [Q1, Q3]	15.0 [7.0, 30.0]	12.0 [8.0, 29.0]
Min, Max	1.0, 89.0	2.0, 98.0
Missing, n (%)	44 (24.0%)	3 (9.4%)
C-reactive protein, mg/l		
Mean (SD)	10.4 (16.9)	12.9 (26.2)
Median [Q1, Q3]	3.2 [1.3, 11.6]	2.4 [0.6, 15.0]
Min, Max	0.0, 93.0	0.1, 116.7
Missing, n (%)	21 (11.5%)	1 (3.1%)
28 swollen joint count		
Mean (SD)	3.3 (4.6)	2.8 (3.4)
Median [Q1, Q3]	2.0 [0.0, 5.0]	2.0 [0.0, 6.0]
Min, Max	0.0, 24.0	0.0, 13.0
Missing, n (%)	4 (2.2%)	1 (3.1%)
28 tender joint count		
Mean (SD)	5.7 (6.1)	3.7 (6.2)
Median [Q1, Q3]	3.0 [1.0, 9.0]	1.0 [0.0, 6.0]
Min, Max	0.0, 28.0	0.0, 26.0
Missing, n (%)	3 (1.6%)	1 (3.1%)
Rheumatoid factor / ACPA status, n (%)		
Negative	72 (39.6%)	12 (37.5%)
Positive	110 (60.4%)	20 (62.5%)
Missing, n (%)	1 (0.5%)	0 (0.0%)
Patient reported pain, NRS(0-10)		
Mean (SD)	6.1 (2.3)	5.1 (2.6)
Median [Q1, Q3]	7.0 [4.0, 8.0]	5.0 [3.0, 7.0]
Min, Max	0.0, 10.0	0.0, 10.0
Missing, n (%)	6 (3.3%)	1 (3.1%)
Patient global health assessment, NRS (0-10)		
Mean (SD)	5.9 (2.1)	5.0 (2.4)
Median [Q1, Q3]	6.0 [5.0, 8.0]	5.0 [3.0, 7.0]
Min, Max	0.0, 10.0	1.0, 10.0
Missing, n (%)	6 (3.3%)	1 (3.1%)
Patient reported fatigue, NRS (0-10)		
Mean (SD)	6.0 (2.5)	4.4 (2.8)
Median [Q1, Q3]	7.0 [4.0, 8.0]	4.0 [2.0, 7.0]
Min, Max	0.0, 10.0	0.0, 10.0
Missing, n (%)	7 (3.8%)	1 (3.1%)
Joint erosions, n (%)		
No	0 (0.0%)	0 (0.0%)
Yes	15 (100.0%)	4 (100.0%)
Missing, n (%)	168 (91.8%)	28 (87.5%)
NSAIDs, n (%)		
No	123 (67.2%)	18 (56.3%)

Yes	60 (32.8%)	14 (43.8%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Analgetics, n (%)		
No	137 (74.9%)	28 (87.5%)
Yes	46 (25.1%)	4 (12.5%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Coxibe, n (%)		
No	159 (86.9%)	28 (87.5%)
Yes	24 (13.1%)	4 (12.5%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Concomitant csDMARD therapy at treatment start, n (%)		
No	114 (62.3%)	20 (62.5%)
Yes	69 (37.7%)	12 (37.5%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Number of prior csDMARDs, n (%)		
<= 1	12 (6.6%)	1 (3.1%)
2	54 (29.5%)	9 (28.1%)
3+	117 (63.9%)	22 (68.8%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Number of prior b/tsDMARDs, n (%)		
0	20 (10.9%)	6 (18.8%)
1	41 (22.4%)	13 (40.6%)
2	17 (9.3%)	4 (12.5%)
3+	105 (57.4%)	9 (28.1%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Ever Exposed to Infliximab, n (%)		
No	151 (82.5%)	20 (62.5%)
Yes	32 (17.5%)	12 (37.5%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Comorbidities		
Malignancy, n (%)		
No	176 (96.2%)	30 (93.8%)
Yes	7 (3.8%)	2 (6.3%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Lymphoma, n (%)		
No	183 (100.0%)	32 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Tuberculosis, n (%)		
No	181 (98.9%)	32 (100.0%)
Yes	2 (1.1%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Chronic hepatitis B or C, n (%)		

No	183 (100.0%)	32 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
HIV, n (%)		
No	183 (100.0%)	32 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
CVD, n (%)		
No	170 (92.9%)	30 (93.8%)
Yes	13 (7.1%)	2 (6.3%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Coronary heart disease, n (%)		
No	174 (95.1%)	31 (96.9%)
Yes	9 (4.9%)	1 (3.1%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Heart failure, n (%)		
No	179 (97.8%)	32 (100.0%)
Yes	4 (2.2%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Hyperlipidemia, n (%)		
No	166 (90.7%)	25 (78.1%)
Yes	17 (9.3%)	7 (21.9%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Hypertension, n (%)		
No	110 (60.1%)	19 (59.4%)
Yes	73 (39.9%)	13 (40.6%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Stroke, n (%)		
No	180 (98.4%)	31 (96.9%)
Yes	3 (1.6%)	1 (3.1%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Diabetes, n (%)		
No	165 (90.2%)	30 (93.8%)
Yes	18 (9.8%)	2 (6.3%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Chronic obstructive pulmonary disease, n (%)		
No	178 (97.3%)	31 (96.9%)
Yes	5 (2.7%)	1 (3.1%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Chronic kidney disease, n (%)		
No	177 (96.7%)	32 (100.0%)
Yes	6 (3.3%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Gastroduodenal ulcer, n (%)		
No	182 (99.5%)	32 (100.0%)

Yes	1 (0.5%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Osteoporosis, n (%)		
No	148 (80.9%)	28 (87.5%)
Yes	35 (19.1%)	4 (12.5%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Crohn's disease or ulcerative colitis, n (%)		
No	168 (91.8%)	30 (93.8%)
Yes	15 (8.2%)	2 (6.3%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
History of total joint replacement, n (%)		
No	161 (89.0%)	29 (90.6%)
Yes	20 (11.0%)	3 (9.4%)
Missing, n (%)	2 (1.1%)	0 (0.0%)

Mean age at index date in the Flixabi exposure group was 56.7 years vs. 57.0 years in the comparator group. Proportions of female patients were 71.9% in the Flixabi group and 70.5% in the comparator group. Proportions of seropositive patients (measured as rheumatoid factor (RF) and/or anti-citrullinated protein antibodies (ACPA)) were 62.5% in the Flixabi group and 60.4% in the comparator group. The mean RA disease duration was 15.3 years in Flixabi patients, as compared to 13.4 years in the comparator group and the median disease duration was 14.4 years and 10.7 years, respectively. Mean disease activity measured by DAS28-ESR was 3.7 for Flixabi and 4.1 for the comparator group, and the median was 3.4 and 4.1, respectively. The percentage of full physical function measured by FFbH was 69.5% in the Flixabi group and 64.4% in the comparator group. The means and medians of patient-reported pain, patient global health assessment and patient-reported fatigue were all worse in the comparator group than in the Flixabi group whereas the proportion of patients using NSAIDs was higher in the Flixabi group. The proportion of patients with prior ever infliximab exposure was 37.5% in the Flixabi and 17.5% in the comparator group, and the proportion of b/ts-naive patients was 18.8% in Flixabi and 10.9% in the comparator group. Treatment with glucocorticoids in the last 6 months prior to index date was more frequent in the comparator group (49.2%) than in the Flixabi group (31.2%). Concomitant csDMARD therapy was similarly distributed between the Flixabi group (37.5%) and the comparator group (37.7%).

No concomitant actual glucocorticoid therapy was given to 34.4% of patients in the Flixabi group and 37.2% of patients in the comparator group. For most reported comorbidities, the proportions were comparable between the Flixabi and the comparator group, however hyperlipidemia was more frequent in the Flixabi (21.9%) than in the comparator group (9.3%) and osteoporosis more frequent in the comparator group (19.1%) than in the Flixabi group (12.5%). The proportion of obese patients was higher in the comparator group (23.1%) than in the Flixabi group (15.6%). The proportion of smoking patients was comparable between the groups, at 34.4% in both. Since 2023, there was no treatment initiation with Flixabi whereas 42.1% of episode in the comparator group were initiated since 2023.

10.3 Outcome data

Table 8 represents the number of patients and summary statistics for on-drug time and total follow-up time across Flixabi and comparator group, depending on the methodology. Although the variability is

high in both groups, the median values indicate that Flixabi patients generally stayed on treatment for longer.

Table 8: Numbers of participants across categories of the main outcomes

		Flixabi	Comparator
On-drug time considering a 90 day risk window in years	No of episodes	32	183
	No of patients	32	174
	Mean (SD)	1.86 (1.78)	1.40 (1.59)
	Median (Q1, Q3)	1.02 (0.53, 3.05)	0.86 (0.48, 1.44)
	Minimum, maximum	0.10, 5.45	0.04, 8
Total follow-up time considering a latency period in years	No of patients	31	147
	Mean (SD)	3.35 (2.09)	2.48 (2.19)
	Median (Q1, Q3)	3.87 (1.23,4.52)	1.58 (0.72,3.85)
	Minimum, maximum	0.00, 7.53	0.02 7.57

The number of patients in the total follow-up period accounts for a 6-months latency period; thus, some episodes were excluded because they did not have sufficient length of follow-up.

The overall numbers of incident events, PY and crude IRs with 95% CI are compared between the Flixabi and the comparator group in the following part.

For all investigated outcomes, numbers are given for the on-drug approach in Table 9. Of note, in case of overlaps in the time at risk of the treatment exposure groups, an event which occurred within overlapping month(s) was assigned to both groups.

For the on-dug approach, no events occured both in the Flixabi and the comparator group for the following outcomes: demyelinating disorders serious (including Multiple Sclerosis, Guillain-Barré Syndrom, Optic Neuritis), central demyelination, serious immunogenicity, pregnancies and their outcomes, BCG breakthrough infection and agranulocytosis in infants with in utero exposure, tuberculosis, congestive heart failure, hepatic failure. No events in the Flixabi group but events in the comparator group were found for the following outcomes:

Serious infections/sepsis (excluing Tuberculosis): there were 5 events in the comparator group. The IR was 19.93 (CI: 6.47, 46.52).

Myocardial infarction: there were 2 events in the comparator group. The IR was 7.87 (CI: 0.95, 28.42).

Serious hematological disorders: there was one event in the comparator group. The IR was 3.92 (CI: 0.10, 21.82).

Neoplasms: there were 4 events in the comparator group. The IR was 16.15 (CI: 4.40, 41.34).

Demyelinating disorders (serious and non-serious): there was one event in the comparator group: The IR was 3.92 (CI: 0.1, 21.83).

Serious gestrointestinal ulcer/perforation: there was one event in the comparator group. The IR was 3.92 (CI: 0.10, 21.80).

Stroke: there was one event in the comparator group. The IR was 3.92 (CI: 0.10, 21.87).

Death: there was one event in the comparator group. The IR was 3.91 (CI: 0.10, 21.80).

No events in the comparator group but events in the Flixabi group were found for the following outcomes:

For VTE (including DVT, DVT postoperative, PE, postprocedural PE, venous thrombosis limb), there was no event in the comparator group but one event in the Flixabi group. The IR was 17.52 (CI: 0.44, 97.63) for the Flixabi group.

Events in the Flixabi- as well as the comparator group were found for following outcomes: for Immunogenicity (serious and non-serious), there were 5 events in the Flixabi group and 14 events in the comparator group. The IR was 96.65 (CI: 31.38, 225.54) for the Flixabi and 57.90 (CI: 31.65, 97.14) for the comparator group.

Table 9: Crude incidence rates for pre-defined outcomes, stratified by treatment applying the on-drug approach with risk window 90 days

	Flixabi					**Comparator group**				
	No.	PY	IR	LCL	UCL	No.	PY	IR	LCL	UCL
Safety endpoints (study protocol)										
Tuberculosis	0	59.49	0	0	62.01	0	255.53	0	0	14.44
Other serious infections	0	59.49	0	0	62.01	5	250.83	19.93	6.47	46.52
Congestive heart failure	0	59.49	0	0	62.01	0	255.53	0	0	14.44
Myocardial infarction	0	59.49	0	0	62.01	2	254.25	7.87	0.95	28.42
Central demyelination	0	59.49	0	0	62.01	0	255.53	0	0	14.44
Serious hematologic disorders	0	59.49	0	0	62.01	1	255.35	3.92	0.10	21.82
Neoplasms	0	59.49	0	0	62.01	4	247.75	16.15	4.40	41.34
Deaths	0	59.49	0	0	62.01	1	255.53	3.91	0.10	21.80
Serious systemic hypersensitivity	0	59.49	0	0	62.01	0	255.53	0	0	14.44
Hepatic failure	0	59.49	0	0	62.01	0	255.53	0	0	14.44
Serious gastrointestinal ulcer/perforation	0	59.49	0	0	62.01	1	255.31	3.92	0.10	21.82
Stroke	0	59.49	0	0	62.01	1	254.79	3.92	0.10	21.87
VTE	1	57.07	17.52	0.44	97.63	0	255.53	0	0	14.44
Pregnancies and their outcomes	0	16.58	0	0	222.44	0	82.27	0	0	44.84

Safety concerns (risk management plan)										
Serious infections/sepsis	0	59.49	0	0	62.01	5	250.83	19.93	6.47	46.52
Demyelinating disorders (serious)	0	59.49	0	0	62.01	0	255.53	0	0	14.44
Demyelinating disorders (all)	0	59.49	0	0	62.01	1	255.27	3.92	0.1	21.83
BCG breakthrough infection &	0	59.49	0	0	62.01	0	255.53	0	0	14.44
Malignancy (serious/all)	0	59.49	0	0	62.01	4	247.75	16.15	4.4	41.34
Immunogenicity serious (serious)	0	59.49	0	0	62.01	0	255.53	0	0	14.44
Immunogenicity (all)	5	51.73	96.65	31.38	225.54	14	241.81	57.9	31.65	97.14

Incidence rates are given per 1,000 patient years. No.: numbers of events.
Abbreviations: IR, incidence rate; LCL, 95% lower confidence limit; PY, patients years; UCL, 95% upper confidence limit;

For malignancy and neoplasms, an ever-exposed approach was also applied with a latency period of 6 months after drug initiation (Table 10).

There was no event in the Flixabi group. For malignancy, there were 5 events in the comparator group. The IR was 14.17 (CI: 4.6, 33.07). For neoplasms there were 6 events in the comparator group with IR was 17.08 (CI: 6.27, 37.17).

Table 10: Crude IR for pre-defined outcomes, stratified by treatment applying the ever-exposed approach

	Flixabi					**Comparator group**				
	No.	PY	IR	LCL	UCL	No.	PY	IR	LCL	UCL
Malignancy	0	103.78	0	0	30.81	5	352.80	14.17	4.6	33.07
Neoplasms	0	103.78	0	0	30.81	6	351.30	17.08	6.27	37.17

Incidence rates are given per 1,000 patient years. No.: numbers of events.
Abbreviations: IR, incidence rate; LCL, 95% lower confidence limit; No., number of events; PY, patients years; UCL, 95% upper confidence limit; Neoplasms is including NMSC

10.4 Main results

To assess the relative risks of pre-defined outcomes in patients initiating Flixabi in relation to the comparator group, HR and 95% CI were calculated. More than 4 events in the Flixabi group were only found for the outcome immunogenicity (all). Therefore, regression models were not applied to the other outcomes due to low number of reported events. Unadjusted (Model A) and adjusted (Model B) relative risks were calculated using extended Cox regression models (Andersen Gill) based on the on-drug approach. For model C, single imputation was first performed to address the missing data. Subsequently, IPTW was applied to weight for imbalances between the groups in the original sample that were found for age, year of treatment start, glucocorticoid use in the 6 months prior to the index date, smoking status, RF/ ACPA, bionative and prior b/tsDMARDs. After weighting, values above the cut-off were retained

and included in the Cox regression analysis. The results of the Cox regression models are presented in Table 11. For Models A and B, no increased risk was observed for Flixabi compared with the comparator group. In Model C, the HR increased after adjustment for confounding. However, the confidence intervals for all three models include 1; therefore, the results do not indicate a statistical significance.

Table 11: Results of the extended Cox regression models (Andersen-Gill) applied to patients exposed to Flixabi in comparison to the comparator group applying the on-drug approach with risk window 90 days

	Treatment	Events	Model A			Model B			Model C		
			HR	LCL	UCL	HR	LCL	UCL	HR	LCL	UCL
Immunogenicity (serious and non-serious)	Comparator	14	*Ref.*	-	-	*Ref.*	-	-	*Ref.*	-	-
	Flixabi	5	1.88	0.65	5.46	1.87	0.64	5.47	2.16	0.59	7.86

Bold indicates significance compared to the reference group. Model A: unadjusted. Model B: adjusted for age and gender. Model C: propensity score based inverse probability adjusted model.
Abbreviations: HR = hazard ratio; LCL = 95% lower confidence limit; n.a. = regression models not applicable due to low number of events (n<4);

10.5 Other analyses

Table 12 and Table 13 present the baseline characteristics for the subgroup analyses in molecule-naive and bio-naive patients.

Table 12: Baseline characteristics, excluding patients with prior use of Infliximab

Variables	Comparator group N = 151	Flixabi N = 20
Sex, n (%)		
Male	45 (29.8%)	6 (30.0%)
Female	106 (70.2%)	14 (70.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Age, years		
Mean (SD)	56.9 (12.8)	56.3 (12.7)
Median [Q1, Q3]	57.9 [50.1, 66.5]	57.7 [47.4, 64.2]
Min, Max	23.4, 82.9	27.6, 81.3
Missing, n (%)	0 (0.0%)	0 (0.0%)
Age categories 1, n (%)		
<= 50 years	37 (24.5%)	5 (25.0%)
> 50 and <= 60 years	44 (29.1%)	8 (40.0%)
> 60 and <= 70 years	47 (31.1%)	4 (20.0%)
> 70 years	23 (15.2%)	3 (15.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Education level, n (%)		
No school diploma	2 (1.6%)	0 (0.0%)
<= 10 years	89 (69.5%)	11 (68.8%)
> 10 years	37 (28.9%)	5 (31.3%)
Missing, n (%)	23 (15.2%)	4 (20.0%)
Enrolling institution, n (%)		
Rheumatology practice	115 (76.2%)	16 (80.0%)

Rheumatology clinic	36 (7.3%)	4 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Average daily glucocorticoid dosis since last visit, n (%)		
No GC	72 (49.0%)	14 (70.0%)
GC > 0 - 5 mg/d	46 (31.3%)	4 (20.0%)
GC > 5 - 10 mg/d	17 (11.6%)	0 (0.0%)
GC > 10 mg/d	12 (8.2%)	2 (10.0%)
Missing, n (%)	4 (2.6%)	0 (0.0%)
Actual average daily glucocorticoid dosis, n (%)		
No GC	58 (38.4%)	6 (30.0%)
GC > 0 - 5 mg/d	52 (34.4%)	7 (35.0%)
GC > 5 - 10 mg/d	26 (17.2%)	5 (25.0%)
GC > 10 mg/d	15 (9.9%)	2 (10.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
% of full physical function		
Mean (SD)	63.0 (24.3)	72.6 (26.0)
Median [Q1, Q3]	69.4 [44.1, 80.6]	80.6 [63.9, 97.2]
Min, Max	2.8, 100.0	22.2, 100.0
Missing, n (%)	8 (5.3%)	1 (5.0%)
Employment status, n (%)		
Employed	77 (51.7%)	10 (50.0%)
Pension	53 (35.6%)	8 (40.0%)
Unemployed	19 (12.8%)	2 (10.0%)
Missing, n (%)	2 (1.3%)	0 (0.0%)
BMI, categorical, n (%)		
Underweight - under 18.5kg/m²	5 (3.3%)	0 (0.0%)
Normal weight - greater than or equal to 18.5kg/m² to 24.9 kg/m²	40 (26.7%)	9 (45.0%)
Overweight - greater than or equal to 25.0 kg/m² to 29.9 kg/m²	65 (43.3%)	6 (30.0%)
Obesity - greater than or equal to 30 kg/m²	40 (26.7%)	5 (25.0%)
Missing, n (%)	1 (0.7%)	0 (0.0%)
Smoking status, n (%)		
Current smoking	46 (30.9%)	5 (25.0%)
Past smoking	53 (35.6%)	7 (35.0%)
Non-smoking	50 (33.6%)	8 (40.0%)
Missing, n (%)	2 (1.3%)	0 (0.0%)
Smoking status binary, n (%)		
Ever smoked	99 (66.4%)	12 (60.0%)
Never smoked	50 (33.6%)	8 (40.0%)
Missing, n (%)	2 (1.3%)	0 (0.0%)
Year of cohort entry, n (%)		
2017	18 (11.9%)	0 (0.0%)

2018	10 (6.6%)	4 (20.0%)
2019	13 (8.6%)	5 (25.0%)
2020	12 (7.9%)	7 (35.0%)
2021	12 (7.9%)	2 (10.0%)
2022	16 (10.6%)	2 (10.0%)
2023	39 (25.8%)	0 (0.0%)
2024	30 (19.9%)	0 (0.0%)
2025	1 (0.7%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Year of treatment start (until 2020 vs. after 2020), n (%)		
Before 2020	41 (27.2%)	9 (45.0%)
2020 or later	110 (72.8%)	11 (55.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
RA disease duration, years		
Mean (SD)	12.2 (9.5)	14.4 (8.5)
Median [Q1, Q3]	10.0 [4.8, 16.6]	13.8 [8.0, 21.3]
Min, Max	0.1, 42.3	1.6, 33.5
Missing, n (%)	0 (0.0%)	0 (0.0%)
DAS28-ESR		
Mean (SD)	4.2 (1.4)	4.1 (1.6)
Median [Q1, Q3]	4.1 [3.2, 5.0]	4.3 [2.7, 5.5]
Min, Max	1.2, 7.8	1.8, 6.3
Missing, n (%)	47 (31.1%)	3 (15.0%)
DAS28-ESR categories, n (%)		
Remission <2.6	18 (17.3%)	4 (23.5%)
Low activity 2.6-3.0	4 (3.8%)	1 (5.9%)
Active disease 3.1-5.0	55 (52.9%)	6 (35.3%)
Very active disease >5.0	27 (26.0%)	6 (35.3%)
Missing, n (%)	47 (31.1%)	3 (15.0%)
ESR, mm/h		
Mean (SD)	21.4 (21.2)	27.1 (28.1)
Median [Q1, Q3]	14.0 [6.0, 30.0]	13.0 [10.0, 36.0]
Min, Max	1.0, 89.0	4.0, 98.0
Missing, n (%)	40 (26.5%)	2 (10.0%)
C-reactive protein, mg/l		
Mean (SD)	10.5 (16.9)	18.6 (31.4)
Median [Q1, Q3]	3.2 [1.4, 12.3]	4.0 [2.1, 17.5]
Min, Max	0.0, 93.0	0.6, 116.7
Missing, n (%)	19 (12.6%)	1 (5.0%)
28 swollen joint count		
Mean (SD)	3.6 (4.9)	4.0 (3.6)
Median [Q1, Q3]	2.0 [0.0, 5.0]	3.0 [1.0, 6.0]
Min, Max	0.0, 24.0	0.0, 13.0
Missing, n (%)	4 (2.6%)	0 (0.0%)
28 tender joint count		

Mean (SD)	6.2 (6.4)	4.5 (6.3)
Median [Q1, Q3]	4.0 [1.0, 10.0]	2.5 [0.0, 6.5]
Min, Max	0.0, 28.0	0.0, 26.0
Missing, n (%)	3 (2.0%)	0 (0.0%)
Rheumatoid factor / ACPA status, n (%)		
Negative	57 (38.0%)	6 (30.0%)
Positive	93 (62.0%)	14 (70.0%)
Missing, n (%)	1 (0.7%)	0 (0.0%)
Patient reported pain, NRS (0-10)		
Mean (SD)	6.2 (2.3)	5.3 (2.7)
Median [Q1, Q3]	7.0 [5.0, 8.0]	6.0 [3.0, 7.0]
Min, Max	0.0, 10.0	0.0, 10.0
Missing, n (%)	5 (3.3%)	1 (5.0%)
Patient global health assessment, NRS (0-10)		
Mean (SD)	6.0 (2.1)	5.4 (2.4)
Median [Q1, Q3]	6.0 [5.0, 8.0]	6.0 [3.0, 8.0]
Min, Max	0.0, 10.0	1.0, 10.0
Missing, n (%)	5 (3.3%)	1 (5.0%)
Patient reported fatigue, NRS (0-10)		
Mean (SD)	6.1 (2.5)	4.3 (3.0)
Median [Q1, Q3]	7.0 [4.0, 8.0]	4.0 [2.0, 6.0]
Min, Max	0.0, 10.0	0.0, 10.0
Missing, n (%)	5 (3.3%)	1 (5.0%)
Joint erosions, n (%)		
No	0 (0.0%)	0 (0.0%)
Yes	15 (100.0%)	4 (100.0%)
Missing, n (%)	136 (90.1%)	16 (80.0%)
NSAIDs, n (%)		
No	101 (66.9%)	12 (60.0%)
Yes	50 (33.1%)	8 (40.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Analgetics, n (%)		
No	112 (74.2%)	17 (85.0%)
Yes	39 (25.8%)	3 (15.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Coxibe, n (%)		
No	133 (88.1%)	17 (85.0%)
Yes	18 (11.9%)	3 (15.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Concomitant csDMARD therapy at treatment start, n (%)		
No	87 (57.6%)	8 (40.0%)
Yes	64 (42.4%)	12 (60.0%)

Missing, n (%)	0 (0.0%)	0 (0.0%)
Number of prior csDMARDs, n (%)		
<= 1	11 (7.3%)	0 (0.0%)
2	46 (30.5%)	6 (30.0%)
3+	94 (62.3%)	14 (70.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Number of prior b/tsDMARDs, n (%)		
0	20 (13.2%)	6 (30.0%)
1	30 (19.9%)	5 (25.0%)
2	14 (9.3%)	3 (15.0%)
3+	87 (57.6%)	6 (30.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Ever Exposed to Infliximab, n (%)		
No	151 (100.0%)	20 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Comorbidities		
Malignancy, n (%)		
No	146 (96.7%)	19 (95.0%)
Yes	5 (3.3%)	1 (5.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Lymphoma, n (%)		
No	151 (100.0%)	20 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Tuberculosis, n (%)		
No	149 (98.7%)	20 (100.0%)
Yes	2 (1.3%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Chronic hepatitis B or C, n (%)		
No	151 (100.0%)	20 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
HIV, n (%)		
No	151 (100.0%)	20 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
CVD, n (%)		
No	141 (93.4%)	20 (100.0%)
Yes	10 (6.6%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Coronary heart disease, n (%)		
No	145 (96.0%)	20 (100.0%)
Yes	6 (4.0%)	0 (0.0%)

Missing, n (%)	0 (0.0%)	0 (0.0%)
Heart failure, n (%)		
No	148 (98.0%)	20 (100.0%)
Yes	3 (2.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Hyperlipidemia, n (%)		
No	135 (89.4%)	15 (75.0%)
Yes	16 (10.6%)	5 (25.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Hypertension, n (%)		
No	89 (58.9%)	12 (60.0%)
Yes	62 (41.1%)	8 (40.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Stroke, n (%)		
No	148 (98.0%)	20 (100.0%)
Yes	3 (2.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Diabetes, n (%)		
No	134 (88.7%)	19 (95.0%)
Yes	17 (11.3%)	1 (5.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Chronic obstructive pulmonary disease, n (%)		
No	147 (97.4%)	20 (100.0%)
Yes	4 (2.6%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Chronic kidney disease, n (%)		
No	146 (96.7%)	20 (100.0%)
Yes	5 (3.3%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Gastroduodenal ulcer, n (%)		
No	150 (99.3%)	20 (100.0%)
Yes	1 (0.7%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Osteoporosis, n (%)		
No	128 (84.8%)	19 (95.0%)
Yes	23 (15.2%)	1 (5.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Crohn's disease or ulcerative colitis, n (%)		
No	139 (92.1%)	18 (90.0%)
Yes	12 (7.9%)	2 (10.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
History of total joint replacement, n (%)		
No	132 (88.6%)	18 (90.0%)

Yes	17 (11.4%)	2 (10.0%)
Missing, n (%)	2 (1.3%)	0 (0.0%)

Table 13: Baseline characteristics, excluding patients with prior use of b/tsDMARDs

Variables	**Comparator group N = 20**	**Flixabi N = 6**
Sex, n (%)		
Male	8 (40.0%)	3 (50.0%)
Female	12 (60.0%)	3 (50.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Age, years		
Mean (SD)	58.0 (11.8)	49.0 (14.0)
Median [Q1, Q3]	61.9 [50.7, 67.3]	50.5 [42.1, 58.4]
Min, Max	33.2, 77.3	27.6, 65.0
Missing, n (%)	0 (0.0%)	0 (0.0%)
Age categories 1, n (%)		
<= 50 years	4 (20.0%)	3 (50.0%)
> 50 and <= 60 years	5 (25.0%)	2 (33.3%)
> 60 and <= 70 years	9 (45.0%)	1 (16.7%)
> 70 years	2 (10.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Education level, n (%)		
No school diploma	1 (5.3%)	0 (0.0%)
<= 10 years	14 (73.7%)	2 (40.0%)
> 10 years	4 (21.1%)	3 (60.0%)
Missing, n (%)	1 (5.0%)	1 (16.7%)
Enrolling institution, n (%)		
Rheumatology practice	20 (100.0%)	4 (66.7%)
Rheumatology clinic	0 (0.0%)	2 (33.3%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Average daily glucocorticoid dosis since last visit, n (%)		
No GC	16 (80.0%)	3 (50.0%)
GC > 0 - 5 mg/d	2 (10.0%)	2 (33.3%)
GC > 5 - 10 mg/d	1 (5.0%)	0 (0.0%)
GC > 10 mg/d	1 (5.0%)	1 (16.7%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Actual average daily glucocorticoid dosis, n (%)		
No GC	9 (45.0%)	0 (0.0%)
GC > 0 - 5 mg/d	7 (35.0%)	3 (50.0%)
GC > 5 - 10 mg/d	1 (5.0%)	2 (33.3%)
GC > 10 mg/d	3 (15.0%)	1 (16.7%)

Missing, n (%)	0 (0.0%)	0 (0.0%)
% of full physical function		
Mean (SD)	59.9 (22.5)	79.2 (23.5)
Median [Q1, Q3]	61.1 [36.1, 86.1]	84.7 [72.2, 97.2]
Min, Max	27.8, 94.4	36.1, 100.0
Missing, n (%)	1 (5.0%)	0 (0.0%)
Employment status, n (%)		
Employed	11 (55.0%)	4 (66.7%)
Pension	7 (35.0%)	1 (16.7%)
Unemployed	2 (10.0%)	1 (16.7%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
BMI, categorical, n (%)		
Underweight - under 18.5kg/m²	1 (5.0%)	0 (0.0%)
Normal weight - greater than or equal to 18.5kg/m² to 24.9 kg/m²	4 (20.0%)	3 (50.0%)
Overweight - greater than or equal to 25.0 kg/m² to 29.9 kg/m²	9 (45.0%)	2 (33.3%)
Obesity - greater than or equal to 30 kg/m²	6 (30.0%)	1 (16.7%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Smoking status, n (%)		
Current smoking	9 (45.0%)	2 (33.3%)
Past smoking	7 (35.0%)	0 (0.0%)
Non-smoking	4 (20.0%)	4 (66.7%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Smoking status binary, n (%)		
Ever smoked	16 (80.0%)	2 (33.3%)
Never smoked	4 (20.0%)	4 (66.7%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Year of cohort entry, n (%)		
2017	8 (40.0%)	0 (0.0%)
2018	3 (15.0%)	2 (33.3%)
2019	4 (20.0%)	1 (16.7%)
2020	1 (5.0%)	2 (33.3%)
2021	2 (10.0%)	0 (0.0%)
2022	0 (0.0%)	1 (16.7%)
2023	1 (5.0%)	0 (0.0%)
2024	1 (5.0%)	0 (0.0%)
2025	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Year of treatment start (until 2020 vs. after 2020), n (%)		
Before 2020	15 (75.0%)	3 (50.0%)
2020 or later	5 (25.0%)	3 (50.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
RA disease duration, years		

Mean (SD)	5.3 (4.7)	12.0 (9.5)
Median [Q1, Q3]	4.6 [1.2, 6.9]	10.6 [3.5, 22.0]
Min, Max	0.1, 16.6	1.6, 23.9
Missing, n (%)	0 (0.0%)	0 (0.0%)
DAS28-ESR		
Mean (SD)	4.7 (2.1)	4.9 (1.5)
Median [Q1, Q3]	5.5 [2.3, 6.2]	5.4 [3.8, 6.2]
Min, Max	2.3, 6.2	2.7, 6.3
Missing, n (%)	17 (85.0%)	0 (0.0%)
DAS28-ESR categories, n (%)		
Remission <2.6	1 (33.3%)	0 (0.0%)
Low activity 2.6-3.0	0 (0.0%)	1 (16.7%)
Active disease 3.1-5.0	0 (0.0%)	2 (33.3%)
Very active disease >5.0	2 (66.7%)	3 (50.0%)
Missing, n (%)	17 (85.0%)	0 (0.0%)
ESR, mm/h		
Mean (SD)	40.0 (40.7)	41.3 (40.0)
Median [Q1, Q3]	39.0 [5.0, 75.0]	23.0 [10.0, 84.0]
Min, Max	2.0, 80.0	10.0, 98.0
Missing, n (%)	16 (80.0%)	0 (0.0%)
C-reactive protein, mg/l		
Mean (SD)	17.9 (18.0)	45.0 (46.7)
Median [Q1, Q3]	15.5 [3.2, 26.5]	31.7 [4.0, 82.7]
Min, Max	1.5, 60.0	2.9, 116.7
Missing, n (%)	10 (50.0%)	0 (0.0%)
28 swollen joint count		
Mean (SD)	4.7 (4.8)	6.3 (3.8)
Median [Q1, Q3]	4.0 [1.0, 6.0]	5.5 [4.0, 8.0]
Min, Max	0.0, 18.0	2.0, 13.0
Missing, n (%)	2 (10.0%)	0 (0.0%)
28 tender joint count		
Mean (SD)	6.1 (5.5)	5.8 (4.6)
Median [Q1, Q3]	5.0 [2.0, 8.0]	6.0 [2.0, 8.0]
Min, Max	0.0, 20.0	0.0, 13.0
Missing, n (%)	1 (5.0%)	0 (0.0%)
Rheumatoid factor / ACPA status, n (%)		
Negative	5 (25.0%)	1 (16.7%)
Positive	15 (75.0%)	5 (83.3%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Patient reported pain, NRS (0-10)		
Mean (SD)	6.9 (1.4)	6.3 (2.2)
Median [Q1, Q3]	7.0 [6.0, 8.0]	6.5 [5.0, 8.0]
Min, Max	4.0, 9.0	3.0, 9.0
Missing, n (%)	1 (5.0%)	0 (0.0%)

Patient global health assessment, NRS (0-10)		
Mean (SD)	6.5 (1.5)	5.7 (2.3)
Median [Q1, Q3]	6.0 [5.0, 8.0]	5.5 [4.0, 8.0]
Min, Max	4.0, 9.0	3.0, 8.0
Missing, n (%)	1 (5.0%)	0 (0.0%)
Patient reported fatigue, NRS (0-10)		
Mean (SD)	6.1 (2.5)	3.2 (2.8)
Median [Q1, Q3]	6.0 [5.0, 8.0]	2.5 [1.0, 6.0]
Min, Max	0.0, 10.0	0.0, 7.0
Missing, n (%)	1 (5.0%)	0 (0.0%)
Joint erosions, n (%)		
No	0 (0.0%)	0 (0.0%)
Yes	4 (100.0%)	1 (100.0%)
Missing, n (%)	16 (80.0%)	5 (83.3%)
NSAIDs, n (%)		
No	10 (50.0%)	2 (33.3%)
Yes	10 (50.0%)	4 (66.7%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Analgetics, n (%)		
No	18 (90.0%)	6 (100.0%)
Yes	2 (10.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Coxibe, n (%)		
No	20 (100.0%)	6 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Concomitant csDMARD therapy at treatment start, n (%)		
No	12 (60.0%)	2 (33.3%)
Yes	8 (40.0%)	4 (66.7%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Number of prior csDMARDs, n (%)		
<= 1	2 (10.0%)	0 (0.0%)
2	4 (20.0%)	1 (16.7%)
3+	14 (70.0%)	5 (83.3%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Number of prior b/tsDMARDs, n (%)		
0	20 (100.0%)	6 (100.0%)
1	0 (0.0%)	0 (0.0%)
2	0 (0.0%)	0 (0.0%)
3+	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)

Ever Exposed to Infliximab, n (%)		
No	20 (100.0%)	6 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Comorbidities		
Malignancy, n (%)		
No	20 (100.0%)	6 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Lymphoma, n (%)		
No	20 (100.0%)	6 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Tuberculosis, n (%)		
No	20 (100.0%)	6 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Chronic hepatitis B or C, n (%)		
No	20 (100.0%)	6 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
HIV, n (%)		
No	20 (100.0%)	6 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
CVD, n (%)		
No	20 (100.0%)	6 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Coronary heart disease, n (%)		
No	20 (100.0%)	6 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Heart failure, n (%)		
No	20 (100.0%)	6 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Hyperlipidemia, n (%)		
No	18 (90.0%)	6 (100.0%)
Yes	2 (10.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Hypertension, n (%)		
No	12 (60.0%)	4 (66.7%)
Yes	8 (40.0%)	2 (33.3%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Stroke, n (%)		

No	20 (100.0%)	6 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Diabetes, n (%)		
No	20 (100.0%)	6 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Chronic obstructive pulmonary disease, n (%)		
No	19 (95.0%)	6 (100.0%)
Yes	1 (5.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Chronic kidney disease, n (%)		
No	20 (100.0%)	6 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Gastroduodenal ulcer, n (%)		
No	20 (100.0%)	6 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Osteoporosis, n (%)		
No	20 (100.0%)	6 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
Crohn's disease or ulcerative colitis, n (%)		
No	20 (100.0%)	6 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Missing, n (%)	0 (0.0%)	0 (0.0%)
History of total joint replacement, n (%)		
No	16 (84.2%)	6 (100.0%)
Yes	3 (15.8%)	0 (0.0%)
Missing, n (%)	1 (5.0%)	0 (0.0%)

Table 14 and Table 15 show crude IR for the subgroup analysis within molecule-naive (no prior use of infliximab) and bio-/ts-naive patients, including cases with at least one event in the outcome assessment.

Table 14: Crude IR for immunogenicity in subgroups (both serious and non-serious) applying on-drug approach with risk window 90 days:

	Flixabi					**Comparator group**				
	No.	PY	IR	LCL	UCL	No.	PY	IR	LCL	UCL
No prior use of infliximab	4	36.26	110.31	30.05	282.43	14	195.86	71.48	39.08	119.93

No prior use of b/tsDMARDs	1	9.23	108.37	2.74	603.82	4	31.30	127.79	34.82	327.19

Table 15: Crude IR for VTE in subgroups applying on-drug approach with risk window 90 days:

	Flixabi					**Comparator group**				
	No.	PY	IR	LCL	UCL	No.	PY	IR	LCL	UCL
No prior use of infliximab	1	39.62	25.24	0.64	140.64	0	209.58	0	0	17.6
No prior use of b/tsDMARDs	1	8.27	120.86	3.06	673.39	0	39.71	0	0	92.89

Since there are no events of the outcomes for the ever-exposed method in Flixabi group, the IR was not calculated separately.

10.6 Adverse events

Safety concerns and occurrence of adverse events in special interest within the treatment groups are described in section 10.3. The adverse events reported during Flixabi treatment in the study are presented by SOC and PT in Table 16. Overall, 62 AEs were reported during the RABBIT study for Flixabi.

Table 16: Summary of adverse events/adverse reactions occurring under Flixabi

SOC	**PT**	**Seriousness**		**Total**
		No	**Yes**	
Eye disorders				2
	Dry eye	1		
	Eye inflammation	1		
Gastrointestinal disorders				6
	Colitis ulcerative		1	
	Diarrhoea	2		
	Nausea	1		
	Vomiting	2		
General disorders and administration site conditions				4
	Pyrexia	2		
	Influenza like illness	1		
	Peripheral swelling	1		
Hepatobiliary disorders				1
	Liver disorder	1		

SOC	PT	Seriousness		Total
		No	Yes	
Immune system disorders				2
	Drug hypersensitivity	1		
	Anaphylactic shock	1		
Infections and infestations				10
	Mastitis	1		
	Vaginal abscess	1		
	Herpes zoster	1		
	Oral herpes	3		
	COVID-19	4		
Injury, poisoning and procedural complications				1
	Ligament sprain	1		
Investigations				2
	Transaminases increased	1		
	Epstein-Barr virus test positive	1		
Musculoskeletal and connective tissue disorders				7
	Bone formation increased	1		
	Joint swelling	1		
	Rheumatoid arthritis		1	
	Fibromyalgia		1	
	Pain in extremity	2		
	Tenosynovitis stenosans	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				2
	Monoclonal gammopathy	1		
	Skin papilloma	1		
Nervous system disorders				9
	Headache	2		
	Migraine	1		
	Dizziness	1		
	Hypoaesthesia	2		
	Paraesthesia	1		
	Restless legs syndrome	1		
	Lumbar radiculopathy		1	
Respiratory, thoracic and mediastinal disorders				3

SOC	PT	Seriousness		Total
		No	Yes	
	Pleurisy	1		
	Pulmonary embolism		1	
	Rhinitis allergic	1		
Skin and subcutaneous tissue disorders				10
	Urticaria	1		
	Ichthyosis acquired	1		
	Dry skin	1		
	Neurodermatitis	2		
	Erythema	1		
	Pruritus	1		
	Rash erythematous	1		
	Psoriasis	2		
Surgical and medical procedures				2
	Knee arthroplasty	1	1	
Vascular disorders				1
	Venous thrombosis limb	1		
Total		**56**	**6**	**62**

11 Discussion

11.1 Key results

The final safety study report summarised and analyzed data collected during the observation of patients with RA treated with Flixabi (index group) and patients treated with Infiximab except Flixabi (comparator group) in daily rheumatologic care who were enrolled and followed up in the German biologics RABBIT register between 1 January 2017 and 30 June 2025. The aim of this post-marketing safety study was to investigate relevant safety outcomes associated with Flixabi in comparison to patients treated with drugs from the comparator group. The pre-defined outcomes comprised tuberculosis, serious infections (excluding tuberculosis) / sepsis, congestive heart failure, myocardial infarction, central demyelination / demyelinating disorders, serious hematologic disorders, neoplasms / malignancy, death, serious systemic hypersensitivity reactions / serious infusion reactions, hepatic failure, serious gastrointestinal ulcer / perforation, stroke, venous thromboembolism, pregnancy and pregnancy outcomes, and immunogenicity.

Under the on-drug approach with 90 days risk window, a total of 215 treatment episodes were eligible for the analyses, including 32 episodes based on 32 patients for Flixabi and 183 episodes based on 174 patients for the comparator group. Mean age at index date was 56.7 years in the Flixabi versus 57.0 years in comparator group. Under the ever-exposed approach, some treatment episodes that did not reach the 6 months latency period were excluded from analysis.

No events occurred in the Flixabi group for several pre-defined safety outcomes where events were observed in the comparator group, including serious infections/sepsis (0 vs. 5 events; IR 0 vs. 19.93 per 1,000 PY), myocardial infarction (0 vs. 2 events; IR 0 vs. 7.87 per 1,000 PY), neoplasms/malignancies (0 vs. 4 events; IR 0 vs. 16.15 per 1,000 PY), serious hematologic disorders (0 vs. 1 event; IR 0 vs. 3.92 per 1,000 PY), demyelinating disorders (0 vs. 1 event; IR 0 vs. 3.92 per 1,000 PY), serious gastrointestinal ulcer/perforation (0 vs. 1 event; IR 0 vs. 3.92 per 1,000 PY), stroke (0 vs. 1 event; IR 0 vs. 3.92 per 1,000 PY), and death (0 vs. 1 event; IR 0 vs. 3.91 per 1,000 PY).

One case of VTE was observed in the Flixabi treatment group. No VTE events were recorded in the comparator group. The unadjusted IR of VTE in the Flixabi group was 17.52 (95% CI: 0.44–97.63), while the unadjusted IR in the comparator group was 0, as no cases occurred.

For any immunogenicity, five events were observed in the Flixabi group, corresponding to an unadjusted IR of 96.65 (95% CI: 31.38–225.54) within 51.73 PY. In the comparator group, 14 events were observed, with an unadjusted IR of 57.9 per 100 PY (95% CI: 31.65–97.14) over 241.81 PY.

HRs for immunogenicity (serious and non-serious) were estimated using three Cox regression models, none of the results showed a significant increase. In the unadjusted analysis (Model A), the HR was 1.88 (95% CI: 0.65–5.46). After adjustment for age and sex (Model B), the HR was 1.87 (95% CI: 0.64–5.47). In Model C, which incorporated additional adjustments, the HR was 2.16 (95% CI: 0.59–7.87). The comparator group served as the reference category in all models.

Across all Cox regression models, the confidence intervals included one, indicating no statistically significant difference in risk between the treatment groups.

Subgroup analyses

(1) Immunogenicity (serious and non-serious)

Among patients with no prior use of infliximab, four hypersensitivity events occurred in the Flixabi group over 36.26 PY, corresponding to an IR of 110.31 (95% CI: 30.05–282.43). In the comparator group, 14 events were observed over 195.86 PY, resulting in an IR of 71.48 (95% CI: 39.08–119.93).

In the subgroup with no prior use of b/tsDMARDs, one hypersensitivity event occurred in the Flixabi group over 9.23 PY, corresponding to an IR of 108.37 PY (95% CI: 2.74–603.82). In the comparator group, 4 events were observed over 31.30 PY, yielding an IR of 127.79 (95% CI: 34.82–327.19).

(2) VTE

Among patients with no prior use of infliximab, one VTE event occurred in the Flixabi group over 39.62 PY, corresponding to an IR of 25.24 (95% CI: 0.64–140.64).

In the subgroup with no prior use of b/tsDMARDs, one VTE event was observed in the Flixabi group over 8.27 PY, corresponding to an IR of 120.86 (95% CI: 3.06–673.39).

No events were reported during the follow-up period for any other outcome of interest under the exposure to Flixabi.

11.2 Limitations

General limitations lie within the study design on which this final report is based. Observational cohort studies on drug treatment examine unselected patients in daily care. Due to non-randomisation of patients to defined treatment arms, these studies are prone to confounding by indication. Treatment decision and therefore exposure to a DMARD are usually based on the availability of drugs, the provider's experience treating patients with them and on patients' characteristics such as age, severity

of symptoms, disease course and specific comorbidities. There may be a channelling of patients with a more severe disease of RA to certain therapies. Even after careful adjustment, such confounding can never be entirely ruled out. Since observational studies follow patients over very long time periods, they are also prone to attrition bias, i.e. selective loss to follow-up. However, drop-out rates in the RABBIT register are rather low.

Another limitation of this study may arise from differences in the observation period. After 2023, no new Flixabi patients were included. We cannot rule out a bias introduced by the selection of the study period.

Given the small number of patients and observed events, the IR and HR estimates are associated with wide confidence intervals; therefore, the findings should therefore be interpreted with caution.

11.3 Interpretation

This PASS was conducted to evaluate the safety profile of Flixabi compared to other infliximab products (originator and biosimilars) in patients with rheumatoid arthritis using real-world data from the German RABBIT register. The study objectives were met by comparing unadjusted incidence rates and multivariable-adjusted risks for pre-defined safety outcomes between treatment groups. For immunogenicity, the only outcome with sufficient events for regression analysis, the adjusted hazard ratio was 2.16 (95% CI: 0.59–7.87), with confidence intervals including 1 across all models, indicating no statistically significant difference between groups. One VTE event occurred in the Flixabi group, resulting in an unadjusted IR of 17.52 per 1,000 PY (95% CI: 0.44–97.63); however, the substantially wide confidence interval reflects considerable imprecision in the estimate due to the limited number of Flixabi-exposed patients (32 episodes) and low event counts, precluding definitive statistical interpretation of the safety findings. No new or unexpected safety signals were identified during the follow-up period from January 2017 to June 2025. The safety findings are consistent with the current Summary of Product Characteristics and Risk Management Plan of Flixabi. However, study limitations must be acknowledged, including the small sample size, low event rates resulting in wide confidence intervals, the observational design prone to confounding by indication, and the fact that no new Flixabi patients were enrolled after 2023, which may introduce selection bias. Despite these limitations, the available evidence suggests that Flixabi demonstrates a comparable safety profile to other infliximab products.supporting the continued favorable benefit-risk balance of Flixabi in the treatment of rheumatoid arthritis.

11.4 Generalisability

In general, RABBIT is a nationwide, population-based cohort study including non-selected patients with established RA in daily routine rheumatological care. No inclusion or exclusion criteria are applied, except that patients must be at least 18 years old at enrolment, have a rheumatologically confirmed diagnoses of RA, experienced RA disease onset after the age of 15, and start a new DMARD treatment. Consequently, the generalisability of the RABBIT results is higher than that of clinical trials. However, the generalisability to the entire field of rheumatology in Germany is limited by differences in prescribing practices between individual institutions. As far as generalisability to patients of other countries is concerned, this could also be limited by the fact that therapeutic decision-making may vary across countries depending on the healthcare system, availability of treatments and requirements.

12 Other information

Not applicable.

13 Conclusion

The use of Flixabi as a treatment option for patients with RA was limited within the RABBIT register. Only a small number of events related to the outcomes of interest were reported among patients exposed to Flixabi. Unadjusted IR were reported for immunogenicity and VTE however risk estimates could be calculated solely for immunogenicity using adjusted methods for cases of any seriousness due to limited number of events.

No new or unexpected safety signals were observed for the evaluated outcomes in patients exposed to Flixabi during the follow-up period from 1 January 2017 to 30 June 2025. However, given the limited sample size and low event rates, the results should be interpreted with caution, and conclusions regarding safety are constrained by these limitations.

14 References

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Appendices

Annex 1. List of stand-alone documents

Statistical Analysis Plan

Annex 2. Additional information

Standardized mean differences (SMD)

Model C (PS based IPTW, adjusted)

Variable	Original	Weighted
Age >50 - ≤60 years (vs. age ≤ 50 years)	-0.130	-0.142
Age >60 - ≤70 years (vs. age ≤ 50 years)	0.167	0.212
Age >70 years (vs. age ≤ 50 years)	0.074	0.039
DAS28-ESR	-0.402	-0.021
Treatment start 2020 (vs. treatment start before 2020)	0.371	0.214
Female sex (yes vs. no)	-0.037	-0.022
FFbH	0.259	0.169
Glucocorticoids > 0 - ≤ 5 mg mean daily dose mg in 6 months prior to index date	0.037	0.118
Glucocorticoids > 10 mg mean daily dose mg in 6 months prior to index date	0.052	-0.068
Glucocorticoids > 5 - ≤ 10 mg mean daily dose mg in 6 months prior to index date	.0.524	0.478
Ever smoker (yes vs. no)	-0.007	-0.141
RF / ACPA positive (yes vs. no)	-0.023	-0.162
prior b/tsDMARD therapy (yes vs. no)	0.220	0.071
RA disease duration	0.189	-0.091

Statistical Analysis Plan

1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the planned statistical analysis to be performed and included in the final summary report for Flixabi (=index drug) by using data from the Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) registry in Germany. It is based on the updated RABBIT study protocol version from 1 January 2021. This SAP describes the statistical methods as well as the measures to be used in addressing the objectives, such as demographic and baseline characteristics, treatment exposure, and safety outcomes of interest.

Safety outcomes, statistical methods, and the covariates used for adjustment in the final study report were agreed between the RABBIT registry holder and the sponsor prior to the conduct of the formal statistical analyses.

1.1 Analysis Objectives

The primary objective of this analysis is the investigation of relevant safety outcomes in patients with rheumatoid arthritis (RA) by:

- Evaluating and comparing crude, unadjusted incidence rates (IR) of pre-defined outcomes in patients exposed to Flixabi (index drug group), and patients treated with infliximab (biologic original (BO) and biosimilar (BS)) except Flixabi (comparator group).
- Estimating and comparing the risk of pre-defined outcomes in patients exposed to index drug in comparison to patients exposed to drugs from the comparator group by applying multivariable adjusted analyses.

1.2 Milestones for the Final Report

The RABBIT registry is an independent study that enrols patients treated with biologic (b)-, conventional synthetic (cs)- and targeted synthetic (ts) disease-modifying anti-rheumatic drugs (DMARDs) beyond the patients included in this study. The milestones in Table 1 therefore include dates that are relevant to the registry but that precede the start of the current study.

Table 1: Milestones of the final report.

Milestone	**Planned date**	**Comments**
Start of data collection in RABBIT cohort 2	1 January 2007	No comments
Enrolment period of the RABBIT cohort	Ongoing	Ongoing enrolment of patients
End of data collection in RABBIT	5 years after inclusion of the last patient	No comments
Start of enrolment of patients on index drug	1 January 2017	No comments
End of enrolment of patients on index drug	Ongoing	Ongoing enrolment of patients
Study progress reports for index drug	Semi-annually	No comments
Start of enrolment and data collection for this report	1 January 2017	No comments
End of enrolment and data collection for this report	30 June 2025	No comments
Database closing data for this report	30 June 2025	No comments
Final SAP for the report		The SAP was finalised on
Final report of index drug	31.03.2026	No comments

2 Statistical Methods

2.1 Data source

This study is based on data of the German biologics registry RABBIT. RABBIT is a prospective observational, longitudinal cohort study to assess the short- and long-term safety and effectiveness of b- and tsDMARDs licensed for the treatment of patients with RA. A control cohort of patients treated with csDMARDs is followed-up in parallel. RABBIT was established in May 2001 in Germany as an independent nationwide ongoing cohort study.

Patients with RA are enrolled in RABBIT and observed in routine clinical care by the treating rheumatologists. The following inclusion criteria must be fulfilled at enrolment:

- age at enrolment >17 years
- age at onset of RA >15 years
- rheumatologist confirmed diagnosis of RA (until 2016, patients had to fulfil at least four of the seven 1987 criteria of the American College of Rheumatology; since 2017, indicating the number of ACR criteria fulfilled is required).
- initiating treatment with a bDMARD (BO or BS), with a tsDMARD, or with a csDMARD (without concomitant b/tsDMARD therapy) after at least one prior DMARD treatment

Due to the inclusion criteria, patients can be enrolled at different stages of the RA disease, and they are not assigned to specific treatments through randomization. Data is reported by physicians and patients at predefined time points of follow-up (enrolment/baseline, at 3 and 6 months, thereafter every 6 months). Once enrolled, patients are followed regardless of treatment changes, treatment cessation or treatment initiation. The type of the treatment administered and the conduct of individual therapy, including dosages, is solely determined by the treating physician in agreement with the patient. Consequently, there is no influence on any treatment decision by the principal investigators, the scientific advisory board, or the pharmaceutical companies sponsoring the study.

After five years of observation, observation time can be extended for another five years.

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

Further details are given in the RABBIT study protocol.

2.2 Study design

This is a non-interventional post-authorisation safety study using data collected by the RABBIT registry. The final report will include therapy and safety data from patients with RA initiating the index drug or a drug from the comparator group from 1 January 2017 until 30 June 2025.

2.3 Study population

The study population consists of patients enrolled in RABBIT that started a treatment with the index drug or a drug from the comparator group from 1 January 2017 until 30 June 2025. General inclusion criteria of patients enrolled into the RABBIT register are given in section 2.1.

The following patients will be included in the final report:

- Index drug group: Patients who initiated Flixabi.
- Comparator group: Patients who initiated infliximab-BO or infliximab-BS except Flixabi.

2.4 Outcomes of interest

Safety outcomes are primarily based on the safety concerns in the index drug risk management plan that are indicated to be addressed by the RABBIT registry study as an additional pharmacovigilance activity. The outcomes to be investigated in the final report are given in Table 2. The definition of outcomes is based on the semi-annual reports provided to the marketing authorisation holder using the Manchester template if not otherwise indicated. AEs and SAEs are registered continuously in a separate AE database. Diagnoses are coded using the Medical Dictionary for Regulatory Activities (MedDRA) on the preferred term(PT) level. The AE/SAE database is updated with every update of MedDRA.

All other suspected adverse reactions reported from the investigators and assessed at the individual case level should be provided and discussed in terms of seriousness.

Summary tabulations of all adverse events/adverse reactions related to Flixabi which are organised by MedDRA system organ class (SOC) on PT level should be provided.

Table 2: Outcomes of interest

Outcome	**Outcome definition**
Safety endpoints as listed in the study protocol:	
Tuberculosis	Based on semi-annual reports
Other serious infections (e.g. pneumonia, infections of the CNS, septicemia, bone or joint infections, opportunistic infections)	Based on semi-annual reports
Congestive heart failure	Based on semi-annual reports
Myocardial infarction	Based on semi-annual reports
Central demyelination	Based on semi-annual reports
serious hematologic disorders (e.g. bone marrow depression, hypoplastic anemia**)**	Based on semi-annual reports
neoplasms (lymphomas, solid malignancies, other neoplasms)	Based on semi-annual reports
deaths	Based on semi-annual reports
serious systemic hypersensitivity reactions / serious infusion reactions	Based on semi-annual reports
hepatic failure	Based on semi-annual reports
serious gastrointestinal ulcer/perforation	Based on semi-annual reports
stroke	Based on semi-annual reports
VTEs (deep vein thrombosis, DVT postoperative, pulmonary embolism, postprocedural PE, venous thrombosis limb)	Based on semi-annual reports
pregnancies and their outcomes	Based on semi-annual reports
Safety concerns (RMP, mail from 11.06.2025)	
Serious infections/sepsis	SOC Infections and infestations
DEMYELINATING DISORDERS (including Multiple Sclerosis, Guillain-Barré Syndrom, Optic Neuritis)	HLGT Demyelinating disorders, PT Chronic inflammatory demyelinating polyradiculoneuropathy, Demyelinating polyneuropathy, Guillain-Barre syndrome, Miller Fisher syndrome, Multifocal motor neuropathy, Optic neuritis, Anti-myelin-associated

	glycoprotein associated polyneuropathy
BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure	SOC Pregnancy, puerperium and perinatal conditions
MALIGNANCY	SMQ (Narrow) Malignant or unspecified tumours
IMMUNOGENICITY	SMQ (Broad) Hypersensitivity, SMQ (Narrow) Hypersensitivity

2.5 Treatment exposure groups

Treatment exposure will be categorized into the following groups:

- **Index drug group**: patients initiating a treatment with index drug (Flixabi). This group includes both bio/ts-naïve and bio/ts-experienced patients.
- **Comparator group**: patients initiating a drug with the active compound infliximab approved for the treatment of RA except Flixabi. This group includes both bio/ts-naïve and bio/ts-experienced patients. The following drugs are eligible: Remicade, Zessly, Remsima and Inflectra.

2.6 Treatment assignment and calculation of the time at risk (patient years)

A patient will be assigned to a treatment exposure group when initiating treatment with one of the drugs from the respective treatment exposure group.

If patients receive concomitant treatment with csDMARD(s), they will still be assigned to the index drug group or comparator group.

Different definitions for the time at risk (patient years, PY) will be applied.

- On-drug approach: Time at risk will be calculated from drug initiation until the occurrence of the event of interest, the stop of treatment, death, end of follow-up, or end of data collection, whichever occurs first. Starting with the first month after discontinuation, an additional three months of exposure (risk window) will be added. In the case that a new treatment is started within the 3-months risk window, and an event occurs within that time, it will be assigned to both groups as will the corresponding PY since index date to the respective group. A limitation of this approach is that effects of the drugs that may need longer time to develop may not be captured, due to censoring three months after drug discontinuation.
- Ever-exposed approach: Time at risk will be calculated from the index date until the occurrence of the event of interest, death, end of follow-up, or end of data collection, whichever occurs first. A patient is considered as once exposed, always at risk, despite switching to another drug. To calculate the index date, a latency period of 6 months after drug initiation is applied to account for the slow development of events, as well as to deal with reverse causation and detection bias. A limitation of this approach is that the time between measurement of the adjustment variables and occurrence of events may be considerable.

2.7 Allocation of events to treatment exposure groups

Events will be allocated to a treatment exposure group if the event occurs during the time at risk of the respective exposure group.

Depending on the outcome of interest, different approaches will be applied:

- On-drug approach: applies to all outcomes
- Ever-exposed approach: applies only to malignancy

2.8 Statistical analyses

Patient characteristics at baseline:

Depending on the treatment a patient receives, he/she will be assigned to the respective treatment exposure group. The treatment exposure groups will be described a) at the time of enrolment into the study (every patient counts only once) and b) at the time of the start of a new treatment either at enrolment or during follow-up observation. In the latter case, every new treatment start will be considered as baseline. This implies that patients can contribute to several exposure groups during the time of observation, and also several times to one exposure group. As summary measures, mean with standard deviation (for continuous variables) or numbers and their according proportion (for categorical variables) will be calculated.

Incidence rates (IR):

For calculating crude, unadjusted IRs, the first event per patient will be taken into account. Pre-defined safety outcomes (table 2) will be listed as cumulative number of incident events during the time of observation, total PY, IR per 1,000 PY, and 95% confidence interval. The calculation of PY is based on the sum of the months at risk per patient and exposure group divided by twelve. To calculate confidence intervals, a Poisson distribution will be assumed.

Relative risk:

Relative risk for an outcome in the index drug group compared to the comparator group will be calculated by Cox regression models with a robust variance estimator capable of handling dependencies between observations as well as some potential deviations from model assumptions, applying propensity score (PS) based inverse probability weights (IPW) methods to control for confounding by indication when estimating the average treatment effect (ATE).

The PS for each patient will be estimated using multivariable logistic regression analysis, in which the outcome is set as the assigned treatment. The PS will be calculated as the predicted probability of initiating the exposure of interest. Propensity scores will be calculated for each outcome separately. Confounders to be added to the PS are presented in Table 3. Models will be calculated with three different sets of covariables (A, B and C). PS weights will be stabilized and winsorized below the 1st percentile and above the 99th percentile. Stabilized weights will be used to reduce variability induced by subjects with large weights and calculated by multiplying the IPW by the proportion of treated or untreated patients depending on the treatment status of the patient. Histograms will be produced to visually depict the overlap in PS in the two treatment groups being compared. Standardized mean differences (SMD) will be used to compare the balance in baseline covariates between treatment exposure groups. The cut-off SMD value indicating relevant imbalance will be chosen as 0.1 (10%). Variables for which this imbalance criterion is not met will be added as additional covariables to the Cox model. Generally, models will only be calculated if the amount of overfitting is acceptable. The amount of overfitting is deemed as acceptable if the number of covariables in the model is less than m/10, where m is the number of events for the considered outcome (Harrell, F.E. (2015), Regression Modeling Strategies, Springer, 2nd edition, page 72).

On-drug approach: The PS will be calculated at the time of each new treatment initiation to model treatment decision. For treatments started at enrolment, data for covariates of the PS will be taken

from the enrolment visit. For treatments started during follow-up, data for covariates of the PS will be taken from the visit date occurring most recently prior to the treatment start date. This means that to adjust for confounding, only covariates measured before or at the time of the new treatment start will be included as covariates to estimate the IPW. For time-varying covariates, the measurements closest in time before the switch to the drug under investigation will be used (defined as baseline for this drug). This allows to control for factors that are proximally related to the treatment switch. Covariates affected by the exposure and assumed to be in the causal path from exposure to outcome (intermediate variables) will not be included in the model as the total causal effect cannot be estimated. Outcome-specific exclusions of patients will be done prior to calculation of the PS (e.g., exclusion of patients with prior malignancies to investigate incident malignancy). Treatment episodes will be handled in the regression analysis by applying extended Cox models (Andersen-Gill).

Ever-exposed approach: The PS will be calculated using data for the covariates from the time of enrolment, without including intermediate variables as explained for the on-drug approach. Likewise, outcome-specific exclusions of patients will be done prior to calculation of the PS. In the ever-exposed approach, PS will be calculated per patient (and not per treatment episode as it is done for the on-drug approach). A Cox proportional hazard regression analysis will be applied.

Unadjusted and adjusted Hazard ratios (HR) and 95% confidence intervals will be provided. Confounders for the Cox regression analyses are given in Table 3. They were pre-defined, in agreement with recommendations from the RABBIT scientific advisory board (and aligned with previous publications from RABBIT). No unadjusted/adjusted Cox analyses will be done for safety outcomes with <4 events in the index drug group.

Table 3: Confounders for the Cox regression analysis.

	Infections	Malignancies	All outcomes but infections and malignancies
Model A	None (crude/ unadjusted)	None (crude/ unadjusted)	None (crude/ unadjusted)
Model B	Age[#] Sex (male vs. female)	Age[#] Sex (male vs. female)	Age[#] Sex (male vs. female)
Model C	PS based IPW *General covariates:* Age[#] Sex (male vs. female) RA disease duration RF/ ACPA (no vs. yes) Year of treatment start (until 2020 vs. after 2020)[#] DAS28 FFbH prior b/tsDMARDs (0 vs. ≥ 1)[#] Glucocorticoid dosage (<5 vs. 5-<10 / ≥ 10 mg/d)[#] Smoking (never vs. ever) *Outcome-specific covariates:* COPD (no vs. yes) Chronic renal disease (no vs. yes)	PS based IPW *General covariates:* Age[#] Sex (male vs. female) RA disease duration RF/ ACPA (no vs. yes) Year of treatment start (until 2020 vs. after 2020)[#] DAS28 FFbH prior b/tsDMARDs(0 vs. ≥ 1)[#] Glucocorticoid dosage (<5 vs. 5-<10 / ≥ 10 mg/d)[#] Smoking (never vs. ever) *Outcome-specific covariates:* None	PS based IPW *General covariates:* Age[#] Sex (male vs. female) RA disease duration RF/ ACPA (no vs. yes) Year of treatment start (until 2020 vs. after 2020)[#] DAS28 FFbH prior b/tsDMARDs (0 vs. ≥ 1)[#] Glucocorticoid dosage (<5 vs. 5-<10 / ≥ 10 mg/d)[#] Smoking (never vs. ever) *Outcome-specific covariates:* None

All covariates without further specification of categories are captured in a continuous way.

[#] For these confounders, the RABBIT team may deem it necessary to change the way in which they are considered in the model. For instance, it may be necessary to account for nonlinear effects for age. For prior bDMARDs, chosen categories might lead to considerable imbalances due to very different distributions of this confounders for the exposure groups. For year of treatment start, different time patterns might lead to considerable imbalances. For glucocorticoid dosage, low numbers for the category "≥ 10 mg/d " might require to combine categories. It might thus be necessary to change the category definitions.

Abbreviations: ACPA = anti-citrullinated protein antibodies; COPD = chronic obstructive pulmonary disease; DAS28 = disease activity score based on 28 joints; FFbH = functional capacity measured by Hannover Functional Status Questionnaire; IPW = inverse probability weights; PS = propensity score; RF = rheumatoid factor.

Additional analyses:

The following subgroup analyses for IRs will be performed if feasible:

- Excluding patients with prior use of infliximab (i.e. patients must be molecule-naive): all outcomes
- Excluding patients with prior use of b/tsDMARDs (i.e. patients must be b/tsDMARD naive): all outcomes
- Stratified analyses by age <65 versus ≥65 years: for serious infections and malignancies

Missing data:

Proportion of missing data will be provided for the main baseline variables and missing information will be addressed by single imputation. The single imputation will be performed by regression with fully conditional specification, including the covariates from Table 3 model C and the outcome. Statistical analyses will then proceed as normal. The robust variance estimator used for all Cox models is expected to avoid an undesired impact of the additional variance of the imputation method on the estimates.