Comparative safety report on RoActemra in ARTIS, analyses through Dec 31st 2016

Introduction

In Sweden, tocilizumab was first made available for the treatment of RA in 2009. From the launch, it has been monitored by the Swedish Biologics Register ARTIS (Anti-Rheumatic Treatment in Sweden) in collaboration with the Swedish Medical Products Agency. Built on the already existing SRQ, (see below), ARTIS was initiated with the introduction of etanercept, the first biological Disease Modifying Anti-Rheumatic Drug (DMARD), in 1999, and serves as a national surveillance program for investigation of safety and effectiveness of new anti-rheumatic drugs. Figure 1 below depicts the accumulated number of patients.

Use of biological treatments in Sweden has never been subject to any formal approvals (with the exception of a period during 2002-2003, when the availability of etanercept was restricted due to manufacturing issues) or mandatory treatment histories or disease indices. Instead, the decision to treat with biologics lies, and has always resided, with the treating rheumatologist. The Swedish Rheumatology Association has issued guidelines for the use of biologics. These guidelines are revised on an annual basis.

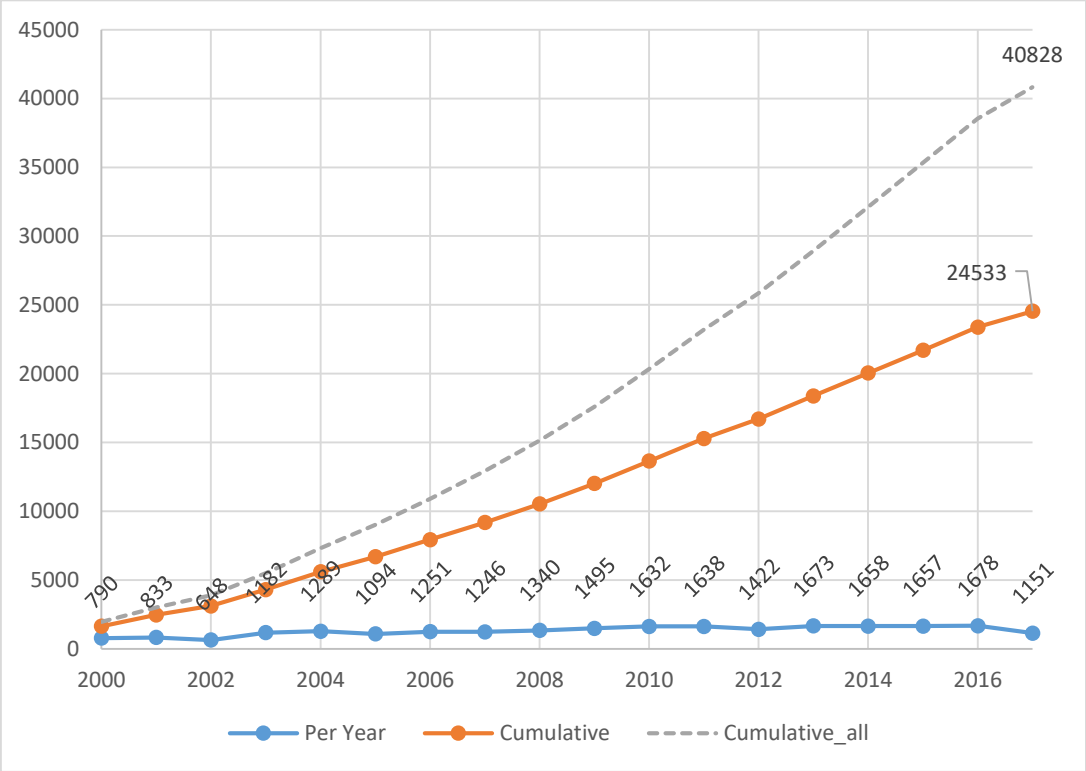

Figure 1. Accumulated number of first ever biologics starts registers in the Swedish Rheumatology Quality Register (SRQ), specifically in its biologics module (ARTIS). Dashed line = across all Rheumatology indications, bold line = RA. Because of sequential discontinuations and switches to a second or third biologic, the total number of biologics treatment initiations is higher (>80,000 treatment starts).

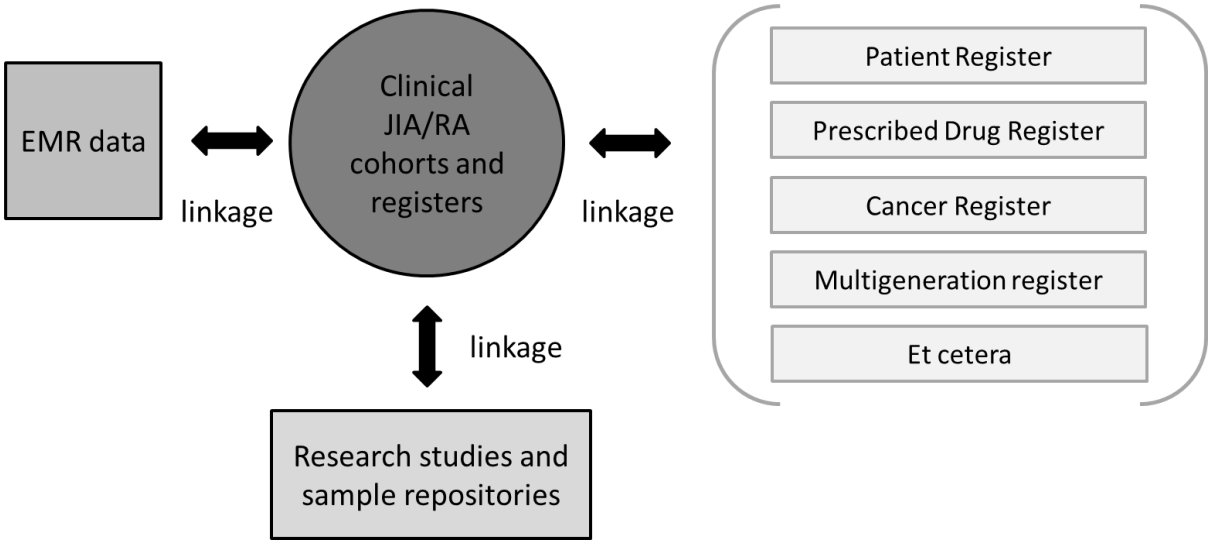

Figure 2. Schematic illustrating how different types of Swedish data may be deterministically linked together. SRQ/ARTIS constitute an example of data sources in the grey circle. EMR Electronic Medical Record.

Roche has had agreements with Karolinska Institutet regarding the safety monitoring of tocilizumab as used in the treatment of RA in Sweden. In these agreements, safety data from the ARTIS program came from two sources:

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

(ii) Data from SRQ/ARTIS are (on a regular basis) linked to data from other national Swedish registers, as depicted in the figure 2 above and further described in the subjects and methods section.

The resulting linkage database is used for all scientific safety reports from ARTIS. Over the years, ARTIS has published on different aspects of safety of biological therapies, including reports on serious infections, TB, malignant lymphomas, other malignancies, cardiovascular risks, and on many other aspects.[1-53] In most of these reports, which all have used a design, comparators, and analytic approach tailored to assess the outcome under study as optimally as possible, biological DMARDs have been assessed as either TNF inhibitors as a class or as non-TNF inhibitors as another class.

In this report, a singular design and analytical framework has been used for the assessment of all safety outcomes under study. As a consequence, this report is comprehensive (all pre-defined safety outcomes in one report) but also include exposure contrasts and time-frames that might not otherwise have been used for each specific outcome. Of note, the main comparison will be to all biological DMARDs (other than tocilizumab), combined in one class.

Objectives

The objective of these analyses is to provide an assessment of pre-specified safety outcomes for tocilizumab as used in the treatment of RA in Sweden. Tocilizumab was approved by EMA 15th January 2009, and has been on the Swedish market soon after. The current analyses are using data from the ARTIS system, 2009 and onwards

Subjects and Methods

Setting

Swedish health-care is tax-funded and offers universal access. Hospital referral is based on geography rather than insurance-status. Patients with RA are typically treated by rheumatologists, the vast majority of whom work in public and hospital-based clinics. Health- and demographic information is recorded in a series of registers with a very high degree of completeness resulting from the mandatory and semi-automated registration. Based on each Swedish resident's unique personal identification number, issued to all Swedish residents alive in 1947 or born thereafter, linkage of data from different registers is possible.[54] The registers are maintained by governmental bodies (the main registers used in this project are held by the National Board of Health and Welfare *(Socialstyrelsen)* and Statistics Sweden), who may perform data linkages and provide de-identified data for research purposes.

Data sources

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

The Swedish Rheumatology Quality of Care Register (SRQ) and ARTIS.
The Swedish Rheumatology Quality Register (SRQ) was started in 1995 by the Swedish Rheumatology Society to improve the healthcare and treatment for patients with rheumatoid arthritis (RA). SRQ followed on regional registry initiatives, to enable a national real-world documentation of many different aspects of RA and developed over time into a harmonized national registry. SRQ was started mainly for patients with RA, but over time it has been expanded to cover several other rheumatic diseases including ankylosing spondylitis and psoriatic arthritis, myositis, systemic lupus erythematosus and additional conditions. Its biologics component ARTIS, is a profession-based register. It covers around 90% of all biologic initiations in Sweden after 1999.[55] Currently, some 21,500 patients with RA initiating some 45,000 biological treatments are enrolled in ARTIS. The SRQ also contains early RA patients, and increasingly, RA patients can be followed from their first RA diagnosis and onwards. In conjunction with each patient visit, the treating rheumatologist enters data on disease activity and anti-rheumatic treatment.

The Swedish Patient Register

The Swedish Patient Register collects information on all hospitalized (inpatient treated) patients, and all visits to non-primary outpatient care (such as a visit to a rheumatologist). Diagnoses are assigned by the discharging physician, as well as date of discharge, discharging hospital and department. Diagnoses are coded according to the ICD, with version 8 used until 1986, version 9 from 1987 to 1996 and ICD10 since 1997. The inpatient component was originally initiated by several counties in 1964, had 85% country-wide coverage in 1983, and is considered complete since 1987. Validation against medical files have found an overall error rate in the main diagnoses of 4% at the ICD chapter level, and 12% at the three digit level.[56] The outpatient component of the Patient register was initiated with nationwide coverage in 2001. Overall, 13% of outpatient visits lack records, but coverage is higher for somatic public care (including most rheumatology care). Chart reviews and validation of the RA diagnosis based on different algorithms applied to the register data indicate a positive predictive value for a register-based diagnosis of RA around 90%.[57,58]

The Swedish Cancer Register.

The Swedish Cancer Register was established in 1958 and contains information on date of cancer (and some selected pre-cancers) onset, and type of cancer according to the ICD classification and morphology/histology. About 99% of cancers have been morphologically verified. Reporting of incident cancers (including invasive malignancies as well as cancer in situ) is mandatory and semi-automated, resulting in an estimated coverage greater than 95%.[59,60]

The Cause of Death Register

The Cause of Death Register is a national register containing information on date and cause of death (underlying and contributory) for all deceased residents, including deaths among Swedish residents who died abroad. The register was started in 1952, and the data is considered complete since 1961. From that year and onward, cause of death is missing for less than 0.5% of deceased individuals, and in 2002, a validation study estimated that only 3.3% had any errors at the three digit level of the ICD-coded underlying cause of death.[61]

The Total Population Register

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

Cohort definitions

Main cohort

All RA patients initiating their first ever treatment with tocilizumab in 2009-2016. This cohort was defined as all patients with RA in ARTIS (a rheumatologist-entered diagnosis of seropositive, seronegative, or unspecified RA) starting tocilizumab as their first or later biological treatment. Crude and standardized rates are presented stratified by previous biological treatment. Entry is defined as date of first tocilizumab treatment start.

Comparator cohorts

A) ***tocilizumab-naïve RA patients initiating a third treatment with a non-tocilizumab biologic agent*** in 2009-2016 This cohort is defined as all patients with RA in ARTIS (a rheumatologist-entered diagnosis of seropositive, seronegative, or unspecified RA) starting infliximab, etanercept, adalimumab, golimumab, rituximab, abatacept, certolizumab pegol, or anakinra as their third biologic treatment. Treatments with the same biologic were counted as separate biological treatments if the previous treatment had been registered as discontinued, and more than 90 days (180 days for rituximab) had passed between discontinuation and the next initiation. Entry is defined as date of treatment start.

B) ***tocilizumab-naïve RA patients initiating a second treatment with a non-tocilizumab biologic agent*** in 2009-2016. This cohort is defined as all patients with RA in ARTIS (a rheumatologist-entered diagnosis of seropositive, seronegative, or unspecified RA) starting infliximab, etanercept, adalimumab, golimumab, rituximab, abatacept, certolizumab pegol, or anakinra as their second biologic treatment. Treatments with the same biologic were counted as separate biological treatments if the previous treatment had been registered as discontinued, and more than 90 days (180 days for rituximab) had passed between discontinuation and the next initiation. Entry is defined as date of treatment start.

C) ***Biologics-naïve RA patients initiating a first treatment with a non-tocilizumab biologic agent*** in 2009-2016. This cohort is defined as all patients with RA in ARTIS (a rheumatologist-entered diagnosis of seropositive, seronegative, or unspecified RA) starting infliximab, etanercept, adalimumab, golimumab, rituximab, abatacept, certolizumab pegol, or anakinra as their first ever biologic treatment. Entry is defined as date of treatment start.

D) ***Biologics-naïve RA patients.*** This cohort is defined as all patients with RA, defined as 2+ registrations with RA in the Patient Register 1996 or later, one of which at a department of rheumatology or internal medicine, as has been used in previous ARTIS publications. Entry is defined as the first date when all inclusion criteria were fulfilled 2009-2016.

E) ***The general Swedish population.*** The collective study population in the biologics-treated cohorts was matched (1:5, by year of birth, sex, county of residence and vital status at the date of first identification of RA 2001-) to the Swedish Population Register. Date of entry in the general population comparator cohorts was set to date of entry of their corresponding RA patient.

Follow-up time and risk windows

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

- outcome of interest (see below),
- first date of emigration from Sweden,
- date of death,
- December 31st 2016

In analyses of cancer incidence, the patients were considered "ever exposed" to their respective cohort membership. Follow-up of all other (non-cancer) outcomes also ended:

- 90 days after discontinuing current biological treatment (where applicable)
- 180 days after discontinuing current treatment with rituximab (where applicable)
- when the patient transitioned to another cohort

Examples of the last point include when a member of the general population cohort developed RA, or a member of cohort C (first-ever initiators of a non-tocilizumab biologic) initiated a second non-tocilizumab biologic treatment.

Outcomes

The following 16 outcomes were analyzed:

1) Hospitalized infections
2) Tuberculosis
3) Opportunistic Infections
4) Malignancy excluding non-melanoma and basal cell invasive/non-invasive skin cancers
5) Non-melanoma and basal cell invasive/non-invasive skin cancers
6) Lymphoma
7) Demyelinating disorders
8) Fatal cardiovascular event
9) Myocardial infarction
10) Stroke
11) Acute cardiovascular event, combining outcomes 7-9
12) Gastro-intestinal perforation
13) Aplastic anemia
14) Serious hepatic event
15) Hospitalizations irrespective of cause (all-cause hospitalization)
16) All-cause mortality

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

Table 1. Outcome Definitions

Outcome	ICD10 codes	Data source
Hospitalized Infections	A00-B99 (excluding A33 and A50), D73.3, E32.1, G00-G02, G04.2, G05-G07, H00.0, H44.0, H60.0-H60.3, H66-H67, H70, I30.1, I40.0, J00-J22, J32, J34.0, J36, J39.0-J39.1, J44.0, J85, J86, K04.4, K04.6, K04.7, K10.2, K11.3, K12.2, K14.0, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.1, K65.2, K65.9, L00-L08, L30.3, M00-M01, M46.2-M46.5, M60.0, M65.0, M71.0, M71.1, M72.6, M86, N13.6, N15.1, N15.9, N30.0 N30.8, N34.0, N41.2, N43.1, N45.2, N45.3, N45.4, N48.2, N61, N70, N73, N75.1	Main diagnosis in inpatient component of Patient Register. If main diagnosis was RA, contributory diagnoses were also allowed.

Tuberculosis	A15-A19	Main diagnosis in inpatient component of Patient Register.
Opportunistic Infections: Zoster, Tuberculosis, Pneumocystosis (or Pneumocystis jirovecii or P. carinii pneumonia), Legionellosis, Coccidioidomycosis, Histoplasmosis, Non-tuberculous mycobacteria, Salmonellosis, Nocardiosis, Blastomycosis, Cryptococcosis, Aspergillosis, Listeriosis, and Toxoplasmosis	A02, A15-A19, A31, A32, A43, A48.1, B02, B38, B39, B40, B44, B45, B58, B59	Main diagnosis in inpatient component of Patient Register. If main diagnosis was RA, contributory diagnoses were also allowed.
Malignancy excluding non-melanoma and basal cell invasive/non-invasive skin cancers	All except C44 and D04 (ICD7=191), and basal cell cancers	The Cancer Register, invasive only
Non-melanoma and basal cell invasive/non-invasive skin cancers.	C44 and D04 (ICD7=191), and basal cell cancers.	The Cancer Register
Lymphoma	ICDO10: C81, C82, C83, C84, C85, C86, C88, C911, C913, C914, C916	The Cancer Register
Demyelinating disorders: demyelinating diseases of the central nervous system and optic neuritis	G04.8, G04.9, G35.9, G36.0, G36.8, G36.9, G37.1, G37.3, G37.5, G37.8, G37.9, H46, H48.1	Main or secondary diagnosis in the Patient register, in- or outpatient component.
Fatal cardiovascular event	I00-I99	The underlying (main) cause recorded in the Cause of Death Register
Acute Myocardial Infarction	I20.0, I21	Main or secondary diagnosis in the Patient register, in- or outpatient component.
Stroke	I60 – I64	Main or secondary diagnosis in the Patient register, in- or outpatient component.
Acute Cardiovascular Event	Combines the three outcomes above: I00-I99 as main cause of death, or I21, I60-I64 as diagnosis	The Cause of Death Register or the Patient Register, as above
GI perforation	K22.3, K25.1, K25.2, K25.5, K25.6, K26.1, K26.2, K26.5, K26.6, K27.1, K27.2, K27.5, K27.6, K28.1, K28.2, K28.5, K28.6, K31.6, K35.0, K35.1, K35.2, K57.0, K57.2, K57.4, K57.8, K63.0, K63.1, K63.2.	Main diagnosis in inpatient component of Patient Register. If main diagnosis was RA, contributory diagnoses were also allowed.
Aplastic anemia	D60-D61	Main or secondary diagnosis in the Patient register, in- or outpatient component.
Serious hepatic events	K70,K71,K72,K73 K74,K75, K76 other than K76.0, and K77 K76.0	Main or secondary diagnosis in the Patient register, in- or outpatient component.
All-cause hospitalization	-	The inpatient component of the Patient Register
All-cause mortality	-	The Cause of Death Register

Sensitivity analysis

Failing a previous bDMARD may be an indicator of inherent characteristics that may be associated with higher risk of adverse events or treatment outcomes. This motivated the series of comparator cohorts, but to further estimate the sensitivity of the comparison, we also ran analyses comparing the tocilizumab cohort to all three biologics-initiator comparator cohorts explicitly stratified by the number of previous biologics, i.e. all patients (treated or not with tocilizumab) are stratified in three categories: no previous biologic, 1 previous biologic, or 2 previous biologics, and patients are compared within each of these 3 categories. Hence in this analysis, no patient starts any bDMARD as a 4^{th} (or more) line therapy.

We also performed analyses where the tocilizumab cohort was compared to the other biologics cohort stratified by:

- disease duration, i.e. all patients (treated or not with tocilizumab) were stratified in two categories: below or above the disease duration's median of the tocilizumab patients.
- DAS28, i.e. all patients (treated or not with tocilizumab) were stratified in two categories: below or above the DAS28 median of the tocilizumab patients.
- HAQ, i.e. all patients (treated or not with tocilizumab) were stratified in two categories: below or above the HAQ median of the tocilizumab patients.
- CRP, i.e. all patients (treated or not with tocilizumab) were stratified in two categories: below or above the CRP median of the tocilizumab patients.

A last sensitivity analysis stratified the tocilizumab group by mode of administration and dose into three subgroups: subcutaneous treatment ("sc"), intravenous treatment with either a monthly dose below ("iv low") or above ("iv high") the median among all iv users of tocilizumab. These groups were compared to the other biologics cohort.

Covariates and adjustments

All analyses were adjusted for age (10-yr bands, categorical) and sex (M/F). In addition, the following covariates (status at start of follow-up) were investigated as potential confounders. To avoid over-parameterization of models, these covariates were categorized relatively broadly:

1. Seropositive disease (RF+/RF-)
2. RA disease duration (<5, 5+ yrs)
3. Calendar year of entry into cohort
4. DAS28 (continuous)
5. HAQ (continuous)
6. Concomitant DMARDs at the time point of cohort entry (Y/N)
7. Concomitant oral steroids at the time point of cohort entry (Y/N)
8. History of malignancy (Y/N)
9. History of hospitalization listing infection, last 5 years (Y/N)
10. History of joint surgery (Y/N)
11. History of COPD, last 5 years (Y/N)
12. History of MI, last 5 years (Y/N)

13. History of diabetes, last 5 years (Y/N)
14. Total number of days spent in hospital last five years
15. (Where applicable) Reason for discontinuation of most recent biologic (safety/inefficacy/other)

Note that RA-related variables (covariates 1-2, 4-7) were only available for the biologics-treated cohorts defined through ARTIS. ICD codes used to define disease history are summarized in Table 2.

Table 2. Definitions of baseline diseases considered as potential confounders

Disease	Data source	ICD 10	ICD 9	ICD 8
Malignancy	The Cancer register	All except benign malignancies	All except benign malignancies	All except benign malignancies
Infection	Inpatient component of Patient Register.	A00-B99, G00-G02, G04.2, G05-G07, H66-H67, H70, J00-J22, J32, J34.0, J36, J38.3, J39.0-J39.1, K10.2, L00-L08, M00-M01, M46.2-M46.5, M86, N10, N30.0	001-139, 320-322, 382-383, 460-466, 475, 480-487, 526E-526F, 590, 680-686, 711A, 711E, 730, 790H	000-136, 320, 322, 381-383, 460-466, 470-474, 480-486, 501, 526.4, 590, 680-686, 710, 720, 782.9
Joint surgery	Operation codes from the Patient register	NGB, NFB, NBB, NHB, NHC, NHE, NHF, NHG	8423-8424, 8400-8415	8426,8419, 8436-8437, 8420-8422
Chronic obstructive pulmonary disease	The Patient Register	J41-J44	491-492, 496	490, 491.01-491.02, 491.04, 492
Diabetes	The Patient Register	E10-E14, O24	250, 648A	250
Myocardial infarction	The Patient Register	I21, I22	410	410

Statistics

Crude incidence and number of events were tabulated for each cohort and outcome. Age/sex-standardized rates were calculated for each outcome, using the tocilizumab cohort as standard. Rates for the tocilizumab cohort were also stratified by the number of previous biologics (0, 1-2, 3+ previous biologics) at the time of tocilizumab start.

Adjusted hazard ratios were estimated with Cox Proportional Hazards Regressions using time since start of follow-up as time scale. To assess the potential confounding effect of baseline covariates and potential impact of missingness, we fitted four models. The first model adjusted for sex and age, and was performed stratified by calendar year of entry (making the model a stratified Cox Regression). The second model adjusted for sex, age, and additionally for pre-baseline comorbidities and health care utilization: prior number of days in inpatient care, history of infection, cancer, MI, diabetes, COPD, and joint replacement surgery. The third model adjusted for all these covariates, but also included RA-specific covariates (pertaining to status at treatment start): RF, HAQ, RA disease duration, DAS28, use of DMARDs and steroids. There were non-negligible amounts of missing data on DAS28 and HAQ, so to ensure that a difference between Model 2 and 3 was not due to loss of observations, we also fitted an additional model, Model 4, where these covariates were modeled as categorical (split in tertiles), and with missing information coded as a separate category. Due to data availability, Model 3 and 4 were only fitted for the biologics-exposed cohorts ascertained through ARTIS. The three latter models, as the first one, were stratified on calendar year of entry.

Covariates were parameterized as described in the preceding section "Covariates and adjustments". Cohort-outcome combinations with less than 5 events were not included in adjusted Cox regressions; only numbers, crude and age/sex-adjusted incidence rates were estimated.

SAS version 9.4 was used for all analyses.

Results

Baseline characteristics

Table 3 describes the demographic and clinical characteristics of the tocilizumab and comparator cohorts. We identified a total of 2068 RA patients initiating tocilizumab treatment between 2009 and 2016. The median age of first tocilizumab initiation was 59 years, 21% were male, and 79% had RF-positive RA. Combination therapy with non-biologic drugs was common, with 60% prescribed any conventional synthetic DMARDs, 57% using oral steroids and 41% using NSAIDs at tocilizumab initiation. Most patients had had RA for a relatively long time before initiating tocilizumab treatment (median time since disease onset was 10.6 years), and disease activity was fairly high at treatment start (median DAS28=5.2). Twenty percent of the patients received tocilizumab as a subcutaneous injection with a median weekly dose of 162 mg. Patients receiving tocilizumab as an intravenous infusion treatment had a median monthly dose of 560 mg (IQR= 480-680).

Although differences were minor, the tocilizumab cohort differed from the other cohorts defined by biologics-initiation by having slightly higher value for DAS28 and CRP, being less often treated with concomitant conventional synthetic DMARDs but more often with oral steroid, and having switched from previous bDMARD for inefficacy reason more often than for safety reason. Of potential importance for the choice of the most appropriate comparator cohort, patients initiating a later biologic treatment, compared to those initiating their first, were more similar to the tocilizumab treated patients.

The biologics-naïve RA cohort was older than the tocilizumab cohort, more often male and RF-negative, had shorter disease duration, and lower DAS28, HAQ and CRP. There were also differences in the use of concomitant synthetic DMARDs, and in the rate of comorbidity history, with the tocilizumab cohort having lower rates of previous malignancies and MI but a higher rate of joint surgery.

Compared to the general population cohort (age and sex matched to the cohorts defined by biologics initiation), the tocilizumab cohort had a higher rate of comorbidities, except a history of malignancies.

Results by outcome

Table 4 displays numbers of patients, numbers of events, crude and standardized incidences for all cohorts and outcomes. Table 5 displays relative risks (hazard ratios) for each of the outcomes analyzed. Whereas HRa is only adjusted for age, sex, and stratified by year of start, HRb-d represent models with additional covariates (see footnote in table). The difference between HRc and HRd resides with the handling of missing data (as defined for these analyses, DAS28 and HAQ are missing for around 20% of the biologics-exposed cohorts). Table 6 displays adjusted relative risks similar to Table 5, but is restricted to RA patients initiating biologic treatment and stratified by number of previous biologics. Tables 7a to 7d display numbers of patients, numbers of events, crude and standardized incidences similar for the tocilizumab cohort and the non-tocilizumab bio-treated RA cohort, both stratified by disease duration (above vs below 2 years) (Table 7a), or by the median DAS28 (Table 7b), HAQ (Table 7c) or CRP (Table 7d). Tables 8a

to 8d display the adjusted relative risks that relate to tables 7. Table 9 display numbers of patients, numbers of events, crude and standardized incidences similar for the tocilizumab cohort which is stratified by the mode of administration and the median dose (for the intravenous mode). Table 10 displays adjusted relative risks for each of the three tocilizumab subgroups defined above, compared to the non-tocilizumab biologics cohort.

Hospitalized infections
During 4140 person-years (PYs) of follow-up among 2068 RA patients initiating tocilizumab treatment 2009-2016, we observed 138 individuals who were hospitalized with a discharge diagnosis listing an infection, resulting in an incidence rate of 3.33/100 PYs. This was higher than the incidence rate in the Swedish general population (HRa= 3.00 (2.53-3.56), slightly attenuated by adjusting for pre-baseline disease history (HRb= 2.08 (1.75-2.47)). The relative risks comparing tocilizumab to other RA cohorts were closed to 1.00 for bionaïve, and initiators of a first or second biologic, but there was a borderline significantly reduced risk in tocilizumab cohort compared to initiators of a third (or beyond) biologic (HRa=0.80 (0.65-0.99)). The HRs were consistent across further stratifications by disease duration, disease activity, and administration/dose.

Tuberculosis
During 4283 person-years (PYs) of follow-up among 2068 RA patients initiating tocilizumab treatment 2009-2016, no individual was diagnosed with tuberculosis in the Swedish Patient Register. In contrast, one or more cases were diagnosed in all other cohorts which also included a higher number of person-years. No other analysis was performed for this outcome.

Opportunistic Infections
During 4269 person-years (PYs) of follow-up among 2068 RA patients initiating tocilizumab treatment 2009-2016, we observed 14 individuals who were hospitalized with opportunistic infections in the Swedish Patient Register, giving an incidence rate of 3.3/1000 PYs. This was higher than the age and sex standardized incidence rate in the Swedish general population (HRa=3.53 (2.06-6.05)) and (non-significantly) higher than the age and sex standardized incidence rate among bionaïve RA patients (HRa=1.47 (0.86-2.52)). These HRs were slightly attenuated when adjusting for pre-baseline disease history. Comparing the tocilizumab cohort to the cohorts starting a bDMARD treatment, the risk for developing an opportunistic infection for patients treated with tocilizumab was not statistically significantly different, but, as for hospitalized infections, a borderline significant reduced risk was apparent for tocilizimab compared to initiators of a third (and beyond) biologic (HRa= 0.55 (0.30-1.03)). Further adjustment did not substantially modify the estimates. The confidence intervals provided by the analyses stratifying explicitly by the number of previous biologic drugs were too large to either confirm or infirm the findings described above. The additional analyses stratified on disease duration, DAS28, HAQ, CRP, mode of administration or dose were underpowered and did not add any further information.

Malignancy excluding non-melanoma and basal cell invasive/non-invasive skin cancers
During 7136 person-years (PYs) of follow-up among 2068 RA patients initiating tocilizumab treatment 2009-2016, we observed 77 individuals who were diagnosed with any malignancy excluding non-melanoma skin cancer, giving an incidence rate of 10.8/1000 PYs. This was almost equivalent to the rate in the Swedish general population (HRa= 1.08 (0.86-1.36)), and

to the rate among RA patients whether bionaïve or starting a first or second bDMARD (HRa range 0.98-1.10, none significant). In contrast, there was an increased risk for tocilizumab patients compared to RA patients starting a third (and beyond) bDMARD (HRa= 1.46 (1.06-2.00)). This estimate remained significant and about the same order of magnitude in all adjusted analyses (HRb to HRd= 1.45 to 1.54). Stratifying explicitly by the number of previous biologic drugs provided an aggregated relative risk of tocilizumab compared to initiating other biologic drugs of 1.25 (0.94-1.66), not substantially modified in the adjusted analyses. The analysis stratified on the mode of administration revealed that this apparent increased risk could be restricted to patients receiving subcutaneous tocilizimab (HRa= 1.99 (1.07-3.67)), with a HR which was not substantially modified across adjustments. The other stratified analyses did not provide additional insights.

Non-melanoma and basal cell invasive/non-invasive skin cancers
During 7118 person-years (PYs) of follow-up among 2068 RA patients initiating tocilizumab treatment 2009-2016, we observed 69 individuals who were diagnosed with non-melanoma or basal cell skin cancers, giving an incidence rate of 9.7/1000 PYs. This was statistically significantly higher than the incidence rate in the Swedish general population (HRa= 1.51 (1.19-1.92)), but not statistically significantly different than the rate among RA patients whether bionaïve or starting a bDMARD (HRa range 0.85-1.19, none significant). Adjustments did not materially change these estimates. None of the stratified analyses revealed any additional feature.

Lymphoma
During 7266 person-years (PYs) of follow-up among 2068 RA patients initiating tocilizumab treatment 2009-2016, we observed 3 individuals who were diagnosed with lymphoma, giving an incidence rate of 0.4/1000 PYs. This rate was similar to the rate observed in the Swedish general population (0.5/1000 PYs) and to the rate in RA patients starting a second (and beyond) biologic (ranging 0.3/1000 - 0.5/1000 PYs). Although the low number of events make it difficult to comment on this, the rate in tocilizumab patients was numerically lower than the rate in RA patients either bionaïve or starting a first bDMARD (0.8/1000 PYs for both these cohorts). No other analysis was performed for this outcome.

Demyelinating disorders
During 4283 person-years (PYs) of follow-up among 2068 RA patients initiating tocilizumab treatment 2009-2016, we observed 1 individual who was diagnosed with demyelinating disorder, which provided an incidence rate of 0.2/1000 PYs. Numerically, this rate was lower than the rate observed in the Swedish general population (1.1/1000 PYs), as well as lower than the rate in RA patients either bionaïve or bio-treated (ranging 0.5/1000 - 0.8/1000 PYs). No other analysis was performed for this outcome.

Acute cardiovascular events
During 4229 person-years (PYs) of follow-up among 2068 RA patients initiating tocilizumab treatment 2009-2016, we observed 61 individuals who were registered with any acute cardiovascular event, giving an incidence rate of 14.4/1000 PYs. Among the specific cardiovascular outcomes, we observed 27 individuals with fatal cardiovascular events, 25 with myocardial infarctions, and 20 with stroke. Note that these events are not mutually exclusive,

and individuals with an acute cardiovascular event could have been registered with more than one type of event.

The rate of any acute cardiovascular events among tocilizumab users was statistically significantly higher than the incidence rate in the Swedish general population (HRa= 1.43 (1.11-1.85), which substantially decreased with adjustment HRb=1.11 (0.86-1.43)), but not statistically significantly different than the rate among RA patients whether bionaïve or starting a bDMARD (HRa range 0.80-1.10, none significant). Further adjustment did not modify these estimates with the exception for bionaïve RA patients. Compared to this cohort, tocilizumab treated patients had a statistically significant decreased risk after adjustment for pre-baseline disease history (HRb= 0.74 (0.58-0.96)). None of the subsequent stratified analyses provided any additional insight.

Regarding fatal cardiovascular events, the rate observed in the tocilizumab cohort was higher than the incidence rate in the Swedish general population (HRa= 2.31 (1.57-3.39)). This relative risk was substantially lowered when adjusting for pre-baseline disease history (HRb= 1.59 (1.08-2.33)). The rate observed in the tocilizumab cohort was similar to the rate in RA bionaïve patients but was higher than the rate observed in the bio-treated RA cohorts (HR ranging 1.45-1.81). These increased risks were not substantially modified by the adjustments (HRb, HRc, HRd) and remained/became significant or borderline significant. Stratifying explicitly by the number of previous biologic drugs provided an aggregated relative risk of tocilizumab compared to initiating other biologic drugs of 1.47 (0.88-2.46), not substantially modified in the adjusted analyses. This analysis also revealed than the risk was substantially more elevated in tocilizumab patients starting their first biologic (HRa= 3.03 (1.46-6.28)), with a hazard ratio which was reduced somewhat in the adjusted analyses but remained statistically significant (HRd= 2.43 (1.10-5.40)). The other stratified analyses showed that this increased risk could also be associated with lower values in DAS28 and in HAQ.

Regarding myocardial infarctions, the rate observed in the tocilizumab cohort was higher than the incidence rate in the Swedish general population (HRa= 1.55 (1.04-2.31)). This relative risk was slightly lowered when adjusting for pre-baseline disease history (HRb= 1.29 (0.87-1.93)). The comparison with the RA cohorts, bionaïve or bDMARD treated revealed a decreased risk (HRa ranging from 0.62 to 0.97, none significant, the former being borderline significant). When adjusting, they all became closer to the null. Stratifying explicitly by the number of previous biologic drugs, the aggregated relative risk of tocilizumab compared to initiating other biologic drugs was a non-significant HR of 0.63 (0.38-1.05). This estimate was even lower in the stratum including patients starting a second biologic, but significance disappeared with the adjustments. None of the subsequent stratified analysis added any insight for this outcome.

Regarding stroke, the incidence rate in the tocilizumab cohort was not different from the incidence rate in the Swedish general population (HRa= 1.05 (0.68-1.64)) but slightly lower than the rates in the other cohorts (HRa ranging 0.66 to 0.96, none significant). The adjusted analyses provided similar relative risks (HRd ranging 0.80 to 0.85, none significant). Stratifying explicitly by the number of previous biologic drugs, the aggregated relative risk of tocilizumab compared to initiating other biologic drugs was a non-significant HR of 0.66 (0.37-1.19), which was not substantially modified with further adjustments. The other stratified analyses did not reveal any additional pattern.

Gastrointestinal perforation

During 4271 person-years (PYs) of follow-up among 2068 RA patients initiating tocilizumab treatment 2009-2016, we observed 16 individuals who were diagnosed with GI perforation giving an incidence rate of 3.7/1000 PYs. This rate was higher than the incidence rate in the Swedish general population (HRa= 5.19 (3.11-8.66)). This relative risk was somewhat lowered when adjusting for pre-baseline disease history (HRb= 3.99 (2.38-6.69)). The rate observed in the tocilizumab cohort was also higher than the rate in RA patients either bionaïve or treated with biologics (HR ranging from 2.01 to 3.18, all significant with the exception of patients starting a third (and beyond) biologic). These increased risks were not substantially modified by the adjustments (HRb, HRc, HRd). Stratifying explicitly by the number of previous biologic drugs provided an aggregated relative risk of tocilizumab compared to initiating other biologic drugs of 2.14 (1.10-4.18), not substantially modified in the adjusted analyses. This analysis also revealed than the risk was confined to tocilizumab patients starting their third biologic (HRa= 4.00 (1.59-10.06)), with a hazard ratio which was not reduced in the adjusted analyses (HRd= 5.15 (1.88-14.12)). In contrast the relative risk was 1 among those starting a second biologic (HRa= 1.00), and with only one event among those starting tocilizumab as first biologic, it was not possible to analyze that stratum further. When stratifying on disease duration (below or above 2 years), an increased risk was observed in the stratum with longer disease duration (HRa= 2.48 (1.23-5.01), not substantially modified with any adjustment). When stratifying on DAS28 or HAQ (below or above the median), an increased risk was observed in the stratum with higher values (HR being 3.67 and 3.85, for DAS28 and HAQ respectively, both significant). However, the two HRs were attenuated somewhat with further adjustments, and statistical significance disappeared. When stratifying on administration mode, the increased risk was confined in the subgroup receiving an intravenous monthly dose of tocilizumab higher than 560 mg (HRa= 3.36 (1.49-7.58), not modified by further adjustments). The analyses stratified on CRP did not reveal any further feature for this outcome.

Aplastic anemia

During 4283 person-years (PYs) of follow-up among 2068 RA patients initiating tocilizumab treatment 2009-2016, we observed 1 individual who was diagnosed with aplastic anemia, which provided an incidence rate of 0.2/1000 PYs. This rate was numerically higher than the rate observed in the Swedish general population (0.1/1000 PYs), and lower than the rate in RA patients either bionaïve or bio-treated (ranging 0.3/1000 - 0.5/1000 PYs). No further analysis was performed for this outcome.

Serious hepatic events

During 4265 person-years (PYs) of follow-up among 2068 RA patients initiating tocilizumab treatment 2009-2016, we observed 15 individuals who were diagnosed with a serious hepatic event, giving an incidence rate of 3.5/1000 PYs. This was statistically significantly higher than the incidence rate in the Swedish general population (HRa= 1.80 (1.07-3.01)). Adjustments substantially attenuated this estimate (1.39 (0.83-2.33)). The rate in the tocilizumab cohort was not statistically significantly different than the rate among RA patients whether bionaïve or starting a bDMARD (HRa range 0.87-1.23, none significant). Further adjustments did not materially change these estimates. Stratifying explicitly by the number of previous biologic drugs did not reveal any particular pattern and the aggregated estimate was 1.26 (0.70-2.27),

not substantially modified by further adjustments. The analysis stratified on the mode of administration revealed that patients with a subcutaneous mode of administration had a borderline significantly higher risk for the outcome (HRa= 2.57 (1.01-6.53)). This risk remained the same when adjusting for pre-baseline disease history, and was somewhat reduced with further adjustments (HRd= 1.95 (0.69-5.51)). No other stratified analyses revealed any additional differences.

Hospitalizations irrespective of cause (all-cause hospitalization)

During 2987 person-years (PYs) of follow-up among 2068 RA patients initiating tocilizumab treatment 2009-2016, we observed 733 individuals who were hospitalized for any cause, giving an incidence rate of 245/1000 PYs. This was higher than the incidence rate in the Swedish general population (HRa= 2.29 (2.12-2.46), reduced to 1.69 (1.57-1.82) when adjusting for pre-baseline disease history), and higher than the rate among bionaïve RA patients (HRa= 1.36 (1.26-1.47)), among RA patients treated with a 1st bDMARD (HRa= 1.36 (1.25-1.47)) and among RA patients treated with a 2nd bDMARD (HRa= 1.17 (1.07-1.27)). The rate in the tocilizumab cohort was in line with the rate of hospitalizations among RA patients starting a 3rd (and beyond) biologic treatment. These four relative risks remained about the same after adjusting for non-RA disease history and RA clinical characteristics. Stratifying explicitly by the number of previous biologic drugs did not reveal any pattern of association, all hazards ratio fluctuating around the null, with the fully adjusted aggregate HR being equal to 1.08 (0.98-1.18). Among the other stratified analyses, we observed that patients in the stratum with DAS28 higher than the median had a borderline significant increased risk for this outcome with all HR (a to d) being equal to 1.2 (1.0-1.4).

All-cause mortality

During 4283 person-years (PYs) of follow-up among 2068 RA patients initiating tocilizumab treatment 2009-2016, we observed 60 deaths, giving a mortality rate of 14/1000 PYs. This was higher than the mortality rate in the Swedish general population (HRa= 1.42 (1.10-1.83)). Adjusting for non-RA disease history lowered this risk (HRb= 1.03 (0.79-1.33)). The mortality rate in the tocilizumab cohort was lower than the mortality rate among bionaïve RA patients (HRa= 0.70 (0.54-0.90), which remained similar after adjustment for pre-baseline disease history), but higher compared to the bio-treated RA patients cohorts (HRa ranging from 1.12 to 1.50). However, only the risk comparing tocilizumab patients to patients starting their 3rd biologic (and beyond) was significant and remained so after adjustment (HRd= 1.60 (1.10-2.33)). Stratifying explicitly by the number of previous biologic drugs provided a fully adjusted aggregate HR of 1.15 (0.82-1.61), but did not reveal any particular pattern. Nor did any of the subsequent stratified analyses.

Discussion

This report describes the relative uptake of tocilizumab in the treatment of RA in Sweden since market approval, and presents a coherent analysis of key *a priori* safety outcomes. We made a number of important observations:

(i) For most outcomes, the HRs were markedly higher when comparing tocilizumab initiators to the general population than when the same tocilizumab cohort was compared to other RA patient subsets. Similarly, many of these HRs were attenuated with additional adjustments. To some extent expected, this pattern illustrates that the treated disease or the treatment context (here: being a patient with RA) is itself an important determinant for the outcomes under study. Thus, an understanding of disease-associated risks is necessary for the interpretation of any treatment-specific risk.

(ii) Incidence rates were often higher for patients initiating a second, third or later biologic than a first biologic, in patients treated with either tocilizumab or another biologic. This further illustrates that the treatment context is an important modifier of the treatment-specific risks (though perhaps not relative risks, once the number of previous biologics are accommodated in the statistical analyses). For the latter reason, one of the core analyses included matching for number of previous biologics used.

(iii) For most outcomes, incidences were not significantly different among tocilizumab initiators compared to other biologics initiators, both before and after adjusting for a set of baseline patient characteristics. The risk for residual confounding should still be kept in mind, and it is always possible that true risk differences are masked by unknown confounders. Even with nationwide data and up to seven years of follow-up, several endpoints were very rare, and the statistical power was thus insufficient to rule out clinically relevant risk differences for, e.g. tuberculosis, demyelinating disorder, lymphoma or aplastic anemia.

(iv) For the cohorts defined by initiation of a biologic treatment, start of follow-up corresponded to a clinical event at which the treated patient was deemed fit enough to tolerate the intended biologic treatment, and likely to remain alive so that the response to treatment could be evaluated. For the biologics-naïve RA cohort, and for the general population cohort, no such assumptions on survival were made, and start of follow-up corresponded to an arbitrary date. Thus, the initial mortality in the biologics-initiator cohorts, but not in the biologics-naïve and the general population cohorts, is likely to be heavily affected by depletion of individuals with poor short-term survival. This may be the explanation for the seemingly protective effect of tocilizumab on mortality, compared to the RA bionaïve cohort.

(v) Several borderline significantly increased risks appeared for tocilizumab compared to other biologics, including a risk for fatal cardiovascular events. This risk increase was more pronounced among patients with high disease activity, and was not mirrored by similarly increased risks for stroke and myocardial infarction. Although this may be worth assessing in other available data sources, several false positive associations would not be unexpected given the number of tests in the current report, and this signal would seem to be restricted to the most severe cardiovascular events, among patients with higher disease activity.

(vi) We observed an increased risk of gastrointestinal perforations among patients treated with tocilizumab, compared with RA patients treated with other biologics. A risk for (lower) gastrointestinal perforations was previously reported from clinical trials of tocilizumab, and an increased risk compared to TNFi has also been reported in two observational studies.[62-64] Although the signal of an increased risk for GI perforations with tocilizumab is not novel, and although there was hints of a dose-effect relationship, we do note several possibly inconsistent findings in our data, where the risk increase was only present among patients with higher disease activity, and a later line of therapy. We are currently following up on this in a directed analysis, with reworked comparator cohorts and additional adjustment for potential confounding variables. In a preliminary presentation of this data at ACR 2018, we reported no statistically significant difference between risk for gastrointestinal perforations on tocilizumab and TNFi. The main explanation for the difference compared to the present results was that we, in the analyses presented at the ACR, had excluded data from 2009 (the year of market entry). We hope to be able to share the results of a more detailed analysis, assessing the possible impact of line of therapy and year of treatment start, as well as possible confounding due to channeling to or away from tocilizumab therapy, as a manuscript for review mid-2019.

Our approach has a number of strengths; (a) A nationwide approach together with the very high coverage of ARTIS resulted in large numbers of subjects and (for some outcomes) comparatively large numbers of events. (b) The population-based setting in a public health care system acted to increase generalizability, although we acknowledge that baseline risks for the outcomes under study, the set-up of other risk factors, as well as the penetration of biological therapies may vary across countries, and thus that the generalizability to other settings (particularly outside of western Europe and the US) may be limited. (c) The prospectively collected longitudinal data on covariates and outcomes ascertained from linkages with external registers independently of RA- or treatment- status clearly reduced the risk of selective outcome ascertainment. At the same time, we cannot rule out surveillance bias as an explanation for some of the contrasts between RA and non-RA cohorts. This bias should be of lesser magnitude the more objective (i.e. less prone to be influenced by surveillance) the outcome under study, and virtually non-existent for mortality. (d) The register linkages allowed for information on covariates including several important potential confounders. (e) Inclusion of several different comparators as defined by alternative treatments, alternative positioning of treatments, RA disease but no biological treatment, and the general population provided a powerful means of estimating risks or hazard ratios that varied with the treated context rather than with the exact treatment, and also the marginal increase in risk with different treatment options compared to risks associated with the treated disease per se.

A series of limitations should also be discussed: (a) The coherent format of the analyses provided an easy overview across all analyses but represented a “best compromise” between feasibility and readability on the one hand and the optimal design and analytic approach for each of the outcomes under study, as exemplified by the outcome gastrointestinal perforation. (b) Whilst our design, comparators, and multitude of data allowed for alternative comparisons and for adjustment for known or tentative confounders, it is likely that residual confounding and channeling effects remain, especially so in analyses in which successive adjustments had marked impact on the HR for tocilizumab. This is especially true since the clinical decision-making process, the components of which our multivariable analyses seek to unpick, is multifactorial and based on – in addition to more easily estimable factors related to indication

(e.g., DAS28) - an elusive mix of personal preferences, subjective estimates of "frailty" and perceived prognosis. (c) Despite truly large numbers of individuals and tocilizumab-treatments under study, several comparisons were based on a relatively small numbers of events and hence resulted in limited statistical precision. (d) Our analyses encompassed more than 100 statistical tests, so spurious statistical significance are to be expected. In general, however, many analyses were either performed in patient groups "nested" within larger groups, or were by other means not "independent" from each other. Accordingly, the interpretation of our results should rather focus on patterns than on the statistical significance of individual tests.

In summary, this report describes the relative occurrence of a series of pre-defined safety outcomes in Swedish patients with RA treated with tocilizumab, or with other anti-rheumatic treatments, compared to the general Swedish population. Our results illustrate risks associated with the treated disease or treatment context rather than with specific treatments, and also the marked potential for, and effects of, channeling to or away from different treatments. Whilst accommodating known or measurable confounding/selection factors, our results are thus liable to residual or unmeasured confounding or selection. With respect to tocilizumab, the overall pattern of risks and relative risks that emerges from these analyses is that of no new safety signals, and of risks that vary across treatment contexts and that seem to be more dependent on the treatment context in which tocilizumab was used/not used than on the individual biologic that was chosen.

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Results tables

Table 3. Baseline characteristics of Swedish RA patients initiating tocilizumab 2009-2016, and comparator cohorts

	Exposed	Comparator Cohorts				
Status at entry	**Tocilizumab**	**3rd biologic**	**2nd biologic**	**1st biologic**	**Biologics-naïve**	**General population**
N patients	2068	2595	5317	9872	58043	66853
Demographics						
Age at start of follow-up (median, IQR)	59 (49-66)	60 (48-68)	59 (48-68)	59 (47-67)	66 (56-76)	59 (48-67)
Gender (% females)	79%	80%	77%	74%	71%	76%
RA-related characteristics						
Rheumatoid factor positive (%)	79%	82%	79%	77%	70%	
Disease duration at start of follow-up (median, IQR))	10.6 (4.7-19.7)	12.8 (7.2-21.6)	10.2 (5.0-19.1)	6.0 (2.2-14.2)	3.9 (1.0-11.1)	
Disease duration category: % above 2 years	89%	98%	93%	77%	62%	
Calendar year of start of follow-up (median)	2013	2013	2013	2012	2009	2012
DAS28 at start of follow-up (median, IQR)	5.2 (4.4-6.1)	4.9 (4.0-5.7)	4.7 (3.8-5.6)	4.8 (4.0-5.7)	3.5 (2.4-4.8)	
HAQ at start of follow-up (median, IQR)	1.3 (0.9-1.8)	1.3 (0.8-1.6)	1.1 (0.6-1.6)	1.0 (0.6-1.5)	0.6 (0.1-1.1)	
Crp at start of follow-up (median, IQR)	12.0 (5.0-32.0)	8.1 (3.8-22.0)	8.0 (3.0-21.0)	8.6 (4.0-21.0)	5.0 (3.0-13.0)	
Concomitant DMARDs at start of follow-up (%)	60%	65%	71%	78%	86%	
Oral steroids at start of follow-up (%)	57%	54%	49%	51%	52%	
NSAIDs at start of follow-up (%)	41%	41%	37%	32%	25%	
Number of previous biologics						
0	15%			100%		
1-2	53%	100%	100%			
3+	31%					
Comorbidity at start of follow-up						
Hx of malignancy (%)	6%	6.9%	7.3%	6.6%	11.4%	7.9%
Hx of hosp infection, last 5 yrs (%)	13.7%	15.8%	13.9%	9.4%	14.3%	4.4%
Hx of joint replacement surgery (%)	30.9%	33.1%	26.2%	17.2%	19.8%	4.6%
Hx of COPD (%)	3.2%	3.3%	3.5%	3%	4.8%	1.5%
Hx of diabetes mellitus (%)	7.7%	8.9%	7.9%	7%	9%	4.5%
Hx of MI (%)	1.9%	1.9%	1.8%	1.5%	3.6%	1.1%
Total days spent in hospital (median, IQR)	2 (0-10)	2 (0-10)	1 (0-8)	0 (0-5)	1 (0-10)	0 (0-2)
Reason for discontinuing previous biologic						
Safety, of those with information (%)	15%	22%	22%			
Inefficacy, of those with information (%)	73%	52%	50%			
Other, of those with information (%)	13%	26%	28%			
Missing, of total (%)	2%	3%	2%			
Administration mode and dose of tocilizumab						
% intravenous vs subcutaneous	73%					
Subcutaneous injection weekly dose in mg (median, IQR)	162 (162-162)					
Intravenous infusion monthly dose in mg (median, IQR)	560 (480-680)					

Table 4. Total number of events, crude and standardized incidence rates							
Outcome	**Cohort**	**Patients**	**Events**	**Person-Years**	**IR**	**Std IR**	**Mean follow-up, yrs**
Hospitalized infections							
	Tocilizumab	2068	138	4139.61	0.0333	0.0333	2.00
	0 previous biologics	317	20	674.54	0.0296		2.13
	1-2 previous biologics	1104	72	2268.75	0.0317		2.06
	3+ previous biologics	647	46	1196.31	0.0385		1.85
	Third bio starters	2595	229	5217.09	0.0439	0.0415	2.01
	Second bio starters	5317	392	11019.75	0.0356	0.0352	2.07
	First bio starters	9872	753	21795.20	0.0345	0.0349	2.21
	Bionaïve RA Patients	58043	10237	247256.53	0.0414	0.0276	4.26
	General Population	66853	2815	272565.62	0.0103	0.0106	4.08
Tuberculosis							
	Tocilizumab	2068	0	4283.40	0.0000	0.0000	2.07
	0 previous biologics	317	0	696.26	0.0000		2.20
	1-2 previous biologics	1104	0	2353.37	0.0000		2.13
	3+ previous biologics	647	0	1233.77	0.0000		1.91
	Third bio starters	2595	1	5581.67	0.0002	0.0002	2.15
	Second bio starters	5317	7	11584.66	0.0006	0.0006	2.18
	First bio starters	9872	14	22807.54	0.0006	0.0006	2.31
	Bionaïve RA Patients	58043	59	271116.18	0.0002	0.0002	4.67
	General Population	66853	20	278714.95	0.0001	0.0001	4.17
Opportunistic infections							
	Tocilizumab	2068	14	4268.87	0.0033	0.0033	2.06
	0 previous biologics	317	4	691.53	0.0058		2.18
	1-2 previous biologics	1104	8	2344.08	0.0034		2.12
	3+ previous biologics	647	2	1233.26	0.0016		1.91
	Third bio starters	2595	34	5517.01	0.0062	0.0060	2.13
	Second bio starters	5317	44	11521.00	0.0038	0.0037	2.17
	First bio starters	9872	96	22683.23	0.0042	0.0044	2.30
	Bionaïve RA Patients	58043	729	269166.05	0.0027	0.0022	4.64
	General Population	66853	245	278108.48	0.0009	0.0009	4.16
Cancer, excluding non-melanoma skin cancers							
	Tocilizumab	2068	77	7135.52	0.0108	0.0108	3.45
	0 previous biologics	317	9	959.30	0.0094		3.03
	1-2 previous biologics	1104	46	3845.90	0.0120		3.48
	3+ previous biologics	647	22	2330.32	0.0094		3.60
	Third bio starters	2595	73	9518.43	0.0077	0.0073	3.67
	Second bio starters	5317	201	19948.86	0.0101	0.0099	3.75
	First bio starters	9872	409	37874.10	0.0108	0.0109	3.84
	Bionaïve RA Patients	58043	4359	297532.82	0.0147	0.0119	5.13
	General Population	66853	2751	272700.61	0.0101	0.0101	4.08

Table 4. Continued

Outcome	Cohort	Patients	Events	Person-Years	IR	Std IR	Mean follow-up. yrs
Non-melanoma and basal cell skin cancers							
	Tocilizumab	2068	69	7118.00	0.0097	0.0097	3.44
	0 previous biologics	317	5	962.27	0.0052		3.04
	1-2 previous biologics	1104	45	3821.16	0.0118		3.46
	3+ previous biologics	647	19	2334.58	0.0081		3.61
	Third bio starters	2595	114	9363.10	0.0122	0.0115	3.61
	Second bio starters	5317	229	19789.43	0.0116	0.0113	3.72
	First bio starters	9872	394	37599.30	0.0105	0.0106	3.81
	Bionaïve RA Patients	58043	3792	295601.95	0.0128	0.0088	5.09
	General Population	66853	1772	274220.85	0.0065	0.0065	4.10
Lymphoma							
	Tocilizumab	2068	3	7265.89	0.0004	0.0004	3.51
	0 previous biologics	317	0	970.50	0.0000		3.06
	1-2 previous biologics	1104	3	3923.35	0.0008		3.55
	3+ previous biologics	647	0	2372.04	0.0000		3.67
	Third bio starters	2595	3	9653.49	0.0003	0.0003	3.72
	Second bio starters	5317	11	20323.61	0.0005	0.0005	3.82
	First bio starters	9872	30	38591.93	0.0008	0.0008	3.91
	Bionaïve RA Patients	58043	317	306957.52	0.0010	0.0008	5.29
	General Population	66853	127	278515.93	0.0005	0.0005	4.17
Demyelinating disorders							
	Tocilizumab	2068	1	4282.92	0.0002	0.0002	2.07
	0 previous biologics	317	0	696.26	0.0000		2.20
	1-2 previous biologics	1104	0	2353.37	0.0000		2.13
	3+ previous biologics	647	1	1233.30	0.0008		1.91
	Third bio starters	2595	3	5578.38	0.0005	0.0005	2.15
	Second bio starters	5317	7	11580.71	0.0006	0.0006	2.18
	First bio starters	9872	17	22768.86	0.0007	0.0008	2.31
	Bionaïve RA Patients	58043	150	270741.58	0.0006	0.0007	4.66
	General Population	66853	289	277853.58	0.0010	0.0011	4.16
Acute cardiovascular event (MI or stroke. fatal or not)							
	Tocilizumab	2068	61	4229.18	0.0144	0.0144	2.05
	0 previous biologics	317	13	686.34	0.0189		2.17
	1-2 previous biologics	1104	26	2324.64	0.0112		2.11
	3+ previous biologics	647	22	1218.20	0.0181		1.88
	Third bio starters	2595	108	5437.19	0.0199	0.0183	2.10
	Second bio starters	5317	188	11350.97	0.0166	0.0162	2.13
	First bio starters	9872	304	22395.26	0.0136	0.0134	2.27
	Bionaïve RA Patients	58043	9145	256952.10	0.0356	0.0193	4.43
	General Population	66853	2664	273958.32	0.0097	0.0101	4.10

Table 4. Continued							
Outcome	**Cohort**	**Patients**	**Events**	**Person-Years**	**IR**	**Std IR**	**Mean follow-up. yrs**
Fatal cardiovascular event							
	Tocilizumab	2068	27	4283.40	0.0063	0.0063	2.07
	0 previous biologics	317	8	696.26	0.0115		2.20
	1-2 previous biologics	1104	9	2353.37	0.0038		2.13
	3+ previous biologics	647	10	1233.77	0.0081		1.91
	Third bio starters	2595	23	5581.94	0.0041	0.0036	2.15
	Second bio starters	5317	56	11590.32	0.0048	0.0046	2.18
	First bio starters	9872	88	22812.51	0.0039	0.0037	2.31
	Bionaïve RA Patients	58043	4955	271292.63	0.0183	0.0074	4.67
	General Population	66853	776	278787.48	0.0028	0.0029	4.17
Myocardial infarction							
	Tocilizumab	2068	25	4257.09	0.0059	0.0059	2.06
	0 previous biologics	317	4	692.98	0.0058		2.19
	1-2 previous biologics	1104	12	2336.90	0.0051		2.12
	3+ previous biologics	647	9	1227.21	0.0073		1.90
	Third bio starters	2595	55	5492.52	0.0100	0.0094	2.12
	Second bio starters	5317	93	11450.09	0.0081	0.0079	2.15
	First bio starters	9872	141	22566.06	0.0062	0.0061	2.29
	Bionaïve RA Patients	58043	3240	263482.68	0.0123	0.0078	4.54
	General Population	66853	1013	276523.21	0.0037	0.0038	4.14
Stroke							
	Tocilizumab	2068	20	4254.51	0.0047	0.0047	2.06
	0 previous biologics	317	4	689.62	0.0058		2.18
	1-2 previous biologics	1104	8	2340.40	0.0034		2.12
	3+ previous biologics	647	8	1224.49	0.0065		1.89
	Third bio starters	2595	43	5518.91	0.0078	0.0071	2.13
	Second bio starters	5317	67	11485.33	0.0058	0.0058	2.16
	First bio starters	9872	115	22637.44	0.0051	0.0051	2.29
	Bionaïve RA Patients	58043	3131	264105.92	0.0119	0.0071	4.55
	General Population	66853	1210	276084.57	0.0044	0.0045	4.13
GI perforation							
	Tocilizumab	2068	16	4271.09	0.0037	0.0037	2.07
	0 previous biologics	317	1	696.14	0.0014		2.20
	1-2 previous biologics	1104	10	2343.24	0.0043		2.12
	3+ previous biologics	647	5	1231.71	0.0041		1.90
	Third bio starters	2595	11	5566.45	0.0020	0.0019	2.15
	Second bio starters	5317	19	11561.37	0.0016	0.0016	2.17
	First bio starters	9872	27	22775.58	0.0012	0.0012	2.31
	Bionaïve RA Patients	58043	472	270193.08	0.0017	0.0013	4.66
	General Population	66853	196	278334.60	0.0007	0.0007	4.16

Table 4. Continued

Outcome	Cohort	Patients	Events	Person-Years	IR	Std IR	Mean follow-up. yrs
Aplastic anemia							
	Tocilizumab	2068	1	4283.26	0.0002	0.0002	2.07
	0 previous biologics	317	0	696.26	0.0000		2.20
	1-2 previous biologics	1104	1	2353.23	0.0004		2.13
	3+ previous biologics	647	0	1233.77	0.0000		1.91
	Third bio starters	2595	0	5581.94	0.0000	0.0000	2.15
	Second bio starters	5317	6	11580.82	0.0005	0.0005	2.18
	First bio starters	9872	7	22801.38	0.0003	0.0003	2.31
	Bionaïve RA Patients	58043	147	271034.64	0.0005	0.0004	4.67
	General Population	66853	25	278747.90	0.0001	0.0001	4.17
Serious hepatic event							
	Tocilizumab	2068	15	4264.82	0.0035	0.0035	2.06
	0 previous biologics	317	4	693.38	0.0058		2.19
	1-2 previous biologics	1104	9	2340.28	0.0038		2.12
	3+ previous biologics	647	2	1231.16	0.0016		1.90
	Third bio starters	2595	22	5535.95	0.0040	0.0040	2.13
	Second bio starters	5317	32	11529.67	0.0028	0.0028	2.17
	First bio starters	9872	75	22697.49	0.0033	0.0034	2.30
	Bionaïve RA Patients	58043	703	269552.50	0.0026	0.0026	4.64
	General Population	66853	440	277786.92	0.0016	0.0016	4.16
Any Hospitalization							
	Tocilizumab	2068	733	2986.86	0.2454	0.2454	1.44
	0 previous biologics	317	89	533.62	0.1668		1.68
	1-2 previous biologics	1104	403	1639.15	0.2459		1.48
	3+ previous biologics	647	241	814.10	0.2960		1.26
	Third bio starters	2595	923	3761.98	0.2453	0.2370	1.45
	Second bio starters	5317	1738	8233.75	0.2111	0.2117	1.55
	First bio starters	9872	3014	17091.74	0.1763	0.1786	1.73
	Bionaïve RA Patients	58043	33056	159959.68	0.2067	0.1595	2.76
	General Population	66853	20785	218169.97	0.0953	0.0969	3.26
All-cause mortality							
	Tocilizumab	2068	60	4283.40	0.0140	0.0140	2.07
	0 previous biologics	317	13	696.26	0.0187		2.20
	1-2 previous biologics	1104	25	2353.37	0.0106		2.13
	3+ previous biologics	647	22	1233.77	0.0178		1.91
	Third bio starters	2595	60	5581.94	0.0107	0.0093	2.15
	Second bio starters	5317	133	11590.32	0.0115	0.0110	2.18
	First bio starters	9872	300	22812.51	0.0132	0.0128	2.31
	Bionaïve RA Patients	58043	12817	271293.40	0.0472	0.0226	4.67
	General Population	66853	2810	278788.23	0.0101	0.0104	4.17

Notes: IR Incidence Rate. Std IR standardised to the age/sex distribution in the tocilizumab cohort.

Table 5. Results from adjusted Cox regressions comparing tocilizumab initiators to comparator cohorts for each outcome

Outcome	Tocilizumab vs.	HRa	95% CI	HRb	95% CI	HRc	95% CI	HRd	95% CI
Hospitalized infections	Third bio starters	0.80	(0.65-0.99)	0.82	(0.66-1.01)	0.80	(0.61-1.04)	0.84	(0.67-1.04)
	Second bio starters	0.95	(0.79-1.16)	0.96	(0.79-1.17)	0.90	(0.70-1.15)	0.91	(0.75-1.11)
	First bio starters	0.96	(0.80-1.15)	0.83	(0.69-1.00)	0.79	(0.62-0.99)	0.78	(0.65-0.94)
	Bionaïve RA Patients	1.16	(0.98-1.37)	1.00	(0.85-1.19)				
	General Population	3.00	(2.53-3.56)	2.08	(1.75-2.47)				
Opportunistic infections	Third bio starters	0.55	(0.30-1.03)	0.56	(0.30-1.04)	0.52	(0.25-1.12)	0.56	(0.30-1.05)
	Second bio starters	0.87	(0.48-1.59)	0.89	(0.49-1.62)	0.98	(0.46-2.07)	0.85	(0.46-1.56)
	First bio starters	0.78	(0.44-1.36)	0.73	(0.41-1.28)	0.78	(0.39-1.55)	0.72	(0.41-1.28)
	Bionaïve RA Patients	1.47	(0.86-2.52)	1.39	(0.81-2.38)				
	General Population	3.53	(2.06-6.05)	3.04	(1.76-5.23)				
All primary invasive cancers excluding non-melanoma skin cancers	Third bio starters	1.46	(1.06-2.00)	1.45	(1.06-2.00)	1.54	(1.01-2.35)	1.52	(1.10-2.11)
	Second bio starters	1.10	(0.84-1.43)	1.11	(0.85-1.44)	1.18	(0.84-1.65)	1.15	(0.88-1.51)
	First bio starters	1.02	(0.80-1.30)	1.04	(0.82-1.33)	1.00	(0.73-1.37)	1.05	(0.82-1.35)
	Bionaïve RA Patients	0.98	(0.78-1.24)	1.02	(0.81-1.28)				
	General Population	1.08	(0.86-1.36)	1.12	(0.89-1.41)				
Non-melanoma and basal cell skin cancers	Third bio starters	0.85	(0.63-1.14)	0.85	(0.63-1.15)	0.77	(0.51-1.15)	0.91	(0.67-1.24)
	Second bio starters	0.87	(0.67-1.14)	0.86	(0.66-1.12)	0.71	(0.49-1.02)	0.89	(0.67-1.17)
	First bio starters	0.93	(0.72-1.20)	0.89	(0.69-1.16)	0.76	(0.54-1.08)	0.87	(0.67-1.13)
	Bionaïve RA Patients	1.19	(0.93-1.51)	1.14	(0.89-1.45)				
	General Population	1.51	(1.19-1.92)	1.40	(1.10-1.79)				
Acute cardiovascular event (MI or stroke. fatal or not)	Third bio starters	0.80	(0.58-1.09)	0.83	(0.60-1.13)	0.90	(0.61-1.33)	0.88	(0.63-1.22)
	Second bio starters	0.92	(0.69-1.23)	0.93	(0.70-1.25)	1.02	(0.72-1.46)	0.93	(0.69-1.25)
	First bio starters	1.10	(0.83-1.45)	1.01	(0.77-1.33)	1.06	(0.76-1.49)	0.99	(0.74-1.31)
	Bionaïve RA Patients	0.80	(0.62-1.03)	0.74	(0.58-0.96)				
	General Population	1.43	(1.11-1.85)	1.11	(0.86-1.43)				
Fatal cardiovascular event	Third bio starters	1.81	(1.04-3.17)	1.89	(1.08-3.29)	1.96	(0.96-3.99)	1.70	(0.95-3.02)
	Second bio starters	1.45	(0.91-2.29)	1.48	(0.94-2.35)	1.61	(0.91-2.84)	1.47	(0.91-2.37)
	First bio starters	1.76	(1.15-2.72)	1.59	(1.04-2.45)	1.82	(1.07-3.10)	1.63	(1.04-2.57)
	Bionaïve RA Patients	0.98	(0.67-1.44)	0.89	(0.61-1.31)				
	General Population	2.31	(1.57-3.39)	1.59	(1.08-2.33)				

Myocardial Infarction	Third bio starters	0.62	(0.39-1.00)	0.65	(0.40-1.04)	0.86	(0.48-1.56)	0.74	(0.45-1.20)
	Second bio starters	0.75	(0.48-1.16)	0.77	(0.50-1.20)	0.90	(0.53-1.54)	0.80	(0.51-1.25)
	First bio starters	0.97	(0.63-1.49)	0.92	(0.60-1.41)	1.01	(0.61-1.69)	0.95	(0.61-1.46)
	Bionaïve RA Patients	0.83	(0.56-1.24)	0.81	(0.54-1.20)				
	General Population	1.55	(1.04-2.31)	1.29	(0.87-1.93)				
Stroke	Third bio starters	0.66	(0.39-1.13)	0.68	(0.40-1.16)	0.79	(0.41-1.53)	0.80	(0.46-1.39)
	Second bio starters	0.85	(0.52-1.40)	0.85	(0.52-1.40)	0.83	(0.46-1.51)	0.85	(0.51-1.41)
	First bio starters	0.96	(0.60-1.54)	0.90	(0.56-1.44)	0.89	(0.50-1.58)	0.84	(0.52-1.36)
	Bionaïve RA Patients	0.75	(0.48-1.17)	0.71	(0.46-1.11)				
	General Population	1.05	(0.68-1.64)	0.87	(0.56-1.35)				
GI perforation	Third bio starters	2.01	(0.93-4.34)	2.06	(0.96-4.44)	2.46	(0.91-6.68)	1.89	(0.85-4.18)
	Second bio starters	2.35	(1.21-4.58)	2.34	(1.20-4.55)	3.10	(1.31-7.32)	2.16	(1.08-4.31)
	First bio starters	3.18	(1.71-5.90)	2.85	(1.53-5.29)	3.17	(1.45-6.90)	2.75	(1.42-5.33)
	Bionaïve RA Patients	2.89	(1.73-4.83)	2.56	(1.53-4.28)				
	General Population	5.19	(3.11-8.66)	3.99	(2.38-6.69)				
Serious hepatic event	Third bio starters	0.87	(0.45-1.68)	0.91	(0.47-1.75)	1.29	(0.53-3.15)	0.79	(0.40-1.57)
	Second bio starters	1.23	(0.67-2.28)	1.24	(0.67-2.29)	1.23	(0.58-2.60)	1.14	(0.60-2.18)
	First bio starters	1.02	(0.59-1.78)	0.92	(0.53-1.60)	1.12	(0.56-2.21)	0.83	(0.46-1.50)
	Bionaïve RA Patients	1.04	(0.62-1.75)	0.96	(0.57-1.61)				
	General Population	1.80	(1.07-3.01)	1.39	(0.83-2.33)				
Any Hospitalization	Third bio starters	1.05	(0.95-1.15)	1.07	(0.97-1.18)	1.11	(0.98-1.26)	1.05	(0.95-1.16)
	Second bio starters	1.17	(1.07-1.27)	1.16	(1.06-1.26)	1.19	(1.06-1.33)	1.11	(1.01-1.21)
	First bio starters	1.36	(1.25-1.47)	1.18	(1.09-1.28)	1.18	(1.06-1.30)	1.11	(1.02-1.21)
	Bionaïve RA Patients	1.36	(1.26-1.47)	1.18	(1.09-1.27)				
	General Population	2.29	(2.12-2.46)	1.69	(1.57-1.82)				
All cause mortality	Third bio starters	1.50	(1.05-2.14)	1.54	(1.08-2.20)	1.60	(0.99-2.60)	1.60	(1.10-2.33)
	Second bio starters	1.32	(0.98-1.79)	1.37	(1.01-1.86)	1.25	(0.84-1.84)	1.36	(0.99-1.86)
	First bio starters	1.12	(0.85-1.48)	1.02	(0.77-1.35)	1.02	(0.71-1.46)	1.03	(0.77-1.37)
	Bionaïve RA Patients	0.70	(0.54-0.90)	0.65	(0.50-0.84)				
	General Population	1.42	(1.10-1.83)	1.03	(0.79-1.33)				

Notes: Analysis was only made for comparisons where both cohorts had at least 5 observed events. HR: Hazard Ratio. CI: Confidence Interval.
HRa: stratified for year at start, adjusted for age and sex
HRb: stratified for year at start. adjusted for age, sex, prior number of days in inpatient care, history of infection, cancer, MI, diabetes, COPD and joint replacement surgery
HRc: stratified for year at start, adjusted for age, sex, prior number of days in inpatient care, history of infection, cancer, MI. diabetes, COPD, joint replacement surgery, Rheumatoid factor, HAQ (linear), RA disease duration, DAS28 (linear), DMARDs and steroids. Complete case analysis.
HRd: as HRc but using a missing indicator and quartiles for HAQ and DAS28.

Table 6. Results from crude and adjusted Cox regressions comparing tocilizumab to other biologic drugs, stratified by the number of previous biologic drugs

Outcome	Number of previous biologics	HRa	95% CI	HRb	95% CI	HRc	95% CI	HRd	95% CI
Hospitalized infections	0	0.77	(0.49-1.20)	0.74	(0.48-1.16)	0.92	(0.54-1.55)	0.76	(0.48-1.19)
	1	0.98	(0.70-1.36)	0.97	(0.70-1.34)	1.26	(0.84-1.88)	0.99	(0.71-1.39)
	2	0.70	(0.48-1.02)	0.75	(0.52-1.09)	0.65	(0.40-1.06)	0.77	(0.53-1.13)
	Aggregate estimate	0.82	(0.66-1.02)	0.83	(0.67-1.03)	0.91	(0.70-1.19)	0.85	(0.68-1.05)
Opportunistic infections	0	1.19	(0.43-3.24)	1.10	(0.40-3.01)	0.96	(0.23-4.02)	1.19	(0.43-3.27)
	1	0.40	(0.10-1.64)	0.40	(0.10-1.66)	0.56	(0.12-2.49)	0.38	(0.09-1.61)
	2	0.93	(0.39-2.23)	0.94	(0.39-2.26)	0.97	(0.34-2.80)	0.97	(0.39-2.38)
	Aggregate estimate	0.80	(0.44-1.46)	0.81	(0.44-1.46)	0.89	(0.44-1.80)	0.82	(0.45-1.49)
All primary invasive cancers excluding non-melanoma skin cancers	0	0.85	(0.44-1.65)	0.83	(0.43-1.60)	0.98	(0.46-2.09)	0.84	(0.43-1.63)
	1	1.42	(0.95-2.13)	1.44	(0.96-2.16)	1.47	(0.87-2.48)	1.52	(1.01-2.30)
	2	1.30	(0.78-2.16)	1.31	(0.79-2.18)	1.06	(0.53-2.11)	1.33	(0.78-2.26)
	Aggregate estimate	1.25	(0.94-1.66)	1.25	(0.94-1.65)	1.26	(0.88-1.81)	1.28	(0.96-1.70)
Non-melanoma and basal cell skin cancers	0	0.43	(0.18-1.04)	0.41	(0.17-0.98)	0.54	(0.20-1.46)	0.45	(0.18-1.09)
	1	0.74	(0.45-1.23)	0.75	(0.45-1.24)	0.56	(0.26-1.21)	0.74	(0.43-1.29)
	2	1.28	(0.85-1.92)	1.30	(0.86-1.95)	0.99	(0.55-1.78)	1.33	(0.87-2.05)
	Aggregate estimate	0.88	(0.66-1.18)	0.89	(0.66-1.19)	0.73	(0.49-1.10)	0.92	(0.68-1.24)
Any cardiovascular event	0	1.29	(0.74-2.26)	1.20	(0.69-2.10)	1.28	(0.65-2.52)	1.17	(0.65-2.10)
	1	0.85	(0.52-1.41)	0.82	(0.50-1.36)	0.86	(0.45-1.63)	0.87	(0.51-1.47)
	2	0.45	(0.23-0.89)	0.49	(0.25-0.97)	0.62	(0.29-1.33)	0.54	(0.27-1.08)
	Aggregate estimate	0.80	(0.57-1.11)	0.80	(0.58-1.12)	0.88	(0.59-1.31)	0.82	(0.59-1.16)
Fatal cardiovascular event	0	3.03	(1.46-6.28)	2.68	(1.28-5.61)	2.90	(1.21-6.96)	2.43	(1.10-5.40)
	1	1.45	(0.68-3.09)	1.40	(0.65-3.03)	0.88	(0.28-2.77)	1.42	(0.63-3.20)
	2	0.26	(0.03-1.92)	0.30	(0.04-2.29)	0.78	(0.09-6.96)	0.36	(0.04-2.89)
	Aggregate estimate	1.47	(0.88-2.46)	1.47	(0.88-2.46)	1.40	(0.73-2.70)	1.41	(0.83-2.42)
Myocardial infarction	0	0.86	(0.32-2.33)	0.80	(0.29-2.17)	0.89	(0.28-2.85)	0.87	(0.32-2.36)
	1	0.80	(0.38-1.65)	0.78	(0.37-1.61)	1.10	(0.46-2.62)	0.80	(0.37-1.77)
	2	0.36	(0.13-1.00)	0.40	(0.14-1.11)	0.37	(0.11-1.27)	0.44	(0.16-1.25)
	Aggregate estimate	0.63	(0.38-1.05)	0.63	(0.38-1.06)	0.77	(0.42-1.41)	0.65	(0.38-1.10)

Stroke	1	0.55	(0.20-1.53)	0.53	(0.19-1.47)	0.54	(0.16-1.80)	0.57	(0.20-1.61)
	2	0.55	(0.20-1.53)	0.56	(0.20-1.56)	0.83	(0.28-2.48)	0.65	(0.22-1.89)
	Aggregate estimate	0.66	(0.37-1.19)	0.67	(0.37-1.21)	0.77	(0.40-1.49)	0.73	(0.40-1.32)
GI perforation	1	1.00	(0.23-4.35)	0.96	(0.22-4.19)	1.83	(0.36-9.32)	0.95	(0.21-4.41)
	2	4.00	(1.59-10.06)	4.24	(1.67-10.74)	4.65	(1.42-15.27)	5.15	(1.88-14.12)
	Aggregate estimate	2.14	(1.10-4.18)	2.18	(1.12-4.26)	2.42	(1.04-5.61)	2.03	(1.00-4.13)
Serious hepatic event	1	1.25	(0.44-3.56)	1.26	(0.44-3.58)	1.22	(0.34-4.35)	1.23	(0.42-3.64)
	Aggregate estimate	1.26	(0.70-2.27)	1.29	(0.72-2.32)	1.33	(0.64-2.77)	1.15	(0.62-2.13)
Any hospitalization	0	0.87	(0.71-1.08)	0.85	(0.69-1.05)	0.90	(0.69-1.17)	0.83	(0.67-1.02)
	1	1.15	(0.99-1.34)	1.14	(0.98-1.32)	1.27	(1.05-1.53)	1.13	(0.97-1.32)
	2	1.12	(0.96-1.31)	1.15	(0.99-1.34)	1.27	(1.05-1.55)	1.16	(1.00-1.36)
	Aggregate estimate	1.08	(0.98-1.18)	1.07	(0.98-1.18)	1.17	(1.04-1.31)	1.07	(0.97-1.18)
All cause mortality	0	1.42	(0.81-2.47)	1.33	(0.76-2.32)	1.76	(0.92-3.37)	1.26	(0.70-2.28)
	1	1.14	(0.68-1.94)	1.14	(0.67-1.94)	0.83	(0.40-1.73)	1.14	(0.66-1.97)
	2	0.89	(0.44-1.80)	1.08	(0.53-2.20)	1.18	(0.43-3.27)	1.21	(0.58-2.53)
	Aggregate estimate	1.15	(0.82-1.61)	1.15	(0.82-1.61)	1.10	(0.71-1.71)	1.15	(0.81-1.63)

Notes: Analysis was only made for comparisons where both cohorts had at least 5 observed events. Some rows were intentionally deleted. HR: Hazard Ratio. CI: Confidence Interval. HRa: stratified for year at start, adjusted for age and sex. HRb: stratified for year at start, adjusted for age, sex, prior number of days in inpatient care, history of infection, cancer, MI, diabetes, COPD and joint replacement surgery. HRc: stratified for year at start, adjusted for age, sex, prior number of days in inpatient care, history of infection, cancer, MI, diabetes, COPD, joint replacement surgery, Rheumatoid factor, HAQ (linear), RA disease duration, DAS28 (linear), DMARDs and steroids; Complete case analysis. HRd: as HRc but using a missing indicator and quartiles for HAQ and DAS28.

Table 7a. Total number of events, crude and standardized incidence rates for the tocilizumab cohort and the other biologics cohort, stratified on disease duration (below or above 2 years)							
Outcome	**Stratified on disease duration**	**Patients**	**Events**	**Person-Years**	**IR**	**Std IR**	**Mean follow-up, yrs**
Hospitalized infections							
Tocilizumab	<= 2 years	216	10	408.84	0.0245	0.0245	1.89
	> 2 years	1833	127	3703.14	0.0343	0.0325	2.02
Other biologics	<= 2 years	2725	162	5369.09	0.0302	0.0353	1.97
	> 2 years	14904	1194	32302.42	0.0370	0.0353	2.17
Tuberculosis							
Tocilizumab	<= 2 years	216	0	423.35	0.0000	0.0000	1.96
	> 2 years	1833	0	3832.03	0.0000	0.0000	2.09
Other biologics	<= 2 years	2725	4	5587.02	0.0007	0.0010	2.05
	> 2 years	14904	18	33998.01	0.0005	0.0008	2.28
Opportunistic infections							
Tocilizumab	<= 2 years	216	0	423.35	0.0000	0.0000	1.96
	> 2 years	1833	14	3817.49	0.0037	0.0038	2.08
Other biologics	<= 2 years	2725	18	5565.87	0.0032	0.0035	2.04
	> 2 years	14904	151	33776.74	0.0045	0.0043	2.27
Cancer excluding non-melanoma skin cancers							
Tocilizumab	<= 2 years	216	4	634.55	0.0063	0.0063	2.94
	> 2 years	1833	73	6455.22	0.0113	0.0109	3.52
Other biologics	<= 2 years	2725	96	9893.54	0.0097	0.0107	3.63
	> 2 years	14904	581	56812.75	0.0102	0.0096	3.81
Non-melanoma and basal cell skin cancers							
Tocilizumab	<= 2 years	216	2	634.66	0.0032	0.0032	2.94
	> 2 years	1833	65	6440.18	0.0101	0.0094	3.51
Other biologics	<= 2 years	2725	69	9861.36	0.0070	0.0076	3.62
	> 2 years	14904	654	56279.16	0.0116	0.0101	3.78
Lymphoma							
Tocilizumab	<= 2 years	216	1	638.41	0.0016	0.0016	2.96
	> 2 years	1833	2	6581.73	0.0003	0.0002	3.59
Other biologics	<= 2 years	2725	6	10061.20	0.0006	0.0006	3.69
	> 2 years	14904	37	57867.73	0.0006	0.0006	3.88
Demyelinating disorders							
Tocilizumab	<= 2 years	216	0	423.35	0.0000	0.0000	1.96
	> 2 years	1833	1	3831.55	0.0003	0.0002	2.09
Other biologics	<= 2 years	2725	5	5575.13	0.0009	0.0009	2.05
	> 2 years	14904	22	33963.98	0.0006	0.0006	2.28
Acute cardiovascular event (MI or stroke. fatal or not)							
Tocilizumab	<= 2 years	216	7	416.12	0.0168	0.0168	1.93
	> 2 years	1833	52	3785.65	0.0137	0.0143	2.07
Other biologics	<= 2 years	2725	57	5506.34	0.0104	0.0123	2.02
	> 2 years	14904	532	33301.13	0.0160	0.0148	2.23

Fatal cardiovascular event							
Tocilizumab	<= 2 years	216	3	423.35	0.0071	0.0071	1.96
	> 2 years	1833	23	3832.03	0.0060	0.0060	2.09
Other biologics	<= 2 years	2725	16	5587.45	0.0029	0.0036	2.05
	> 2 years	14904	148	34008.48	0.0044	0.0039	2.28
Non-fatal myocardial infarction							
Tocilizumab	<= 2 years	216	2	419.86	0.0048	0.0048	1.94
	> 2 years	1833	22	3809.82	0.0058	0.0060	2.08
Other biologics	<= 2 years	2725	30	5533.56	0.0054	0.0065	2.03
	> 2 years	14904	254	33594.60	0.0076	0.0071	2.25
Non-fatal stroke							
Tocilizumab	<= 2 years	216	4	419.61	0.0095	0.0095	1.94
	> 2 years	1833	16	3806.88	0.0042	0.0045	2.08
Other biologics	<= 2 years	2725	18	5558.61	0.0032	0.0033	2.04
	> 2 years	14904	203	33698.79	0.0060	0.0056	2.26
GI perforation							
Tocilizumab	<= 2 years	216	1	423.22	0.0024	0.0024	1.96
	> 2 years	1833	15	3819.84	0.0039	0.0040	2.08
Other biologics	<= 2 years	2725	8	5581.76	0.0014	0.0019	2.05
	> 2 years	14904	47	33936.31	0.0014	0.0013	2.28
Aplastic anemia							
Tocilizumab	<= 2 years	216	0	423.35	0.0000	0.0000	1.96
	> 2 years	1833	1	3831.89	0.0003	0.0003	2.09
Other biologics	<= 2 years	2725	2	5582.00	0.0004	0.0003	2.05
	> 2 years	14904	11	33993.30	0.0003	0.0003	2.28
Serious hepatic event							
Tocilizumab	<= 2 years	216	2	421.58	0.0047	0.0047	1.95
	> 2 years	1833	13	3815.21	0.0034	0.0039	2.08
Other biologics	<= 2 years	2725	22	5551.55	0.0040	0.0045	2.04
	> 2 years	14904	106	33822.98	0.0031	0.0031	2.27
Any Hospitalization							
Tocilizumab	<= 2 years	216	59	323.26	0.1825	0.1825	1.50
	> 2 years	1833	669	2640.89	0.2533	0.2457	1.44
Other biologics	<= 2 years	2725	728	4301.06	0.1693	0.1861	1.58
	> 2 years	14904	4874	24539.26	0.1986	0.1943	1.65
All-cause mortality							
Tocilizumab	<= 2 years	216	3	423.35	0.0071	0.0071	1.96
	> 2 years	1833	56	3832.03	0.0146	0.0139	2.09
Other biologics	<= 2 years	2725	55	5587.45	0.0098	0.0123	2.05
	> 2 years	14904	429	34008.48	0.0126	0.0115	2.28
Notes: IR Incidence Rate. Std IR standardised to the age/sex distribution in the tocilizumab first stratum cohort.							

Table 8a. Results from crude and adjusted Cox regressions comparing tocilizumab to other biologic drugs, stratified by the disease duration (below or above 2 years)									
Outcome	**Disease duration with cut-off value = 2 years**	**HRa**	**95% CI**	**HRb**	**95% CI**	**HRc**	**95% CI**	**HRd**	**95% CI**
Hospitalized infections	≤ 2 years	0.82	(0.43-1.59)	0.78	(0.40-1.52)	0.80	(0.39-1.66)	0.79	(0.40-1.55)
	> 2 years	0.85	(0.67-1.06)	0.85	(0.67-1.06)	0.87	(0.68-1.11)	0.86	(0.68-1.08)
	Aggregate estimate	0.84	(0.68-1.05)	0.84	(0.68-1.05)	0.87	(0.69-1.09)	0.85	(0.69-1.06)
Opportunistic infections	> 2 years	1.01	(0.56-1.84)	1.01	(0.56-1.84)	0.87	(0.43-1.73)	0.99	(0.54-1.81)
	Aggregate estimate	0.92	(0.51-1.67)	0.92	(0.51-1.66)	0.78	(0.39-1.55)	0.89	(0.49-1.62)
Cancer excluding non-melanoma skin cancers	> 2 years	1.27	(0.95-1.71)	1.27	(0.95-1.70)	1.38	(1.01-1.89)	1.30	(0.97-1.75)
	Aggregate estimate	1.23	(0.92-1.62)	1.23	(0.92-1.62)	1.35	(1.00-1.82)	1.25	(0.94-1.67)
Non-melanoma and basal cell skin cancers	> 2 years	0.97	(0.72-1.30)	0.96	(0.71-1.30)	0.79	(0.55-1.13)	0.97	(0.71-1.31)
	Aggregate estimate	0.92	(0.68-1.23)	0.91	(0.68-1.23)	0.75	(0.53-1.07)	0.92	(0.68-1.25)
Cardiovascular event	≤ 2 years	1.29	(0.55-3.07)	1.16	(0.49-2.77)	1.25	(0.48-3.28)	1.18	(0.49-2.87)
	> 2 years	0.73	(0.50-1.05)	0.72	(0.50-1.04)	0.78	(0.52-1.16)	0.76	(0.52-1.10)
	Aggregate estimate	0.79	(0.56-1.10)	0.78	(0.56-1.09)	0.83	(0.58-1.20)	0.81	(0.58-1.14)
Fatal Cardiovascular event	> 2 years	1.30	(0.74-2.28)	1.35	(0.77-2.36)	1.18	(0.63-2.23)	1.29	(0.72-2.32)
	Aggregate estimate	1.44	(0.86-2.41)	1.43	(0.85-2.41)	1.26	(0.70-2.25)	1.36	(0.79-2.34)
Myocardial infarction	> 2 years	0.60	(0.34-1.06)	0.60	(0.34-1.06)	0.70	(0.39-1.27)	0.67	(0.38-1.17)
	Aggregate estimate	0.60	(0.35-1.02)	0.60	(0.35-1.02)	0.74	(0.42-1.28)	0.68	(0.40-1.15)
Stroke	> 2 years	0.50	(0.24-1.02)	0.50	(0.24-1.01)	0.62	(0.30-1.29)	0.54	(0.26-1.11)
	Aggregate estimate	0.67	(0.37-1.21)	0.65	(0.36-1.18)	0.73	(0.39-1.36)	0.69	(0.38-1.26)
GI perforation	> 2 years	2.48	(1.23-5.01)	2.48	(1.23-5.01)	1.99	(0.85-4.65)	2.04	(0.97-4.27)
	Aggregate estimate	2.26	(1.16-4.41)	2.26	(1.16-4.42)	1.76	(0.78-3.96)	1.83	(0.90-3.73)
Serious hepatic event	> 2 years	1.32	(0.70-2.50)	1.35	(0.71-2.54)	1.11	(0.52-2.34)	1.21	(0.62-2.37)
	Aggregate estimate	1.31	(0.73-2.36)	1.32	(0.74-2.37)	1.15	(0.59-2.24)	1.20	(0.65-2.20)
Any hospitalization	≤ 2 years	1.00	(0.76-1.31)	0.99	(0.75-1.31)	0.99	(0.72-1.34)	0.99	(0.75-1.31)
	> 2 years	1.11	(1.00-1.23)	1.09	(0.99-1.21)	1.13	(1.02-1.26)	1.09	(0.98-1.21)
	Aggregate estimate	1.10	(1.00-1.21)	1.08	(0.99-1.19)	1.12	(1.01-1.24)	1.08	(0.98-1.19)

All cause mortality	> 2 years	1.19	(0.83-1.69)	1.21	(0.85-1.72)	1.31	(0.90-1.91)	1.23	(0.86-1.76)
	Aggregate estimate	1.17	(0.83-1.64)	1.17	(0.83-1.64)	1.24	(0.87-1.79)	1.18	(0.83-1.67)

Notes: Analysis was only made for comparisons where both cohorts had at least 5 observed events. Some rows were intentionally deleted. HR: Hazard Ratio. CI: Confidence Interval. HRa: stratified for year at start, adjusted for age and sex. HRb: stratified for year at start, adjusted for age, sex, prior number of days in inpatient care, history of infection, cancer, MI, diabetes, COPD and joint replacement surgery. HRc: stratified for year at start, adjusted for age, sex, prior number of days in inpatient care, history of infection, cancer, MI, diabetes, COPD, joint replacement surgery, Rheumatoid factor, DMARDs and steroids; Complete case analysis. HRd: as HRc but using a missing indicators.

Table 7b. Total number of events, crude and standardized incidence rates for the tocilizumab cohort and the other biologics cohort, stratified on the median of DAS28 in the tocilizumab cohort (i.e. 5.24).

Outcome	Stratified on DAS28	Patients	Events	Person-Years	IR	Std IR	Mean follow-up, yrs
Hospitalized infections							
Tocilizumab	≤ median	725	37	1447.85	0.0256	0.0256	2.00
	> median	713	62	1534.65	0.0404	0.0389	2.15
Other biologics	≤ median	7316	494	15963.44	0.0309	0.0313	2.18
	> median	4128	398	8897.43	0.0447	0.0397	2.16
Tuberculosis							
Tocilizumab	≤ median	725	0	1479.49	0.0000	0.0000	2.04
	> median	713	0	1602.37	0.0000	0.0000	2.25
Other biologics	≤ median	7316	7	16649.75	0.0004	0.0004	2.28
	> median	4128	9	9459.24	0.0010	0.0009	2.29
Opportunistic infections							
Tocilizumab	≤ median	725	5	1473.86	0.0034	0.0034	2.03
	> median	713	6	1594.13	0.0038	0.0035	2.24
Other biologics	≤ median	7316	65	16546.32	0.0039	0.0038	2.26
	> median	4128	52	9385.68	0.0055	0.0049	2.27
Cancer, excluding non-melanoma and basal cell skin cancers							
Tocilizumab	≤ median	725	30	2427.59	0.0124	0.0124	3.35
	> median	713	26	2786.35	0.0093	0.0146	3.91
Other biologics	≤ median	7316	282	28014.05	0.0101	0.0100	3.83
	> median	4128	186	17361.45	0.0107	0.0097	4.21
Non-melanoma and basal cell skin cancers							
Tocilizumab	≤ median	725	20	2429.42	0.0082	0.0082	3.35
	> median	713	26	2773.56	0.0094	0.0096	3.89
Other biologics	≤ median	7316	313	27721.34	0.0113	0.0114	3.79
	> median	4128	187	17208.19	0.0109	0.0092	4.17
Lymphoma							
Tocilizumab	≤ median	725	0	2472.61	0.0000	0.0000	3.41
	> median	713	1	2828.76	0.0004	0.0003	3.97
Other biologics	≤ median	7316	13	28516.01	0.0005	0.0004	3.90
	> median	4128	16	17684.01	0.0009	0.0008	4.28
Demyelinating disorders							
Tocilizumab	≤ median	725	1	1479.01	0.0007	0.0007	2.04
	> median	713	0	1602.37	0.0000	0.0000	2.25
Other biologics	≤ median	7316	10	16630.51	0.0006	0.0006	2.27
	> median	4128	7	9445.90	0.0007	0.0007	2.29
Acute cardiovascular event (MI or stroke, fatal or not)							
Tocilizumab	≤ median	725	23	1459.59	0.0158	0.0158	2.01
	> median	713	27	1577.75	0.0171	0.0148	2.21
Other biologics	≤ median	7316	209	16352.57	0.0128	0.0129	2.24
	> median	4128	197	9239.50	0.0213	0.0178	2.24

Fatal cardiovascular event							
Tocilizumab	≤ median	725	11	1479.49	0.0074	0.0074	2.04
	> median	713	12	1602.37	0.0075	0.0061	2.25
Other biologics	≤ median	7316	54	16651.41	0.0032	0.0032	2.28
	> median	4128	63	9461.61	0.0067	0.0052	2.29
Non-fatal myocardial infarction							
Tocilizumab	≤ median	725	10	1465.55	0.0068	0.0068	2.02
	> median	713	11	1593.45	0.0069	0.0056	2.23
Other biologics	≤ median	7316	104	16477.14	0.0063	0.0064	2.25
	> median	4128	90	9343.62	0.0096	0.0084	2.26
Non-fatal stroke							
Tocilizumab	≤ median	725	6	1473.50	0.0041	0.0041	2.03
	> median	713	10	1585.72	0.0063	0.0063	2.22
Other biologics	≤ median	7316	85	16516.16	0.0051	0.0051	2.26
	> median	4128	73	9354.23	0.0078	0.0064	2.27
GI perforation							
Tocilizumab	≤ median	725	5	1476.06	0.0034	0.0034	2.04
	> median	713	9	1596.69	0.0056	0.0047	2.24
Other biologics	≤ median	7316	21	16630.19	0.0013	0.0012	2.27
	> median	4128	15	9439.06	0.0016	0.0013	2.29
Aplastic anemia							
Tocilizumab	≤ median	725	1	1479.34	0.0007	0.0007	2.04
	> median	713	0	1602.37	0.0000	0.0000	2.25
Other biologics	≤ median	7316	8	16643.73	0.0005	0.0005	2.27
	> median	4128	3	9449.69	0.0003	0.0004	2.29
Serious hepatic event							
Tocilizumab	≤ median	725	6	1475.01	0.0041	0.0041	2.03
	> median	713	6	1591.89	0.0038	0.0040	2.23
Other biologics	≤ median	7316	51	16579.87	0.0031	0.0031	2.27
	> median	4128	34	9385.68	0.0036	0.0036	2.27
Any Hospitalization							
Tocilizumab	≤ median	725	236	1088.64	0.2168	0.2168	1.50
	> median	713	297	1001.14	0.2967	0.3020	1.40
Other biologics	≤ median	7316	2123	12543.13	0.1693	0.1733	1.71
	> median	4128	1528	6523.77	0.2342	0.2143	1.58
All-cause mortality							
Tocilizumab	≤ median	725	22	1479.49	0.0149	0.0149	2.04
	> median	713	24	1602.37	0.0150	0.0116	2.25
Other biologics	≤ median	7316	165	16651.41	0.0099	0.0098	2.28
	> median	4128	178	9461.61	0.0188	0.0148	2.29
Notes: IR Incidence Rate. Std IR standardised to the age/sex distribution in the tocilizumab first stratum cohort.							

Table 8b. Results from crude and adjusted Cox regressions comparing tocilizumab to other biologic drugs, stratified by das28 (with the median of the tocilizumab group as cutoff value i.e. 5.24)									
Outcome	**Das28**	**HRa**	**95% CI**	**HRb**	**95% CI**	**HRc**	**95% CI**	**HRd**	**95% CI**
Hospitalized infections	≤ median	0.82	(0.56-1.21)	0.80	(0.54-1.18)	0.79	(0.53-1.17)	0.79	(0.53-1.17)
	> median	0.86	(0.62-1.20)	0.86	(0.61-1.20)	0.88	(0.63-1.23)	0.88	(0.63-1.23)
	Aggregate estimate	0.84	(0.66-1.09)	0.83	(0.65-1.07)	0.84	(0.65-1.09)	0.84	(0.65-1.09)
Opportunistic infections	≤ median	0.92	(0.33-2.56)	0.92	(0.33-2.56)	0.85	(0.30-2.38)	0.85	(0.30-2.38)
	> median	0.80	(0.31-2.06)	0.82	(0.32-2.10)	0.83	(0.32-2.15)	0.83	(0.32-2.15)
	Aggregate estimate	0.86	(0.43-1.72)	0.86	(0.43-1.72)	0.84	(0.42-1.68)	0.84	(0.42-1.68)
All primary invasive cancers excluding NMSC	≤ median	1.42	(0.91-2.22)	1.41	(0.90-2.20)	1.46	(0.93-2.29)	1.46	(0.93-2.29)
	> median	1.07	(0.65-1.77)	1.09	(0.66-1.79)	1.08	(0.65-1.81)	1.08	(0.65-1.81)
	Aggregate estimate	1.25	(0.89-1.74)	1.25	(0.89-1.74)	1.27	(0.90-1.78)	1.27	(0.90-1.78)
Non-melanoma and basal cell skin cancers	≤ median	0.72	(0.43-1.21)	0.70	(0.41-1.18)	0.65	(0.38-1.12)	0.65	(0.38-1.12)
	> median	0.89	(0.53-1.47)	0.87	(0.52-1.45)	0.90	(0.53-1.52)	0.90	(0.53-1.52)
	Aggregate estimate	0.79	(0.55-1.14)	0.78	(0.54-1.12)	0.77	(0.53-1.12)	0.77	(0.53-1.12)
Cardiovascular event	≤ median	1.05	(0.62-1.77)	1.03	(0.61-1.74)	0.99	(0.57-1.71)	0.99	(0.57-1.71)
	> median	0.67	(0.40-1.14)	0.67	(0.40-1.13)	0.79	(0.47-1.33)	0.79	(0.47-1.33)
	Aggregate estimate	0.83	(0.57-1.20)	0.83	(0.58-1.21)	0.89	(0.61-1.30)	0.89	(0.61-1.30)
Fatal cardiovascular event	≤ median	2.09	(0.86-5.08)	1.98	(0.79-4.95)	1.55	(0.57-4.23)	1.55	(0.57-4.23)
	> median	1.03	(0.46-2.31)	1.07	(0.48-2.39)	1.19	(0.53-2.68)	1.19	(0.53-2.68)
	Aggregate estimate	1.37	(0.75-2.48)	1.45	(0.80-2.62)	1.40	(0.75-2.60)	1.40	(0.75-2.60)
Myocardial infarction	≤ median	1.08	(0.51-2.27)	1.09	(0.52-2.30)	1.17	(0.55-2.48)	1.17	(0.55-2.48)
	> median	0.49	(0.21-1.14)	0.48	(0.21-1.12)	0.61	(0.26-1.42)	0.61	(0.26-1.42)
	Aggregate estimate	0.72	(0.42-1.26)	0.72	(0.41-1.26)	0.83	(0.48-1.46)	0.83	(0.48-1.46)
Stroke	≤ median	0.60	(0.22-1.65)	0.61	(0.22-1.68)	0.63	(0.23-1.78)	0.63	(0.23-1.78)
	> median	0.71	(0.30-1.68)	0.71	(0.30-1.67)	0.78	(0.33-1.83)	0.78	(0.33-1.83)
	Aggregate estimate	0.66	(0.34-1.27)	0.67	(0.35-1.28)	0.72	(0.37-1.38)	0.72	(0.37-1.38)
GI perforation	≤ median	1.80	(0.52-6.25)	1.93	(0.55-6.82)	1.76	(0.49-6.35)	1.76	(0.49-6.35)
	> median	3.67	(1.35-9.99)	3.66	(1.32-10.15)	2.83	(0.94-8.57)	2.83	(0.94-8.57)
	Aggregate estimate	2.65	(1.24-5.70)	2.61	(1.21-5.64)	2.09	(0.92-4.73)	2.09	(0.92-4.73)
Serious hepatic event	≤ median	1.52	(0.59-3.90)	1.60	(0.62-4.13)	1.51	(0.58-3.92)	1.51	(0.58-3.92)
	> median	1.19	(0.45-3.12)	1.14	(0.43-3.00)	1.15	(0.43-3.07)	1.15	(0.43-3.07)
	Aggregate estimate	1.34	(0.68-2.64)	1.35	(0.68-2.66)	1.35	(0.68-2.68)	1.35	(0.68-2.68)

Any hospitalization	≤ median	1.11	(0.94-1.31)	1.08	(0.91-1.27)	1.07	(0.90-1.26)	1.07	(0.90-1.26)
	> median	1.17	(1.01-1.37)	1.18	(1.02-1.38)	1.21	(1.04-1.41)	1.21	(1.04-1.41)
	Aggregate estimate	1.15	(1.03-1.28)	1.14	(1.02-1.28)	1.15	(1.03-1.29)	1.15	(1.03-1.29)
All cause mortality	≤ median	1.69	(0.97-2.94)	1.52	(0.86-2.70)	1.35	(0.74-2.47)	1.35	(0.74-2.47)
	> median	0.76	(0.44-1.33)	0.79	(0.45-1.38)	0.85	(0.49-1.49)	0.85	(0.49-1.49)
	Aggregate estimate	1.08	(0.73-1.60)	1.09	(0.74-1.62)	1.08	(0.72-1.62)	1.08	(0.72-1.62)

Notes: Analysis was only made for comparisons where both cohorts had at least 5 observed events. Some rows were intentionally deleted. HR: Hazard Ratio. CI: Confidence Interval. HRa: stratified for year at start, adjusted for age and sex. HRb: stratified for year at start, adjusted for age, sex, prior number of days in inpatient care, history of infection, cancer, MI, diabetes, COPD and joint replacement surgery. HRc: stratified for year at start, adjusted for age, sex, prior number of days in inpatient care, history of infection, cancer, MI, diabetes, COPD, joint replacement surgery, Rheumatoid factor, DMARDs and steroids; Complete case analysis. HRd: as HRc but using a missing indicators.

Table 7c. Total number of events, crude and standardized incidence rates for the tocilizumab cohort and the other biologics cohort, stratified on the median of HAQ in the tocilizumab cohort (i.e. 1.25).

Outcome	Stratified on HAQ	Patients	Events	Person-Years	IR	Std IR	Mean follow-up, yrs
Hospitalized infections							
Tocilizumab	≤ median	779	43	1655.09	0.0260	0.0260	2.12
	> median	703	56	1390.16	0.0403	0.0325	1.98
Other biologics	≤ median	7911	464	17869.09	0.0260	0.0262	2.26
	> median	4228	466	8431.79	0.0553	0.0446	1.99
Tuberculosis							
Tocilizumab	≤ median	779	0	1706.79	0.0000	0.0000	2.19
	> median	703	0	1442.17	0.0000	0.0000	2.05
Other biologics	≤ median	7911	9	18545.31	0.0005	0.0005	2.34
	> median	4228	7	9062.04	0.0008	0.0008	2.14
Opportunistic infections							
Tocilizumab	≤ median	779	3	1702.32	0.0018	0.0018	2.19
	> median	703	7	1433.02	0.0049	0.0035	2.04
Other biologics	≤ median	7911	66	18448.43	0.0036	0.0036	2.33
	> median	4228	52	8974.62	0.0058	0.0050	2.12
Cancer							
Tocilizumab	≤ median	779	29	2760.62	0.0105	0.0105	3.54
	> median	703	26	2563.10	0.0101	0.0095	3.65
Other biologics	≤ median	7911	305	31004.39	0.0098	0.0099	3.92
	> median	4228	177	16897.67	0.0105	0.0094	4.00
Non-melanoma and basal cell skin cancers							
Tocilizumab	≤ median	779	19	2760.61	0.0069	0.0069	3.54
	> median	703	25	2556.42	0.0098	0.0080	3.64
Other biologics	≤ median	7911	285	30853.48	0.0092	0.0092	3.90
	> median	4228	227	16624.09	0.0137	0.0105	3.93
Lymphoma							
Tocilizumab	≤ median	779	2	2801.94	0.0007	0.0007	3.60
	> median	703	1	2607.56	0.0004	0.0003	3.71
Other biologics	≤ median	7911	16	31571.41	0.0005	0.0005	3.99
	> median	4228	13	17201.19	0.0008	0.0007	4.07
Demyelinating disorders							
Tocilizumab	≤ median	779	0	1706.79	0.0000	0.0000	2.19
	> median	703	1	1441.69	0.0007	0.0011	2.05
Other biologics	≤ median	7911	8	18537.47	0.0004	0.0004	2.34
	> median	4228	9	9034.08	0.0010	0.0010	2.14
Acute cardiovascular event (MI or stroke, fatal or not)							
Tocilizumab	≤ median	779	18	1690.75	0.0106	0.0106	2.17
	> median	703	32	1414.65	0.0226	0.0169	2.01
Other biologics	≤ median	7911	208	18242.72	0.0114	0.0116	2.31
	> median	4228	216	8798.47	0.0245	0.0191	2.08

Fatal cardiovascular event							
Tocilizumab	≤ median	779	8	1706.79	0.0047	0.0047	2.19
	> median	703	15	1442.17	0.0104	0.0060	2.05
Other biologics	≤ median	7911	50	18549.46	0.0027	0.0027	2.34
	> median	4228	73	9063.74	0.0081	0.0051	2.14
Non-fatal myocardial infarction							
Tocilizumab	≤ median	779	8	1700.31	0.0047	0.0047	2.18
	> median	703	14	1425.08	0.0098	0.0078	2.03
Other biologics	≤ median	7911	112	18356.12	0.0061	0.0062	2.32
	> median	4228	91	8926.44	0.0102	0.0096	2.11
Non-fatal stroke							
Tocilizumab	≤ median	779	6	1696.53	0.0035	0.0035	2.18
	> median	703	9	1431.47	0.0063	0.0050	2.04
Other biologics	≤ median	7911	75	18430.38	0.0041	0.0041	2.33
	> median	4228	92	8926.73	0.0103	0.0071	2.11
GI perforation							
Tocilizumab	≤ median	779	7	1702.51	0.0041	0.0041	2.19
	> median	703	6	1437.48	0.0042	0.0037	2.04
Other biologics	≤ median	7911	22	18522.60	0.0012	0.0011	2.34
	> median	4228	15	9044.61	0.0017	0.0015	2.14
Aplastic anemia							
Tocilizumab	≤ median	779	1	1706.65	0.0006	0.0006	2.19
	> median	703	0	1442.17	0.0000	0.0000	2.05
Other biologics	≤ median	7911	9	18530.64	0.0005	0.0005	2.34
	> median	4228	3	9062.45	0.0003	0.0003	2.14
Serious hepatic event							
Tocilizumab	≤ median	779	8	1693.15	0.0047	0.0047	2.17
	> median	703	3	1440.91	0.0021	0.0019	2.05
Other biologics	≤ median	7911	49	18484.63	0.0027	0.0027	2.34
	> median	4228	34	8985.59	0.0038	0.0041	2.13
Any Hospitalization							
Tocilizumab	≤ median	779	240	1244.41	0.1929	0.1929	1.60
	> median	703	306	913.00	0.3352	0.3045	1.30
Other biologics	≤ median	7911	2111	14390.55	0.1467	0.1479	1.82
	> median	4228	1705	5830.39	0.2924	0.2553	1.38
All-cause mortality							
Tocilizumab	≤ median	779	14	1706.79	0.0082	0.0082	2.19
	> median	703	31	1442.17	0.0215	0.0131	2.05
Other biologics	≤ median	7911	147	18549.46	0.0079	0.0078	2.34
	> median	4228	196	9063.74	0.0216	0.0153	2.14
Notes: IR Incidence Rate. Std IR standardised to the age/sex distribution in the tocilizumab first stratum cohort.							

Table 8c. Results from crude and adjusted Cox regressions comparing tocilizumab to other biologic drugs, stratified by HAQ (with the median of the tocilizumab group as cutoff value, i.e. 1.25)									
Outcome	**HAQ**	**HRa**	**95% CI**	**HRb**	**95% CI**	**HRc**	**95% CI**	**HRd**	**95% CI**
Hospitalized infections	≤ median	0.99	(0.69-1.42)	0.94	(0.65-1.34)	0.93	(0.65-1.35)	0.93	(0.65-1.35)
	> median	0.75	(0.53-1.06)	0.80	(0.56-1.14)	0.86	(0.60-1.22)	0.86	(0.60-1.22)
	Aggregate estimate	0.85	(0.66-1.10)	0.87	(0.67-1.11)	0.90	(0.70-1.16)	0.90	(0.70-1.16)
Opportunistic infections	> median	1.51	(0.67-3.39)	1.59	(0.70-3.59)	1.49	(0.65-3.40)	1.49	(0.65-3.40)
	Aggregate estimate	0.91	(0.46-1.81)	0.92	(0.46-1.84)	0.90	(0.45-1.79)	0.90	(0.45-1.79)
All primary invasive cancers excluding nmsc	≤ median	1.21	(0.78-1.87)	1.21	(0.78-1.87)	1.26	(0.81-1.95)	1.26	(0.81-1.95)
	> median	1.08	(0.64-1.82)	1.07	(0.63-1.82)	1.04	(0.60-1.79)	1.04	(0.60-1.79)
	Aggregate estimate	1.16	(0.83-1.62)	1.16	(0.83-1.62)	1.17	(0.83-1.64)	1.17	(0.83-1.64)
Non-melanoma and basal cell skin cancers	≤ median	0.73	(0.42-1.25)	0.73	(0.42-1.26)	0.78	(0.45-1.35)	0.78	(0.45-1.35)
	> median	0.68	(0.40-1.16)	0.69	(0.40-1.17)	0.63	(0.35-1.11)	0.63	(0.35-1.11)
	Aggregate estimate	0.71	(0.48-1.03)	0.71	(0.48-1.03)	0.69	(0.47-1.03)	0.69	(0.47-1.03)
Cardiovascular event	≤ median	1.03	(0.61-1.73)	1.00	(0.59-1.68)	1.00	(0.59-1.69)	1.00	(0.59-1.69)
	> median	0.67	(0.39-1.15)	0.72	(0.42-1.24)	0.86	(0.49-1.50)	0.86	(0.49-1.50)
	Aggregate estimate	0.82	(0.56-1.19)	0.83	(0.57-1.21)	0.91	(0.62-1.34)	0.91	(0.62-1.34)
Fatal cardiovascular event	≤ median	2.47	(1.08-5.64)	2.13	(0.92-4.95)	2.12	(0.91-4.93)	2.12	(0.91-4.93)
	> median	0.85	(0.36-2.01)	0.97	(0.41-2.31)	0.96	(0.37-2.48)	0.96	(0.37-2.48)
	Aggregate estimate	1.35	(0.74-2.44)	1.40	(0.77-2.53)	1.42	(0.76-2.64)	1.42	(0.76-2.64)
Myocardial infarction	≤ median	0.82	(0.38-1.79)	0.80	(0.37-1.75)	0.82	(0.37-1.79)	0.82	(0.37-1.79)
	> median	0.60	(0.26-1.38)	0.60	(0.26-1.40)	0.81	(0.34-1.89)	0.81	(0.34-1.89)
	Aggregate estimate	0.70	(0.40-1.24)	0.69	(0.39-1.22)	0.81	(0.45-1.44)	0.81	(0.45-1.44)
Stroke	≤ median	1.02	(0.43-2.37)	0.96	(0.41-2.25)	0.96	(0.41-2.27)	0.96	(0.41-2.27)
	> median	0.42	(0.15-1.15)	0.45	(0.16-1.23)	0.54	(0.19-1.50)	0.54	(0.19-1.50)
	Aggregate estimate	0.65	(0.34-1.24)	0.67	(0.35-1.27)	0.74	(0.38-1.42)	0.74	(0.38-1.42)
GI perforation	≤ median	2.41	(0.88-6.63)	2.16	(0.78-5.99)	2.03	(0.72-5.71)	2.03	(0.72-5.71)
	> median	3.85	(1.22-12.19)	3.62	(1.12-11.73)	2.50	(0.65-9.65)	2.50	(0.65-9.65)
	Aggregate estimate	2.86	(1.34-6.11)	2.75	(1.28-5.91)	2.27	(1.01-5.10)	2.27	(1.01-5.10)
Serious hepatic event	≤ median	1.93	(0.85-4.38)	1.99	(0.87-4.52)	1.78	(0.78-4.06)	1.78	(0.78-4.06)
	Aggregate estimate	1.30	(0.64-2.64)	1.33	(0.66-2.70)	1.29	(0.63-2.64)	1.29	(0.63-2.64)
Any hospitalization	≤ median	1.18	(1.01-1.39)	1.14	(0.97-1.34)	1.14	(0.97-1.33)	1.14	(0.97-1.33)
	> median	1.08	(0.93-1.26)	1.11	(0.95-1.30)	1.16	(0.99-1.36)	1.16	(0.99-1.36)
	Aggregate estimate	1.13	(1.01-1.26)	1.13	(1.01-1.26)	1.15	(1.03-1.28)	1.15	(1.03-1.28)

All cause mortality	≤ median	1.36	(0.74-2.49)	1.35	(0.73-2.49)	1.44	(0.77-2.67)	1.44	(0.77-2.67)
	> median	0.94	(0.56-1.59)	1.06	(0.62-1.80)	1.10	(0.63-1.92)	1.10	(0.63-1.92)
	Aggregate estimate	1.09	(0.73-1.62)	1.13	(0.76-1.69)	1.18	(0.78-1.78)	1.18	(0.78-1.78)

Notes: Analysis was only made for comparisons where both cohorts had at least 5 observed events. Some rows were intentionally deleted. HR: Hazard Ratio. CI: Confidence Interval. HRa: stratified for year at start, adjusted for age and sex. HRb: stratified for year at start, adjusted for age, sex, prior number of days in inpatient care, history of infection, cancer, MI, diabetes, COPD and joint replacement surgery. HRc: stratified for year at start, adjusted for age, sex, prior number of days in inpatient care, history of infection, cancer, MI, diabetes, COPD, joint replacement surgery, Rheumatoid factor, DMARDs and steroids; Complete case analysis. HRd: as HRc but using a missing indicators.

Table 7d. Total number of events, crude and standardized incidence rates for the tocilizumab cohort and the other biologics cohort, stratified on the median of CRP in the tocilizumab cohort (i.e. 12.0).

Outcome	Stratified on CRP	Patients	Events	Person-Years	IR	Std IR	Mean follow-up, yrs
Hospitalized infections							
Tocilizumab	≤ median	836	42	1577.43	0.0266	0.0266	1.89
	> median	831	76	1844.29	0.0412	0.0389	2.22
Other biologics	≤ median	8322	533	17960.54	0.0297	0.0295	2.16
	> median	5143	525	11183.68	0.0469	0.0376	2.17
Tuberculosis							
Tocilizumab	≤ median	836	0	1608.68	0.0000	0.0000	1.92
	> median	831	0	1931.19	0.0000	0.0000	2.32
Other biologics	≤ median	8322	9	18717.52	0.0005	0.0005	2.25
	> median	5143	11	11927.83	0.0009	0.0008	2.32
Opportunistic infections							
Tocilizumab	≤ median	836	2	1607.54	0.0012	0.0012	1.92
	> median	831	9	1918.46	0.0047	0.0042	2.31
Other biologics	≤ median	8322	61	18615.95	0.0033	0.0033	2.24
	> median	5143	74	11829.64	0.0063	0.0054	2.30
Cancer							
Tocilizumab	≤ median	836	26	2930.34	0.0089	0.0089	3.51
	> median	831	40	3087.43	0.0130	0.0115	3.72
Other biologics	≤ median	8322	285	32162.18	0.0089	0.0086	3.86
	> median	5143	257	20720.33	0.0124	0.0103	4.03
Non-melanoma and basal cell skin cancers							
Tocilizumab	≤ median	836	21	2917.89	0.0072	0.0072	3.49
	> median	831	32	3091.42	0.0104	0.0091	3.72
Other biologics	≤ median	8322	334	31775.46	0.0105	0.0103	3.82
	> median	5143	238	20622.88	0.0115	0.0085	4.01
Lymphoma							
Tocilizumab	≤ median	836	2	2959.57	0.0007	0.0007	3.54
	> median	831	1	3158.41	0.0003	0.0003	3.80
Other biologics	≤ median	8322	13	32674.77	0.0004	0.0004	3.93
	> median	5143	22	21179.14	0.0010	0.0008	4.12
Demyelinating disorders							
Tocilizumab	≤ median	836	1	1608.21	0.0006	0.0006	1.92
	> median	831	0	1931.19	0.0000	0.0000	2.32
Other biologics	≤ median	8322	9	18696.86	0.0005	0.0005	2.25
	> median	5143	9	11916.19	0.0008	0.0008	2.32
Acute cardiovascular event (MI or stroke, fatal or not)							
Tocilizumab	≤ median	836	17	1597.96	0.0106	0.0106	1.91
	> median	831	38	1893.82	0.0201	0.0167	2.28
Other biologics	≤ median	8322	222	18412.82	0.0121	0.0118	2.21
	> median	5143	249	11627.77	0.0214	0.0154	2.26

Fatal cardiovascular event							
Tocilizumab	≤ median	836	8	1608.68	0.0050	0.0050	1.92
	> median	831	16	1931.19	0.0083	0.0062	2.32
Other biologics	≤ median	8322	61	18720.77	0.0033	0.0030	2.25
	> median	5143	80	11934.22	0.0067	0.0043	2.32
Non-fatal myocardial infarction							
Tocilizumab	≤ median	836	5	1603.08	0.0031	0.0031	1.92
	> median	831	18	1912.96	0.0094	0.0077	2.30
Other biologics	≤ median	8322	108	18550.86	0.0058	0.0057	2.23
	> median	5143	119	11743.26	0.0101	0.0074	2.28
Non-fatal stroke							
Tocilizumab	≤ median	836	6	1603.56	0.0037	0.0037	1.92
	> median	831	12	1911.07	0.0063	0.0054	2.30
Other biologics	≤ median	8322	84	18577.21	0.0045	0.0044	2.23
	> median	5143	93	11809.44	0.0079	0.0057	2.30
GI perforation							
Tocilizumab	≤ median	836	4	1607.62	0.0025	0.0025	1.92
	> median	831	10	1923.13	0.0052	0.0041	2.31
Other biologics	≤ median	8322	20	18698.17	0.0011	0.0010	2.25
	> median	5143	21	11897.98	0.0018	0.0014	2.31
Aplastic anemia							
Tocilizumab	≤ median	836	0	1608.68	0.0000	0.0000	1.92
	> median	831	1	1931.05	0.0005	0.0003	2.32
Other biologics	≤ median	8322	6	18713.09	0.0003	0.0003	2.25
	> median	5143	5	11928.01	0.0004	0.0004	2.32
Serious hepatic event							
Tocilizumab	≤ median	836	7	1599.15	0.0044	0.0044	1.91
	> median	831	5	1925.77	0.0026	0.0026	2.32
Other biologics	≤ median	8322	57	18633.52	0.0031	0.0031	2.24
	> median	5143	41	11858.38	0.0035	0.0036	2.31
Any Hospitalization							
Tocilizumab	≤ median	836	258	1166.86	0.2211	0.2211	1.40
	> median	831	360	1243.83	0.2894	0.2744	1.50
Other biologics	≤ median	8322	2356	14158.45	0.1664	0.1631	1.70
	> median	5143	1974	8100.50	0.2437	0.2079	1.58
All-cause mortality							
Tocilizumab	≤ median	836	17	1608.68	0.0106	0.0106	1.92
	> median	831	38	1931.19	0.0197	0.0155	2.32
Other biologics	≤ median	8322	164	18720.77	0.0088	0.0082	2.25
	> median	5143	237	11934.22	0.0199	0.0134	2.32
Notes: IR Incidence Rate. Std IR standardised to the age/sex distribution in the tocilizumab first stratum cohort.							

Table 8d. Results from crude and adjusted Cox regressions comparing tocilizumab to other biologic drugs, stratified by crp (with the median of the tocilizumab group as cutoff value, i.e. 12.0)									
Outcome	**CRP**	**HRa**	**95% CI**	**HRb**	**95% CI**	**HRc**	**95% CI**	**HRd**	**95% CI**
Hospitalized infections	≤ median	0.88	(0.60-1.28)	0.88	(0.61-1.28)	0.90	(0.62-1.31)	0.90	(0.62-1.31)
	> median	0.83	(0.61-1.12)	0.84	(0.62-1.13)	0.86	(0.64-1.17)	0.86	(0.64-1.17)
	Aggregate estimate	0.85	(0.67-1.07)	0.85	(0.67-1.08)	0.87	(0.69-1.10)	0.87	(0.69-1.10)
Opportunistic infections	> median	0.82	(0.37-1.82)	0.86	(0.39-1.89)	0.89	(0.40-1.99)	0.89	(0.40-1.99)
	Aggregate estimate	0.74	(0.37-1.47)	0.75	(0.38-1.50)	0.75	(0.38-1.50)	0.75	(0.38-1.50)
All primary invasive cancers excluding nmsc	≤ median	1.19	(0.74-1.92)	1.20	(0.75-1.93)	1.21	(0.75-1.95)	1.21	(0.75-1.95)
	> median	1.28	(0.87-1.90)	1.28	(0.86-1.89)	1.29	(0.86-1.92)	1.29	(0.86-1.92)
	Aggregate estimate	1.25	(0.92-1.69)	1.25	(0.92-1.69)	1.26	(0.93-1.72)	1.26	(0.93-1.72)
Non-melanoma and basal cell skin cancers	≤ median	0.74	(0.44-1.22)	0.71	(0.43-1.19)	0.74	(0.44-1.23)	0.74	(0.44-1.23)
	> median	0.80	(0.50-1.27)	0.82	(0.51-1.30)	0.77	(0.47-1.26)	0.77	(0.47-1.26)
	Aggregate estimate	0.77	(0.55-1.08)	0.76	(0.54-1.07)	0.75	(0.53-1.07)	0.75	(0.53-1.07)
Cardiovascular event	≤ median	0.74	(0.41-1.33)	0.74	(0.41-1.33)	0.80	(0.44-1.44)	0.80	(0.44-1.44)
	> median	0.87	(0.56-1.36)	0.87	(0.56-1.37)	0.94	(0.60-1.49)	0.94	(0.60-1.49)
	Aggregate estimate	0.83	(0.58-1.18)	0.82	(0.58-1.18)	0.88	(0.61-1.26)	0.88	(0.61-1.26)
Fatal cardiovascular event	≤ median	1.54	(0.65-3.66)	1.59	(0.67-3.79)	1.66	(0.69-4.01)	1.66	(0.69-4.01)
	> median	1.11	(0.53-2.36)	1.09	(0.51-2.31)	1.09	(0.49-2.45)	1.09	(0.49-2.45)
	Aggregate estimate	1.28	(0.72-2.26)	1.26	(0.71-2.22)	1.25	(0.69-2.26)	1.25	(0.69-2.26)
Myocardial infarction	≤ median	0.37	(0.12-1.18)	0.37	(0.12-1.18)	0.41	(0.13-1.32)	0.41	(0.13-1.32)
	> median	0.90	(0.49-1.65)	0.90	(0.49-1.66)	1.06	(0.57-1.96)	1.06	(0.57-1.96)
	Aggregate estimate	0.70	(0.41-1.20)	0.70	(0.41-1.19)	0.81	(0.47-1.38)	0.81	(0.47-1.38)
Stroke	≤ median	0.89	(0.36-2.24)	0.92	(0.37-2.31)	1.00	(0.40-2.53)	1.00	(0.40-2.53)
	> median	0.51	(0.21-1.28)	0.53	(0.21-1.33)	0.57	(0.23-1.43)	0.57	(0.23-1.43)
	Aggregate estimate	0.66	(0.35-1.26)	0.68	(0.35-1.29)	0.73	(0.38-1.41)	0.73	(0.38-1.41)
GI perforation	> median	2.63	(1.02-6.81)	2.41	(0.92-6.32)	2.00	(0.70-5.73)	2.00	(0.70-5.73)
	Aggregate estimate	2.34	(1.10-4.94)	2.31	(1.08-4.91)	1.80	(0.81-4.01)	1.80	(0.81-4.01)
Serious hepatic event	≤ median	1.64	(0.69-3.87)	1.67	(0.70-3.98)	1.68	(0.70-4.02)	1.68	(0.70-4.02)
	> median	0.79	(0.28-2.28)	0.81	(0.28-2.34)	0.75	(0.26-2.18)	0.75	(0.26-2.18)
	Aggregate estimate	1.19	(0.61-2.32)	1.20	(0.61-2.34)	1.16	(0.59-2.29)	1.16	(0.59-2.29)
Any hospitalization	≤ median	1.13	(0.96-1.32)	1.12	(0.96-1.31)	1.12	(0.96-1.31)	1.12	(0.96-1.31)
	> median	1.09	(0.95-1.25)	1.09	(0.95-1.25)	1.12	(0.97-1.29)	1.12	(0.97-1.29)
	Aggregate estimate	1.11	(1.00-1.23)	1.10	(1.00-1.23)	1.12	(1.01-1.24)	1.12	(1.01-1.24)

All cause mortality	≤ median	1.38	(0.75-2.52)	1.43	(0.78-2.62)	1.49	(0.81-2.75)	1.49	(0.81-2.75)
	> median	1.01	(0.65-1.59)	1.02	(0.65-1.60)	1.06	(0.66-1.69)	1.06	(0.66-1.69)
	Aggregate estimate	1.13	(0.79-1.63)	1.11	(0.78-1.60)	1.15	(0.79-1.67)	1.15	(0.79-1.67)

Notes: Analysis was only made for comparisons where both cohorts had at least 5 observed events. Some rows were intentionally deleted. HR: Hazard Ratio. CI: Confidence Interval. HRa: stratified for year at start, adjusted for age and sex. HRb: stratified for year at start, adjusted for age, sex, prior number of days in inpatient care, history of infection, cancer, MI, diabetes, COPD and joint replacement surgery. HRc: stratified for year at start, adjusted for age, sex, prior number of days in inpatient care, history of infection, cancer, MI, diabetes, COPD, joint replacement surgery, Rheumatoid factor, DMARDs and steroids; Complete case analysis. HRd: as HRc but using a missing indicators.

Table 9. Total number of events, crude and standardized incidence rates for the tocilizumab cohort, stratified on the mode of administration (subcutaneous or intravenous (iv)) and the median monthly dose for the iv group (with doses ≤ 560 mg/month as low dose, and doses > 560 mg/month as high dose).

Outcome	Stratified on administration mode and iv dose	Patients	Events	Person-Years	IR	Std IR	Mean follow-up, yrs
Hospitalized infections							
Tocilizumab	iv_low dose	781	70	1825.02	0.0384	0.0384	2.34
	iv_high dose	718	48	1736.13	0.0276	0.0357	2.42
	subcutaneous	551	18	551.58	0.0326	0.0326	1.00
Tuberculosis							
Tocilizumab	iv_low dose	781	0	1894.28	0.0000	0.0000	2.43
	iv_high dose	718	0	1792.30	0.0000	0.0000	2.50
	subcutaneous	551	0	565.99	0.0000	0.0000	1.03
Opportunistic infections							
Tocilizumab	iv_low dose	781	9	1888.05	0.0048	0.0048	2.42
	iv_high dose	718	3	1784.50	0.0017	0.0031	2.49
	subcutaneous	551	2	565.50	0.0035	0.0029	1.03
Cancer							
Tocilizumab	iv_low dose	781	36	3298.92	0.0109	0.0109	4.22
	iv_high dose	718	29	2991.13	0.0097	0.0075	4.17
	subcutaneous	551	12	786.07	0.0153	0.0138	1.43
Non-melanoma and basal cell skin cancers							
Tocilizumab	iv_low dose	781	28	3278.72	0.0085	0.0085	4.20
	iv_high dose	718	31	2981.37	0.0104	0.0106	4.15
	subcutaneous	551	10	798.51	0.0125	0.0181	1.45
Lymphoma							
Tocilizumab	iv_low dose	781	0	3356.48	0.0000	0.0000	4.30
	iv_high dose	718	2	3048.85	0.0007	0.0012	4.25
	subcutaneous	551	1	801.16	0.0012	0.0012	1.45
Demyelinating disorders							
Tocilizumab	iv_low dose	781	1	1893.80	0.0005	0.0005	2.42
	iv_high dose	718	0	1792.30	0.0000	0.0000	2.50
	subcutaneous	551	0	565.99	0.0000	0.0000	1.03
Acute cardiovascular event (MI or stroke, fatal or not)							
Tocilizumab	iv_low dose	781	31	1870.24	0.0166	0.0166	2.39
	iv_high dose	718	23	1765.07	0.0130	0.0112	2.46
	subcutaneous	551	6	565.27	0.0106	0.0197	1.03
Fatal cardiovascular event							
Tocilizumab	iv_low dose	781	14	1894.28	0.0074	0.0074	2.43
	iv_high dose	718	10	1792.30	0.0056	0.0061	2.50
	subcutaneous	551	3	565.99	0.0053	0.0121	1.03

Non-fatal myocardial infarction							
Tocilizumab	iv_low dose	781	11	1887.52	0.0058	0.0058	2.42
	iv_high dose	718	10	1775.70	0.0056	0.0041	2.47
	subcutaneous	551	3	565.28	0.0053	0.0077	1.03
Non-fatal stroke							
Tocilizumab	iv_low dose	781	14	1876.73	0.0075	0.0075	2.40
	iv_high dose	718	5	1780.96	0.0028	0.0012	2.48
	subcutaneous	551	1	565.99	0.0018	0.0022	1.03
GI perforation							
Tocilizumab	iv_low dose	781	7	1891.29	0.0037	0.0037	2.42
	iv_high dose	718	8	1783.51	0.0045	0.0052	2.48
	subcutaneous	551	1	565.46	0.0018	0.0012	1.03
Aplastic anemia							
Tocilizumab	iv_low dose	781	1	1894.14	0.0005	0.0005	2.43
	iv_high dose	718	0	1792.30	0.0000	0.0000	2.50
	subcutaneous	551	0	565.99	0.0000	0.0000	1.03
Serious hepatic event							
Tocilizumab	iv_low dose	781	3	1889.08	0.0016	0.0016	2.42
	iv_high dose	718	7	1783.24	0.0039	0.0021	2.48
	subcutaneous	551	5	561.68	0.0089	0.0076	1.02
Any Hospitalization							
Tocilizumab	iv_low dose	781	336	1261.71	0.2663	0.2663	1.62
	iv_high dose	718	275	1233.10	0.2230	0.2311	1.72
	subcutaneous	551	116	470.05	0.2468	0.2612	0.85
All-cause mortality							
Tocilizumab	iv_low dose	781	31	1894.28	0.0164	0.0164	2.43
	iv_high dose	718	21	1792.30	0.0117	0.0136	2.50
	subcutaneous	551	8	565.99	0.0141	0.0189	1.03
Notes: IR Incidence Rate. Std IR standardised to the age/sex distribution in the tocilizumab first stratum cohort.							

Table 10. Results from crude and adjusted Cox regressions comparing three subgroups for tocilizumab to other biologic drugs, the three subgroups being defined by the mode of administration and the dose received per month.

Outcome	Administration mode and dose/month	HRa	95% CI	HRb	95% CI	HRc	95% CI	HRd	95% CI
Hospitalized infections	iv_low dose	0.89	(0.66-1.21)	0.84	(0.62-1.14)	0.82	(0.58-1.15)	0.86	(0.63-1.17)
	iv_high dose	0.80	(0.58-1.11)	0.85	(0.62-1.17)	0.86	(0.61-1.21)	0.86	(0.62-1.19)
	subcutaneous	0.94	(0.55-1.60)	0.98	(0.57-1.67)	1.12	(0.64-1.96)	0.96	(0.56-1.64)
Opportunistic infections	iv_low dose	1.34	(0.65-2.74)	1.30	(0.63-2.66)	1.16	(0.50-2.66)	1.28	(0.62-2.63)
All primary invasive cancers excluding non-melanoma skin cancers	iv_low dose	1.15	(0.76-1.76)	1.15	(0.76-1.75)	1.36	(0.88-2.10)	1.19	(0.78-1.82)
	iv_high dose	1.00	(0.65-1.56)	1.00	(0.65-1.56)	1.06	(0.66-1.68)	1.00	(0.64-1.57)
	subcutaneous	1.99	(1.07-3.67)	1.97	(1.06-3.64)	2.05	(1.04-4.06)	2.04	(1.10-3.78)
Non-melanoma and basal cell skin cancers	iv_low dose	0.76	(0.49-1.20)	0.76	(0.49-1.19)	0.60	(0.34-1.04)	0.79	(0.50-1.24)
	iv_high dose	0.99	(0.65-1.51)	1.00	(0.65-1.51)	0.82	(0.51-1.34)	1.00	(0.65-1.54)
	subcutaneous	1.05	(0.49-2.24)	1.05	(0.49-2.23)	1.02	(0.41-2.49)	0.98	(0.44-2.23)
Cardiovascular event	iv_low dose	0.81	(0.50-1.31)	0.78	(0.48-1.27)	0.87	(0.51-1.46)	0.84	(0.52-1.37)
	iv_high dose	0.86	(0.55-1.36)	0.90	(0.57-1.41)	0.95	(0.59-1.54)	0.91	(0.57-1.46)
	subcutaneous	0.72	(0.27-1.96)	0.72	(0.27-1.96)	0.73	(0.23-2.33)	0.77	(0.28-2.10)
Fatal cardiovascular event	iv_low dose	1.33	(0.65-2.73)	1.23	(0.60-2.54)	1.24	(0.57-2.70)	1.30	(0.63-2.68)
	iv_high dose	1.36	(0.66-2.82)	1.50	(0.72-3.11)	1.20	(0.52-2.78)	1.35	(0.62-2.94)
Non-fatal myocardial infarction	iv_low dose	0.50	(0.21-1.22)	0.50	(0.21-1.22)	0.65	(0.27-1.60)	0.55	(0.23-1.35)
	iv_high dose	0.82	(0.43-1.56)	0.85	(0.45-1.60)	1.01	(0.53-1.93)	0.92	(0.48-1.75)
Non-fatal stroke	iv_low dose	0.87	(0.41-1.85)	0.84	(0.39-1.79)	0.89	(0.39-2.03)	0.90	(0.42-1.93)
	iv_high dose	0.47	(0.18-1.28)	0.49	(0.18-1.33)	0.59	(0.22-1.62)	0.53	(0.20-1.45)
GI perforation	iv_low dose	1.36	(0.42-4.39)	1.33	(0.41-4.32)	0.94	(0.22-3.98)	0.80	(0.19-3.34)
	iv_high dose	3.36	(1.49-7.58)	3.61	(1.59-8.15)	2.61	(0.98-6.92)	3.38	(1.48-7.72)
Serious hepatic event	iv_high dose	1.38	(0.60-3.16)	1.42	(0.62-3.27)	1.55	(0.66-3.60)	1.40	(0.61-3.23)
	subcutaneous	2.57	(1.01-6.53)	2.62	(1.02-6.71)	1.19	(0.28-5.01)	1.95	(0.69-5.51)
Any hospitalization	iv_low dose	1.15	(1.00-1.32)	1.10	(0.96-1.27)	1.10	(0.94-1.28)	1.09	(0.95-1.26)
	iv_high dose	1.02	(0.88-1.17)	1.03	(0.90-1.19)	1.11	(0.96-1.30)	1.05	(0.91-1.21)
	subcutaneous	1.16	(0.93-1.44)	1.18	(0.95-1.47)	1.17	(0.92-1.50)	1.15	(0.92-1.44)
All cause mortality	iv_low dose	1.17	(0.74-1.86)	1.14	(0.72-1.81)	1.32	(0.81-2.15)	1.21	(0.76-1.92)
	iv_high dose	0.90	(0.53-1.55)	0.93	(0.54-1.61)	0.90	(0.50-1.62)	0.90	(0.51-1.58)
	subcutaneous	1.82	(0.74-4.49)	1.88	(0.76-4.66)	2.08	(0.83-5.22)	1.86	(0.75-4.62)

Notes: Analysis was only made for comparisons where both cohorts had at least 5 observed events. Some rows were intentionally deleted. HR: Hazard Ratio. CI: Confidence Interval. HRa: stratified for year at start, adjusted for age and sex. HRb: stratified for year at start, adjusted for age, sex, prior number of days in

inpatient care, history of infection, cancer, MI, diabetes, COPD and joint replacement surgery. HRc: stratified for year at start, adjusted for age, sex, prior number of days in inpatient care, history of infection, cancer, MI, diabetes, COPD, joint replacement surgery, Rheumatoid factor, HAQ (linear), RA disease duration, DAS28 (linear), DMARDs and steroids; Complete case analysis. HRd: as HRc but using a missing indicator and quartiles for HAQ and DAS28.