NI PASS PROTOCOL (SECONDARY DATA USE)

TITLE:	**A SECONDARY DATA USE STUDY OF LONG TERM SAFETY OF TOCILIZUMAB BASED ON ANTI RHEUMATIC THERAPY IN SWEDEN (ARTIS) PATIENT REGISTRY**
PROTOCOL NUMBER:	WA22480
VERSION NUMBER:	1.0
EU PAS REGISTER NUMBER:	To be determined
ACTIVE SUBSTANCE:	Tocilizumab
STUDIED MEDICINAL PRODUCT:	Tocilizumab
AUTHOR:	[redacted] Global Product Development, Genentech, A Member of the Roche Group, South San Francisco, CA 94080-4990 [redacted]
DATE FINAL:	See electronic date stamp below

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	09-Dec-2016 18:27:13
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Based on protocol template Version 2.0 released on 30 Oct 2016

PRODUCT REFERENCE NUMBER:	
PROCEDURE NUMBER	
JOINT PASS	
RESEARCH QUESTION AND OBJECTIVES:	Long term surveillance of tocilizumab drug safety in clinical practice
COUNTRY OF STUDY POPULATION:	Sweden
MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration Ltd 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom
MAH CONTACT PERSON:	[redacted], [redacted] **Rheumatology** **Stockholm, Sweden** [redacted]

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS 5
2. RESPONSIBLE PARTIES 6
3. ABSTRACT/SYNOPSIS 7
4. AMENDMENTS AND UPDATES 10
5. MILESTONES 11
6. RATIONALE AND BACKGROUND 11
7. RESEARCH QUESTION AND OBJECTIVES 11
8. RESEARCH METHODS 12
   - 8.1 Study Design 12
   - 8.2 Setting 12
   - 8.3 Variables 12
     - 8.3.1 Primary Safety Variables 12
     - 8.3.2 Other Variables 13
     - Demographic variables 13
     - Disease diagnosis variables 13
     - Treatment variables 13
     - Treatment effectiveness variables 13
   - 8.4 Data Source(s) 14
   - 8.5 Study Size 14
   - 8.6 Data Management 15
   - 8.7 Data Analysis 15
     - 8.7.1 Safety Analysis 15
     - 8.7.2 Other Analyses 15
   - 8.8 Data Quality Assurance and Quality Control 16
     - 8.8.1 Study Documentation 16
     - Retention of Records 16
     - 8.8.2 Data Quality 16
   - 8.9 Limitations of the research method 17
   - 8.10 Other aspects 17

9. PROTECTION OF HUMAN PATIENTS 17
9.1 Informed Consent 17
9.2 Compliance with Laws and Regulations 18
9.3 Institutional Review Board or Ethics Committee 18
10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS 18
10.1 Adverse Events 19
10.2 Serious Adverse Events 19
10.3 Non-Serious Adverse Events of Special Interest 20
11. PLANS FOR DISSEMINATION AND COMMUNICATION OF STUDY RESULTS 20
ARTIS Registry Personnel 22

LIST OF APPENDICES

Appendix 1 List of Stand-Alone Documents Not Included in the Protocol 22

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Rheumatology
ARTIS	Anti-Rheumatic Therapy in Sweden (Registry)
ATC	Anatomical Therapeutic Chemical (Classification System)
CRP	C-Reactive Protein
DAS	Disease Activity Score
DMARD	Disease-Modifying Anti-Rheumatic Drug
EC	Ethics Committee
EMA	European Medicines Agency
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiological Practice
HAQ	Health Assessment Questionnaire
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
MAH	Marketing Authorization Holder
MPA	Medical Products Agency (Sweden)
NIS	Non-Interventional Study
PASS	Post Approval Safety Study
PBRER	Periodic Risk-Benefit Evaluation Report
RA	Rheumatoid Arthritis
RTX	Rituxan
QPPV	Qualified Person for Pharmacovigilance
SAP	Statistical Analysis Plan

2. RESPONSIBLE PARTIES

Protocol Development Responsible

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Complementary information is given in Appendix 1

3. ABSTRACT/SYNOPSIS

TITLE:	A SECONDARY DATA USE STUDY OF LONG TERM SAFETY OF TOCILIZUMAB BASED ON ANTI RHEUMATIC THERAPY IN SWEDEN (ARTIS) PATIENT REGISTRY
PROTOCOL NUMBER:	WA22480
VERSION NUMBER:	1.0
DATE OF SYNOPSIS:	November 3, 2016
EU PAS REGISTER NUMBER:	To be determined
STUDIED MEDICINAL PRODUCT:	Tocilizumab (Actemra®)
SCIENTIFIC RESPONSIBLE	[redacted]
MAIN AUTHOR	[redacted] Global Product Development Genentech, A Member of the Roche Group South San Francisco, CA 94080-4990 [redacted]
PHASE:	Non-interventional study (NIS), Phase IV
INDICATION:	Rheumatoid Arthritis
MARKETING AUTHORIZATION HOLDER:	Roche Registration Ltd 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom
Rationale and background	Roche has collaborated with ARTIS to provide EMA with tocilizumab safety data since formalizing an agreement in 2009. Since 2009, Roche has been a secondary data user of existing ARTIS registry data and has not been involved in primary data collection. This secondary data use protocol makes explicit the nature of this collaboration: Roche plays no role in the design, conduct, or day-to-day management of the ARTIS study; its role is limited solely to the funding of data extraction and analysis. In

	exchange, ARTIS provides Roche with six-monthly aggregate data reports and a final report, as discussed below and in Section 8.4. The ARTIS registry has a generic protocol for all participating drugs. Roche developed this secondary data use protocol in order to clarify the nature of this research collaboration between ARTIS and Roche. EMA encourages new drugs, after marketing approval, to be monitored for safety in the everyday clinical setting. Safety data collected post-approval is important for the development & confirmation of the safety profile of any drug, and particularly those with a novel mechanism of action with no similar drugs on the market For Rheumatoid Arthritis (RA) and other chronic inflammatory diseases subject to prolonged treatment with drugs that influence immune function, there is a concern whether the inflammatory disease or its treatment might increase the risk of certain comorbidities. Data not only from patients treated with such new agents but also data from contemporary RA-patients in general is needed to conduct long term safety evaluations.
Research question and objectives	Primary Objective: To study long term safety of tocilizumab in routine clinical practice. 1. To provide descriptive six-monthly reports of incidence rates of safety events of interest in tocilizumab patients for inclusion in the PBRER 2. To conduct an adjusted multivariate analysis of data comparing risk of serious adverse events of interest in tocilizumab treated patients as compared with multiple RA biologic and non-biologic treated patients and a general population comparison cohorts
Study design	Retrospective secondary data use study nested within Anti-Rheumatic Therapy in Sweden (ARTIS) patient registry
Population	Tocilizumab treated patients in ARTIS and multiple comparator RA and general population cohorts
Variables	Patient demographics, treatment variables, safety variables and disease activity/severity variables
Data sources	ARTIS patient registry and linkage to multiple Swedish national population registers
Study size	Approximately 2500 tocilizumab patients (ever treated) with repeated data extracts and final linkage to Swedish national registers
Data Analysis	Descriptive data on incidence rates of safety events of interest and a final adjusted analysis that compares risk of safety events in tocilizumab treated group with multiple RA and general population cohorts

Milestones	Six-monthly descriptive reports of safety events in tocilizumab arm of the study that will be included in the PBRER, an interim report and a final report that links study to national Swedish registers. Final reports will adjust for baseline differences in study cohorts **Start Date of Study:** The study start date is the date of the initial dataset creation. The start date is 21 Apr 2009. **End of Study** The end of the study will be the date from which the dataset is complete. The planned end of study date is 31 March 2017 and with a final study report that links data to Swedish national population registers in December 2018.

4. AMENDMENTS AND UPDATES

None

This protocol clarifies the relationship between the Roche data extracts and the ARTIS registry, and confirms that this study involves the use of secondary data.

Roche has collaborated with ARTIS to provide EMA with tocilizumab safety data since formalizing an agreement in April 2009.The ARTIS registry founded around 2000 by the Karolinska Institute has a generic protocol for the primary data collection. Roche plays no role in the design, conduct, or day-to-day management of the ARTIS registry. Since finalizing the agreement in 2009, Roche has extracted and used the data from the established ARTIS registry for the purpose outlined in this study protocol.

5. MILESTONES

Milestone	Planned Date
Registration of the protocol in the EU PAS register	December 15, 2016
Start of dataset creation	April 21, 2009
End of dataset creation	January 15, 2017
Interim report	April 15, 2014
Registration of the results in the EU PAS register	February 20, 2019
Final report of study results (CSR)	December 31, 2018

6. RATIONALE AND BACKGROUND

For Rheumatoid Arthritis (RA) and other chronic inflammatory diseases subject to prolonged treatment with drugs that influence immune function, there is a concern whether the inflammatory disease or its treatment might increase the risk of certain comorbidities. Data not only from patients treated with such new agents but also data from contemporary RA-patients in general is needed to conduct long term safety evaluations.

At the Approval of tocilizumab, EMA requested the collection of long-term safety using existing disease registries. Roche identified ARTIS as an appropriate data source and proposed to collaborate with Karolinska Institute which has scientific oversight of the ARTIS registry. This study is a Post Approval Safety Study (PASS) using data collected by the ARTIS registry aimed to provide long-term safety on TCZ. As per research agreement, Principal Physician will periodically analyse extracted data from the registry and provide reports with aggregated safety data to Roche, which will be submitted to the EMA through the PBRER twice a year. An interim (2014) and final reports (2019) will also be provided including data on the risk of safety events in tocilizumab and multiple RA and general population comparator cohorts. The report will adjust for baseline differences for the study cohorts.

The ARTIS registry covers approximately 90% of all biologics starts (first, second, third biologic, etc.) in Sweden. Currently >15 000 patients with RA initiating >20 000 biological treatments are included as part of the registry. Additionally ARTIS has > 29000 non-biologics treated RA patients and access to many more general population comparators. The strength of ARTIS is that it contains unique links to multiple population-based national Swedish registers.

7. RESEARCH QUESTION AND OBJECTIVES

Primary Objectives:

The primary objective of this study is to provide long term safety evaluation of tocilizumab in routine clinical practice. Specifically the primary objectives of this study are:

3. To provide descriptive six-monthly reports of incidence rates of safety events of interest in tocilizumab patients for inclusion in the PBRER

4. To conduct an adjusted multivariate analysis of data comparing risk of serious adverse events of interest in tocilizumab treated patients as compared with multiple RA biologic and non-biologic treated patients and a general population comparison cohorts

8. RESEARCH METHODS

Multivariate adjustment methods will be used to account for confounding by indication and other bias to allow for more valid safety comparisons.

8.1 STUDY DESIGN

This is a retrospective secondary data use cohort study based on the ARTIS Swedish patient registry. For the purposes of the PBRER descriptive six-monthly reports, the study will consist of tocilizumab treated patients only. For the purposes of the final report the study will consist of the following patient cohorts

1. Tocilizumab treated patients

2. Biologics treated patients: those may be further stratified as needed

3. Biologics naïve patients (non-biologic DMARD treated)

4. General non-RA population

8.2 SETTING

The ARTIS registry contains > 90 of all biologics treated patients in Sweden and is very representative of the RA population in Sweden. ARTIS also has the ability to link to general population representative cohorts for comparison purposes.

8.3 VARIABLES

8.3.1 Primary Safety Variables

Events in (1) tocilizumab recipients will be compared with those in patients with (2) anti-TNF therapy and (3) standard DMARD treated subjects.
For each of above three groups, incidence rates of the following primary endpoints will be determined:

- Serious infection requiring hospitalization

- Malignancy (categorized by primary site)

- 1) Myocardial infarction 2) Stroke [ischaemic/haemorrhagic]) leading to hospitalization
- Death
- GI perforations
- Serious hepatic events
- Tuberculosis

Other outcomes, occurrence of the following events will be assessed from the adverse events reporting; no comparator data are, however, available for these events:

- occurrence of serious hypersensitivity reactions (depending on data availability)
- Demyelinating disorders
- Lower gastrointestinal ulcer/bleeding/perforation
- Aplastic anaemia/pancytopenia
- Lymphoproliferative tumour

8.3.2 Other Variables

Demographic variables

Personal identification number including date of birth, sex and date of entry in registry. Demographic variables relating to personal identifiers are kept in strict confidentiality following the ARTIS protocol and are not shared with Roche or anyone outside key numbers of the ARTIS physicians.

Disease diagnosis variables

Rheumatological diagnosis, date of disease debut, RA criteria, RA factor, (X-ray findings, Heredity), Hospital, County, (Other concurrent diseases). (variables within parentheses have limited coverage.)

Treatment variables

Biologics (including dates of treatment initiation, and cessation), concurrent DMARDs, Corticosteroids, and analgesics by the time of biologics treatment initiation, and during the follow-up (included in the ARTIS cohort), previous medication since diagnosis of the rheumatic disease (DMARD, corticosteroids, included in the Early Arthritis cohort).

Treatment effectiveness variables

C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), health assessment questionnaire (HAQ), number of swollen and tender joints, and patient's and doctor's global assessment of disease, disease activity scores (DAS 28), the European league against rheumatism (EULAR) response criteria, and the American College of Rheumatology criterion of improvement (ACR 20-50). All of these measures are collected repeatedly during the surveillance, test dates are recorded.

8.4 DATA SOURCE(S)

ARTIS registry uses a structured reporting of serious and non-serious adverse events to the study secretariat by the treating physicians on a pre-designed form similar to the form used by The Swedish Medical Products Agency (MPA) for regular spontaneous reporting of serious adverse drug reactions in general.

For the PBRER six-monthly report of incidence rates of adverse events of interest in the tocilizumab arm, ARTIS will extract aggregate data from the registry and submit to the MAH for inclusion in the PBRER.

For the final study report, this study will leverage ARTIS' patient record linkage to ascertain safety endpoints of interest including the following national registers:

1. The Swedish Patient Register: Nationwide near-complete capture of discharge diagnoses from inpatients. Diagnoses are listed as assigned by the discharging physician and coded according to ICD (version 9 and 10 codes).

2. The Swedish Outpatients Register: Nationwide data on visit diagnoses (one per visit) since 2001. Diagnoses are as assigned by the treating doctor, and coded according to ICD (version 10). Overall coverage around 70%, higher for somatic public care (most rheumatology and pulmonary medicine care is public).

3. The Swedish Prescribed Drug register: Nationwide capture of all dispensed drugs, 2005 – present, coded according to the ATC drug classification coding system.

4. Population and cause of death registers. Nationwide near complete capture of residents, emigrations, and dates/causes of deaths, the latter categorized according to ICD versions 9 and 10. For each deceased subject, one underlying and up to 20 contributory causes are assigned based on data from the death certificate.

8.5 STUDY SIZE

This is a secondary data use study of an existing registry. It is difficult to estimate the exact number of patients that will be treated with tocilizumab (Actemra®). For the descriptive six-monthly PBRER reports, no sample size calculation is necessary and sample size calculations will therefore not be conducted. For the final multivariate adjusted study report, the study will use all available patients treated with tocilizumab in the database.

8.6 DATA MANAGEMENT

Trained personnel from ARTIS will perform the actual programming, testing and extraction of data, as well as the handling and data management. Clinical experts from the Karolinska Institute will be included in the study and provide expertise on the interpretation of the data retrieved from the registry.

The data will be transferred electronically to the MAH.

The MAH will perform oversight of the data management and analysis of this study.

8.7 DATA ANALYSIS

8.7.1 Safety Analysis

Roche will collaborate with ARTIS physicians to develop a study statistical analysis plan (SAP) that will outline the details of the multivariate analysis methodology. SAP will follow best practices for pharmacoepidemiology research.

8.7.2 Other Analyses

To minimize selection bias, the study will use an incident user design by defining the study cohort entry by drug use, specifically the initiation of the study drug or the initiation of a comparator drug. This design has several advantages, including the avoidance of immortal time bias, depletion of susceptible, and it ensures a clear temporality in the study. The investigators will ensure proper choice of comparison group to minimize confounding by indication. Additionally, the study investigators will adjust for baseline differences between study cohorts. A number of pre-specified sensitivity analyses will be employed to investigate the impact of residual confounding.

Statistical analyses will be performed under the authority of Roche as Marketing Authorization Holder (MAH). Study analyses will be conducted according to the approved SAP that will follow best practices for pharmacoepidemiology and comparative safety research.

Discrete or continuous variables will be summarized in terms of mean, standard deviation, median, and first and third quartile. Categorical variables will be summarized in terms of frequencies of categories. Treatment groups will be compared using Kruskal–Wallis tests for discrete or continuous variables and Fisher’s exact tests for categorical variables.

8.8 DATA QUALITY ASSURANCE AND QUALITY CONTROL

8.8.1 Study Documentation

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 and documentation of IRB/EC and governmental notification.

The MAH shall ensure that the dataset 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.

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

Retention of Records

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 another party or moving them to another location.

8.8.2 Data Quality

MAH should ensure that appropriate Quality Assurance for data which are going to be extracted and or analyzed as part of this study must have been in place at the time the data was collected through primary data collection mechanism.

The ARTIS registry which provides data used in this study must ensure that their computer systems are complete, accurate, and reliable and have consistent intended performance. Data changes must be documented (i.e. audit trail) and have a security system that prevents unauthorized access to data. The ARTIS registry is governed by the National Board of Health and Welfare and reporting of information to them is compulsory by all HCPs. Rigorous validation work is constantly ongoing from the health authority in order to ensure that data are complete, comprehensive and with the highest quality possible.

8.9 LIMITATIONS OF THE RESEARCH METHOD

Non-randomized retrospective studies have number of methodological challenges that limit the causal interpretability of the findings. Those primarily are confounding, selection bias and information bias (measurement error). Careful attention to the methodological aspects of the design and analysis of observational database studies minimizes their limitations and allows them to provide important insights into drug safety (Suissa and Garbe, 2007; Ali, 2013).

A major concern for studying tocilizumab is confounding by indication. Tocilizumab became available in the Sweden in 2009. By then, multiple biological therapies were already approved and widely used for the treatment of rheumatoid arthritis. As a result, until recently, tocilizumab has largely been given to RA patients who are severe or refractory and who may have already failed (or cycled between) multiple biologic DMARDs. This “indication” may not be always measurable. Inadequate adjustment for this confounding will give rise to spurious associations. The investigators will ensure proper choice of comparison group to minimize confounding by indication. Additionally, the study investigators will adjust for baseline differences between study cohorts. A number of pre-specified sensitivity analyses will be employed to investigate the impact of residual confounding.

To minimize selection bias, the study will use an incident user design by defining the study cohort entry by drug use, specifically the initiation of the study drug or the initiation of a comparator drug. This design has several advantages, including the avoidance of immortal time bias, depletion of susceptible, and it ensures a clear temporality in the study (Ray, 2003; Johnson, 2013).

8.10 OTHER ASPECTS

Not applicable

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.In case it is not possible/practical to obtain 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 and linkage of information) records for the proposed use ahead of study initiation.

In the unusual circumstance that individual patients can be identified directly from their data received, then approval to use that data should be sought where possible.

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 OR ETHICS COMMITTEE

The ARTIS "feeder" registry protocol and relevant supporting information was approved by the IRB/IEC at Karolinska Institute before the study was initiated. *Roche SDU study protocol was approved following all Roche processes. No requirement for IRB or Ethics approval for SDU studies*

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.

ARTIS physicians follows international and Swedish laws for reporting adverse events to the Swedish authorities as per local and EU laws.

All adverse events collected in the ARTIS registry for patients receiving tocilizumab will be extracted and summarized in any interim safety analyses and in the final study report and publication.

These aggregate summaries may include and are not limited to the following adverse event types:

- Serious Adverse Events, including all deaths
- Adverse Events of Special Interest

- 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 not 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).

10.3 NON-SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST

AEs of special interest for this study include the following:

- Cases of potential medicine-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law
- Suspected transmission of an infectious agent by the study medicine, as defined below:
- Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term only applies when a contamination of the study medicine is suspected.

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.

REFERENCES

Suissa S, Garbe E. Primer: administrative health databases in observational studies of drug effects--advantages and disadvantages. Nat Clin Pract Rheumatol. 2007 Dec;3(12):725-32.

Ali KA. Methodological Challenges in Observational Research: A Pharmaco-epidemiological Perspective *British Journal of Pharmaceutical Research 3(2): 161-175, 2013*

Appendix 1
List of Stand-Alone Documents Not Included in the Protocol

ARTIS Registry Personnel

Principal investigator

[redacted]

Senior research advisor

[redacted]

Senior epidemiologists

[redacted]

Senior biostatistician

[redacted]

Collaborator at The Swedish Medical Products Agency

[redacted]

Research nurse / Epidemiology assistant

[redacted]

Database responsibility

[redacted]

Biostatistician and programmer

[redacted]

Regional collaborators (members of the steering committee)

[redacted]