NI PASS PROTOCOL (SECONDARY DATA USE)

TITLE:	**COMPARATIVE SAFETY OF TOCILIZUMAB VERSUS OTHER BIOLOGIC DMARDS IN PATIENTS WITH RHEUMATOID ARTHRITIS: A LARGE MULTI-DATABASE COHORT STUDY**
PROTOCOL NUMBER:	MA39102
VERSION NUMBER:	1.0
[redacted] **LEAD AUTHOR:** **Roche LEAD AUTHOR**	[redacted] USA Phone: [redacted]; Fax: [redacted] Email: [redacted]
DATE FINAL:	See electronic date stamp below

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Signatory (Clinical)	04-Aug-2017 09:59:44 04-Aug-2017 10:53:19

Based on protocol template Version 2.0 released on 30 Oct 2016

EU PAS REGISTER NUMBER:	EUPAS19948
ACTIVE SUBSTANCE:	Tocilizumab
STUDIED MEDICINAL PRODUCT:	Tocilizumab
PRODUCT REFERENCE NUMBER:	NA
PROCEDURE NUMBER{S}:	NA
JOINT PASS	No
RESEARCH QUESTION AND OBJECTIVES:	The main objective of this NIS is to compare rates of different safety events including malignancy excluding non-melanoma skin cancer [NMSC], serious bacterial or viral infection, opportunistic infection and herpes zoster, between tocilizumab and tumor necrosis factor-alpha inhibitors.
COUNTRY OF STUDY POPULATION:	USA
MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration Ltd 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom
MAH CONTACT PERSON:	[redacted] MD , MBA [redacted]. Hoffmann-La Roche Ltd [redacted] Grenzacherstrasse 124 CH - 4070 Basel tel: [redacted] mobile: [redacted]

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
bDMARD	Biologic disease-modifying antirheumatic drug
[redacted]	[redacted]
CCAE	Commercial Claims and Encounters
CI	Confidence interval
COBRA	Consolidated Omnibus Budget Reconciliation Act
CRO	Contract research organization
CPT	Current Procedural Terminology
DMARD	Disease-modifying antirheumatic drug
EC	Ethics Committee
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiological Practice
HPV	Human papillomavirus
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPE	International Society of Pharmacoepidemiology
ISPOR	International Society For Pharmacoeconomics and Outcomes Research
HR	Hazard ratio
NDC	National drug code
NMSC	Non-melanoma skin cancer
NSAID	Nonsteroidal antiinflammatory drug
PS	Propensity score
QPPV	Qualified Person for Pharmacovigilance
RA	Rheumatoid arthritis
TCZ	Tocilizumab
TNFi	Tumor necrosis factor inhibitor

2. RESPONSIBLE PARTIES

Protocol Development Responsible

[redacted] MD, ScD

Principal Investigator

[redacted]

Phone: [redacted]; Fax: [redacted]

Email: [redacted]

Scientific Responsible

[redacted] MD , MBA

[redacted] Hoffmann-La Roche Ltd

[redacted]

Grenzacherstrasse 124

CH - 4070 Basel

tel: [redacted]

mobile: [redacted]

NIS Data Science Responsible

3. ABSTRACT/SYNOPSIS

TITLE:	**COMPARATIVE SAFETY OF TOCILIZUMAB VERSUS OTHER BIOLOGIC DMARDS IN PATIENTS WITH RHEUMATOID ARTHRITIS: A LARGE MULTI-DATABASE COHORT STUDY**
PROTOCOL NUMBER:	MA39102
VERSION NUMBER:	1.0
DATE OF SYNOPSIS:	[redacted]
EU PAS REGISTER NUMBER:	EUPAS19948
STUDIED MEDICINAL PRODUCT:	Tocilizumab (ACTEMRA®)
SCIENTIFIC RESPONSIBLE:	[redacted]
[redacted] **MAIN AUTHOR:**	[redacted]
Roche Main AUTHOR	[redacted]
PHASE:	IV, non-interventional study
INDICATION:	Rheumatoid Arthritis
MARKETING AUTHORIZATION HOLDER:	Roche Registration Ltd 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom

Rationale and Background

Because the majority of previous safety studies on TCZ did not include a direct comparison to a different biologic drug, and if they did so, were small, high-quality population-representative evidence on comparative safety of TCZ versus other biologics for RA on the risk of serious infection and malignancy is needed.

Research Question and Objectives

The primary objectives (specified as Aims here and throughout the protocol) for this study are:

- Aim 1: To examine the rate of malignancy excluding non-melanoma skin cancer (NMSC) in RA patients starting TCZ versus TNFi
- Aim 2: To investigate the rate of serious bacterial, viral or opportunistic infection in RA patients starting TCZ versus TNFi.

Study Design

Cohort study based on three large healthcare administrative claims databases (i.e. three separate RA cohorts will be created from each database.)

[redacted]

Variables

Primary Safety Variables

The primary variables for this study are as follows:

- Aim 1: incident malignancies excluding NMSC defined by using previously validated claims-based algorithms
- Aim 2: serious infections including bacterial, viral or opportunistic infection considered as an individual and composite endpoint of any claim

[redacted]

Data Sources

This study will use three large healthcare administrative claims databases based in the US. The data sources are Medicare (2008-2015), IMS PharMetrics (2006-2015) and Truven MarketScan (2009-2015) databases.

[redacted]

Data Analysis

The primary analysis will be propensity score (PS) matched time to event safety analyses for each outcome comparing risk in TCZ compared with a specified comparator. [redacted]

Analyses will be performed in each of the three databases separately and then, if deemed appropriate [redacted] the HRs will be pooled [redacted] for a [redacted], weighted HR. Additional analyses include descriptive statistics, incorporation of time-varying confounders, and pre-specified sensitivity analyses to evaluate the robustness of some of the parameter assumptions.

Milestones

Start Date of Study:

The study start date will be the earliest date of the study dataset creation among the three databases. The planned start date is July 15, 2017.

End of Study

The end of the study will be the date when analysis of data required to fulfill study objectives is complete. The planned end of study date is May 31, 2018.

4. AMENDMENTS AND UPDATES

5. MILESTONES

Milestone	Planned Date
Registration of protocol in the EU PAS register	Jun 2017
Start of study dataset creation	July 2017
Database-specific analyses run	November 2017
Pooled analyses run	December 2017
Submission to EULAR 2018	January 2018
Analyses finalized	April 2018
End of study	May 2018
Final report of study results (CSR)	May 2018
Registration of the results in the EU PAS register	May 2018

6. RATIONALE AND BACKGROUND

The American College of Rheumatology (ACR) guidelines emphasize early and sustained use of DMARDs for RA (Saag et al 2008; Singh et al 2012). Over the past few decades, major advances have occurred in understanding of the pathophysiologic mechanism underlying rheumatoid arthritis (RA). To date, there are many non-biologic DMARDs and biologic DMARDs (bDMARD) available and approved for treatment of RA. Tocilizumab (TCZ) was approved in the United States in January 2010 for RA. Currently, TCZ is mostly used as a second- or third-line biologic treatment.

While bDMARDs are highly effective in reducing RA activity and improving patient outcomes, these agents have been also associated with increased risks of adverse events such as infection and withdrawals due to adverse event (Singh et al 2012; Ramiro et al 2014; Michaud et al 2014). Recent meta-analyses of randomized controlled trials of bDMARDs including mostly tumor necrosis factor-alpha inhibitors (TNFi) showed that the risk of serious infection is increased among adalimumab-, certolizumab pegol-, or infliximab-treated patients versus the control but a decreased risk in etanercept-treated (Ramiro et al 2014; Michaud et al 2014). These studies indicate the existence of potentially important differences in the safety profile among five TNFi drugs and highlight the need for further research in head-to-head comparison between different bDMARDs.

Since TCZ is a relatively new drug, even fewer studies have conducted a head-to-head comparative safety study of TCZ versus other biologics. For cardiovascular safety study, the full report of the ENTRACTE trial will be available in near future. In addition to the ENTRACTE study, our group has conducted a large-scale multi-database cohort study that examined cardiovascular safety associated with TCZ use versus TNFi among patients with RA. In our cardiovascular cohort study, we utilized three large U.S. public and commercial health plans (e.g. Medicare, IMS PharMetrics and Truven MarketScan)

and found no increased rates of cardiovascular events in TCZ users versus TNFi (Kim et al 2017).

A number of cohort studies based on claims or a patient registry have studied the risk of serious infections or malignancy in bDMARDs (mainly TNFi) compared to non-biologic DMARDs. In a systematic review of 49 observational studies (Ramiro et al 2014), bDMARDs as well as non-biologics were generally safe but patients on TNFi had a higher risk of tuberculosis and serious infections and may have a slightly higher risk of herpes zoster versus non-biologic DMARDs. The risk of all types of malignancies or lymphoma did not appear to be increased in TNFi users but the risk of melanoma appeared to be higher in TNFi users compared to non-biologics. This systematic review published in 2014 identified only 2 studies that included non-TNFi biologics but neither presented data specific to non-TNFi. A recently published study that used data from clinical trials of TCZ showed the adjudicated malignancy rate (95% CI) of 1.26 per 100 person-years (1.09 to 1.44) and the standardized incidence ratio (95% CI) for all malignancies combined, excluding non-melanoma skin cancer, of 1.36 (1.01 to 1.80) for the U.S. and 1.81 (1.44 to 2.23) for non-US populations compared to those for the general populations (Rubbert-Roth et al 2016). The higher ratios were mainly driven by higher rates in lung and bronchus (US/non-US) malignancies and prostate cancer and non-Hodgkin lymphoma (non-US) in RA patients (Rubbert-Roth et al 2016). In another long-term post-marketing observational surveillance study of TCZ in Japan (Yamamoto et al 2015), the rate of serious infection was constant over the 3-year of TCZ treatment and the proportion of malignancy during followup was 2.24% (0.83/100 patient-yrs) with the standardized incidence ratio of 0.79 (95% CI, 0.66 to 0.95). A cohort study using Medicare data (2006-2011) showed the adjusted hazard ratio of 1.10 (95%CI 0.89-1.34) for hospitalized infection in TCZ users versus abatacept (Yun et al 2016).

In general, these previous safety studies on TCZ were small and/or did not include a direct comparison to a different biologic drug except for ENTRACTE trial and the study by Yun et al 2016. Therefore, high-quality population-representative evidence on comparative safety of TCZ versus other biologics for RA on the risk of serious infection and malignancy is urgently needed.

7. RESEARCH QUESTION AND OBJECTIVES

7.1 RESEARCH QUESTION

The main objective of this NIS study is to compare rates of different safety events that include malignancy excluding non-melanoma skin cancer (NMSC) and hospitalizations for serious infection including bacterial or viral infection, opportunistic infection and herpes zoster in RA patients using TCZ compared to TNFi.

7.2 OBJECTIVES

The primary objectives (specified as Aims here and throughout the protocol) for this study are as follows:

- Aim 1: To examine the rate of malignancy excluding NMSC in RA patients starting TCZ versus TNFi.
- Aim 2: To investigate the rate of serious bacterial, viral or opportunistic infection in RA patients starting TCZ versus TNFi.

Further details on the outcome are presented in Section 8.3.1.

8. RESEARCH METHODS

8.1 STUDY DESIGN

Using data from the 3 large U.S. insurance claims databases, we will conduct a cohort study of patients with RA (from three separate cohorts) initiating TCZ versus TNFi [redacted] or other biologic DMARDs [redacted]

8.2 SETTING

This study will be performed within multiple large healthcare administrative claims databases based in the US. The data sources are Medicare (2010-2015), IMS PharMetrics (2011-2015) and Truven MarketScan (2011-2015) databases. [redacted]

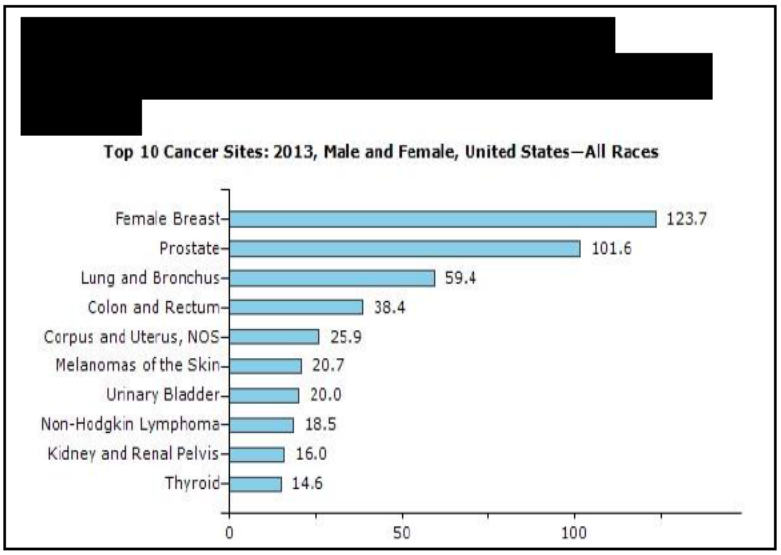
8.3 VARIABLES

8.3.1 Primary Safety Variables

The primary safety variables of interest will be defined by Aim:

- For Aim 1: The primary outcome is incident malignancy excluding NMSC. [redacted]

[redacted]



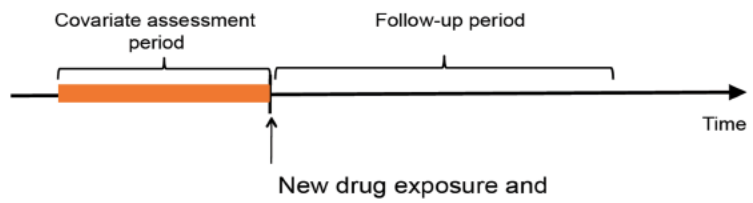
- For Aim 2: The primary outcome is a composite endpoint of any serious infection including bacterial, viral or opportunistic infection.

[redacted]

separately. We will exclude patients who take more than one

[redacted]

Figure 2: Basic study design



[redacted]

[redacted]

8.4 DATA SOURCE(S)

As mentioned previously, three data sources will be used:

- Centers for Medicare and Medicaid Services (CMS) database

  The Centers for Medicare & Medicaid Service (CMS) database includes [redacted]

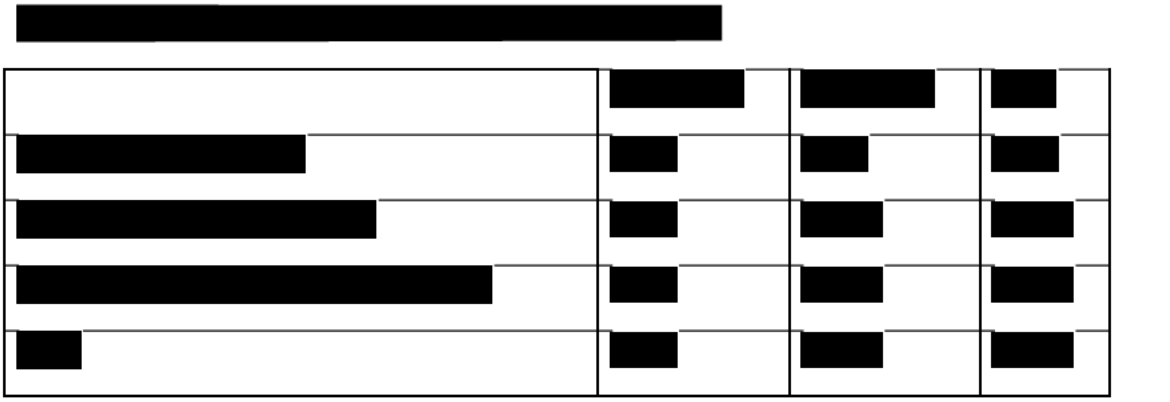
- IMS PharMetrics Plus database

  [redacted]

- Truven MarketScan database

  [redacted]

[redacted]



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[redacted]

8.7 DATA ANALYSIS

8.7.1 Safety Analyses

This is a secondary data use post authorization safety study. The primary and secondary endpoints are safety endpoints. All the analysis presented in this protocol are relevant to the safety analysis. [redacted]:

- [redacted]

  [redacted]

- [redacted]

  [redacted]

- [redacted]

  [redacted]

- [redacted]

  [redacted]

- [redacted]

8.7.2 Other Analyses

All the aforementioned steps will be considered for secondary cohorts.

8.8 DATA QUALITY ASSURANCE AND QUALITY CONTROL

The MAH must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol

amendments, Informed Consent Forms (if applicable), and documentation of IRB and governmental approval.

The MAH/PI[redacted] shall ensure that the datasets and statistical programs used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection.

[redacted] will comply with the MAH procedures regarding content, archiving and records management of process documents.

Within the confines of the data use agreements for using the above three data sources, the following may be exercised to ensure appropriate quality:

- Outcome Inspection

  The [redacted] Safety application allows investigators to conduct an exposure-blinded claims profile review of all patients who develop a study outcome. A claims profile is calendar time-sorted list of all healthcare encounters of a patient listing all diagnoses, procedures, interventions and medications associated with each encounter (Egbring 2010).

Retention of Records for Roche

Records and documents pertaining to the conduct of this study must be retained for at least 15 years after completion of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the marketing authorization holder. Written notification should be provided to the marketing authorization holder prior to transferring any records to the MAH at the end of the Agreement period.

[redacted]

9. PROTECTION OF HUMAN PATIENTS

9.1 INFORMED CONSENT

ensure that patients at the occasion of the primary data collection have explicitly agreed to any secondary use of their data.

For this study, the data have been de-identified by each vendor (Medicare, IMS, Truven) prior to our receipt of the data in accordance with the relevant provisions of HIPAA and therefore no consent/authorization is required.

In case it is not possible/practical to obtain or retrieve informed consent for use of secondary data in a NIS; certain other precautions must be taken, including:

- Ensuring data are anonymised / pseudonymised
- Ensuring final analysis data are anonymised / pseudonymised
- Ensuring possibility of linkage back to individual identified patients is impossible or tightly controlled
- Obtaining ethical committee approval for use of data as proposed (e.g., the review of and extraction of information from individual medical charts) records for the proposed use ahead of study initiation.

9.2 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the Guidelines for GPP published by the International Society of Pharmacoepidemiology (ISPE) and the laws and regulations of the country in which the research is conducted. The study will comply with

national and European Union requirements for ensuring the well-being and rights of participants in non-interventional post-authorization safety studies.

9.3 INSTITUTIONAL REVIEW BOARD

This protocol and relevant supporting information must be submitted to the IRB by the Scientific Responsible and reviewed and approved by the IRB before the study is initiated.

The Scientific Responsible is responsible for providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This is an NI-PASS involving the use of secondary data and the reporting of adverse reactions in the form of ICSRs is not required.

It is assumed that safety reporting of data which are going to be extracted/analyzed as part of this study have been appropriately performed and documented at the time this data were collected through primary data collection mechanism at the sites. No drug attribution for any adverse event observed after exposure is possible in secondary data bases using reimbursement claims.

All adverse events extracted from the data source for the study as specified in the protocol will be summarized as part of any interim safety analyses and in the final study report and final publication.

As per protocol, these aggregate summaries may include the following adverse event types:

- Serious Adverse Events, including all deaths
- Non-serious Adverse Events
- Pregnancy
- Abnormal laboratory findings with or without associated AEs
- Overdose, abuse, misuse, medication error (including potentially exposed in case of medication error or intercepted medication error), occupational exposure, quality defect with or without associated AEs
- Reports of lack of efficacy

- Drug interactions

10.1 ADVERSE EVENTS

According to the International Conference of Harmonisation (ICH), an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., electrocardiogram [ECG], X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study medicine.

10.2 SERIOUS ADVERSE EVENTS

An SAE is any AE that meets any of the following criteria:

- Is fatal (i.e., the AE actually causes or leads to death)
- Is life-threatening (NOTE: The term “life-threatening” refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient’s ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study medicine
- Is a significant medical event in the physician’s judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms “severe” and “serious” are <u>not</u> synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE criteria; the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

11. PLANS FOR DISSEMINATION AND COMMUNICATION OF STUDY RESULTS

Regardless of the outcome of NI-PASS, the marketing authorization holder is dedicated to openly providing information on the NI-PASS to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The marketing authorization holder will comply with all requirements for publication of study results.

We will submit at least one abstract for each aim to national or international Rheumatology scientific meetings (e.g., annual American College of Rheumatology meeting or European League Against Rheumatism meeting). We plan to write and publish at least 2 papers in high-quality peer-reviewed rheumatology journals.

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Appendix 1
List of Researchers

- [redacted] Personnel
  - [redacted], MD, ScD, MSCE, Assistant Professor of Medicine at [redacted] and [redacted]
  - [redacted] MD, ScD, Professor of Medicine at [redacted] and [redacted] Professor of Epidemiology at [redacted]
  - [redacted], MD, MPH, Professor of Medicine at [redacted] and [redacted]
  - [redacted], PhD, MS, Instructor in Medicine at [redacted] and [redacted]
  - [redacted], PhD, Assistant Professor of Medicine at [redacted] Biostatistician at [redacted]
  - [redacted], MS, Research Analyst at [redacted] and [redacted]
  - [redacted], PhD, Research Specialist at [redacted] and [redacted]
- Genentech/Hoffmann La-Roche Personnel
  - [redacted], PhD, MPH, Principal Research Scientist at Genentech
  - [redacted] PhD, MPH, Research Scientist at Genentech
  - [redacted], MD, MBA, [redacted] at Hoffmann La-Roche
  - [redacted], MD, [redacted] at Genentech
  - [redacted], MD, Safety Scientist at Genentech

- [redacted], MD, [redacted] at Genentech