NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Patient-Reported outcomes in rheumatoid arthritis patients treated with tofacitinib or biological disease-modifying antirheumatic drugs (DMARDs) in real life conditions
Protocol number	A3921284
Protocol version identifier	2.1
Date of last version of protocol	12 December 2018
Active substance	L04AA29 Tofacitinib
Medicinal product	XELJANZ
Sponsor	Pfizer Inc.
Research question and objectives	This study is aimed to describe the outcomes related to physical activity, activity of disease, quality of life, work productivity and safety in Latin-American patients with Rheumatoid Arthritis (RA) treated with tofacitinib or biological DMARDs after failure to respond to conventional DMARDs in real-life conditions
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1. DISCLOSURE STATEMENT

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2. SPONSOR SIGNATURE

I have read and approve this protocol. My signature, in conjunction with the signature of the investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the ethical principles that have their origins in the Declaration of Helsinki, and applicable privacy laws.

PPD

PPD Signature	12-Dec-2018 Date of signature (DD Mmm YYYY)	9:00am UTC-5 Time (Time zone)

PPD

PPD

Name

3. INVESTIGATOR SIGNATURE

I have read and approve this protocol. My signature, in conjunction with the signature of the sponsor, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the ethical principles that have their origins in the Declaration of Helsinki, and applicable privacy laws.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care under applicable regulations.

_____	_____	_____
Investigator Signature	Date of signature (DD Mmm YYYY)	Time (Time zone)

_____
Investigator Name and Title

4. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Rheumatology
AE	Adverse Event
AEM	Adverse Event Monitoring
ARCSA	*"Agencia Nacional de Regulación Control y Vigilancia Sanitaria"*
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DAS28	Disease Activity Score 28
DGDF	"*Dirección General de Drogas y Farmacias"*
DIGEMID	"*Dirección General de Medicamentos e Insumos y Drogas*"
DMARDs	Disease-modifying Antirheumatic Drugs
EBV	Epstein Barr Virus
EDP	Exposure During Pregnancy
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FN	Physical function
GH	General Health
HAQ-DI	Health Assessment Questionnaire – Disability Index
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INVIMA	*"Instituto Nacional de Vigilancia de Medicamentos y Alimentos"*
IRB	Institutional Review Board
ISP	*"Instituto de Salud Pública"*
JAK	Janus Kinase
LSLV	Last Subject Last Visit
MDHAQ	Multidimensional Health Assessment Questionnaire
MTX	Methotrexate
NI	Non-Interventional
NIS	Non-Interventional Study
PN	Pain
PRO	Patient Reported Outcome

PTGL	Patient global
RA	Rheumatoid Arthritis
RAPID	Routine Assessment of Patients Index Data
SAE	Serious Adverse Event
SHP	specific health problem
SRSD	Single reference safety document
TNF	Tumor Necrosis Factor
WPAI	Work Productivity and Activity Impairment

5. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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*Contacts in charge of leading the project

Country Coordinating Investigators

The study is multicentric with multiple investigators

6. FLOWCHART

Visit	Pre-visit*	Day 1	Day180
Verification of inclusion criteria	●		
Verification of exclusion criteria	●		
Informed consent		●	
Demographic data		●	
Medical record	●	●	
Current treatment	●	●	
Clinical data		●	●
RAPID3 Measurement		●	●
EQ-5D Measurement		●	●
WPAI Measurement		●	●
Adapted HAQ-DI Measurement		●	●
Evaluation of adverse events identified through medical record			●
Spontaneously reporting of adverse events by patient		◄——————►	
Record for loss of follow-up		◄——————►	

*Criteria verification

7. ABSTRACT

Study title: Patient-Reported outcomes in rheumatoid arthritis patients treated with tofacitinib or biological disease-modifying antirheumatic drugs (DMARDs) in real life conditions					
Protocol Number	A3921284	**Phase**	4	**Type**	Observational
Condition/Disease	People with Rheumatoid Arthritis				
Number of subjects	320 patients		**Permanence of subjects in the study**		6 months
Participant countries (number of sites)	Colombia (11), Peru (4), Ecuador (1)		**Duration of study**		16 months

Rational

Biological therapies are drugs that emerged almost a decade ago for preventing or reducing the swelling caused by Rheumatoid Arthritis (RA) after failure from a conventional drug such as methotrexate (MTX). These are molecules consisting of proteins produced by living organisms that act on very specific mechanisms of a cell, organ or system (1–4) .

Furthermore, there are also chemically synthesized molecules produced from chemical precursors for the treatment of arthritis; tofacitinib is a chemically synthesized drug targeted to block the pathway of an enzyme called Janus kinase (JAK), involved in body's immune response, and fighting swelling from inside the cell.

Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. Tofacitinib 5 mg twice daily (BID) and tofacitinib 10 mg BID have demonstrated consistent efficacy in reducing the signs and symptoms of RA, and showed improvements in the Patient-Reported Outcomes (PROs), with manageable safety profiles across six Phase 3 studies, either as monotherapy or in combination with conventional disease-modifying antirheumatic drugs (DMARDs) (5–10).

Although there are several studies for the assessment of efficacy (including patient reported outcomes) and safety of tofacitinib compared with placebo or methotrexate in the treatment of RA, there is limited information on its use in current practice in Latin America. Additionally, there are no data comparing tofacitinib with biological DMARDs directly in real conditions. Studies focusing on these comparisons are of great importance for all physicians involved in the management of RA patients.

Additionally, tofacitinib safety profile has demonstrated to be consistent in long-term extension studies (11). In the indirect comparison, tofacitinib has a similar safety profile to biological DMARDs. However, Latin-American physicians expect to see similar results with their patients.

Objectives

The objective of this study is to describe the outcomes related to physical activity, activity of disease, quality of life, work productivity and safety in Latin-American patients with RA treated with tofacitinib or biological DMARDs after failure to respond to conventional DMARDs in real-life conditions.

Study design

This will be a non-interventional, hybrid study (prospective and retrospective data collection) comparing tofacitinib to biologic DMARD treatments in patients with RA after failure of conventional DMARDs, in second line of therapy.

Inclusion criteria:

- Patients ≥ 18 years of age at the time of recruitment
- Patient diagnosed with moderate to severe RA ≥ 6 months before enrollment
- Patients with DAS28 score ≥ 3.2
- Patients who have had an inadequate response to the continuous use of methotrexate or combination of conventional DMARDs for at least 12 weeks before the study without dose change within the last 8 weeks before enrollment in the study.

- Patients with no biological DMARDs use in patient history.
- Patients prescribed with tofacitinib or biological DMARDs in the last two weeks at doses established in ACR guidelines published in 2015 and following medical criteria.
- Acceptance for patients to participate in the study and signing of the informed consent.

Exclusion criteria:

- Patients who do not have the ability to answer the questionnaires by themselves or who have any kind of mental disorder that may affect their answers.
- Patients diagnosed with autoimmune rheumatic diseases other than RA and Sjogren's syndrome.
- Patients treated with biological DMARDs in monotherapy.
- Participation in other studies involving investigational drug(s) (Phases 1-4) within 4 weeks or 5 half-lives (whichever is longer) after discontinuation of the investigational compound before the current study begins and/or during study participation.
- Pregnant or breastfeeding women.
- Patients with any current malignancy or a history of malignancy, with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ.
- Patients with lymphoproliferative disorders (e.g., Epstein Barr Virus (EBV) related lymphoproliferative disorder), a history of lymphoma, leukemia, or signs and symptoms suggestive of current lymphatic disease.

Recruitment mode:

Convenience sampling in the tofacitinib arm and randomized in the biological DMARD arm will be performed

Randomized recruitment into the arm of tofacitinib cannot be used because of the low group of patients with the drug.

Data collection:

The information may only be collected once the protocol has been approved by Pfizer and the Ethics Committee of the sites, training on adverse events (AE) reporting has been provided, and the informed consent form has been signed by the parties. After the potential patients to be included in the study are identified, the treating physician (rheumatologist) will verify the inclusion/exclusion criteria for determining the patient eligibility and will complete the baseline information.

The investigator will apply health assessment questionnaires at the beginning of recruitment (month zero) and Month 6 of follow-up. Before sending the information to Pfizer in a standard form for subsequent analysis, data from patients must be codified and verified by the CRO to assure that we will receive complete information and that patients would not be identified by Pfizer.

Outcomes

- Information reported by patients (*Patient Reported Outcomes* [PRO]) on disease activity, functional status, quality of life and work productivity.
- Frequency of adverse events.

Data sources:

- Patients, through application of PROs:
  - *Routine Assessment of Patients Index Data* (RAPID3) and DAS28: Disease activity
  - *Adapted Health Assessment Questionnaire* (HAQ-DI): Functional status
  - *EuroQol Questionnaire* (EQ-5D): Quality of life
  - *Work Productivity and Activity Impairment* (WPAI): Work productivity
  - Spontaneously reported safety information
- Medical records

– Clinical and demographic information of patients: age, sex, comorbidities, concomitant medications, risk factors – Characteristics of the disease: duration of the disease, laboratory test data. – Treatment: previous and current treatment
Data analysis: The information collected by the Clinical Research Organization (CRO) will be analyzed by Pfizer through a statistical management plan. Initially, the sample will be matched using propensity score calculated from baseline variables. For effectiveness outcomes, a descriptive analysis will be performed for all variables. Second, Functional status (adapted HAQ-DI), Quality of life (EQ-5D), work productivity (WPAI) and Disease activity (RAPID3) will be analyzed with paired t test or Wilcoxon test and will be matched using propensity score to adjust potential confounding variables. For safety outcomes, all the safety data will be summarized through appropriate data tabulations, descriptive statistics, and graphical presentation.

First Patient First Visit	15 April 2017	**Last Patient Last Visit**	30 August 2019
Last Patient First Visit	28 February 2019	**Estimated duration of recruitment**	22 months

8. AMENDMENTS AND UPDATES

Any significant change in the study requires an amendment of the protocol. Any investigator cannot make any changes to the study without the approval of the sponsor and the Ethics Committee. All protocol amendments should be reviewed and approved following the same process as the original protocol.

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
1	30-Nov-16	Administrative	1-3, 6-7, 9, 12 Annex 3	• Sections of disclosure statement, sponsor and investigator signature, flowchart were included • Planned dates for milestones were updated • Dominican Republic was excluded • Sampling process is widely explained • Expands on description to analyze the causality and severity of AE • Coding of patients description is included • EQ-5D-3L version will be used	• To adapt the protocol to Latin America requirements of Ethical Committees • There is more experience with EQ-5D-3L version in Latin America
2	03 Dec-18	Sustantial	Pages 12, 14, 21, 27, 34, 36, Annex 2	• The collection process of the HAQ-DI is detailed since 8 questions of that questionnaire will be evaluated in RAPID3. • It is clarified that an adapted HAQ-DI is being used.	• Authorization by Stanford University to use it in this way. • Execute changes in the protocol by deviation of protocol version 2.0
3	03 Dec 18	Administrative	Pages 13, 15, 22, 23, 25	• Chile was eliminated as a participating country. • The number of participating centers per country was updated. • The dates of the study milestones were updated.	• Updating information as the study progresses.

9. MILESTONES

Milestone	Planned date
Final protocol and data collection form	13 December 2016
Start of data collection	15 April 2017
End of data collection	28 February 2019
Final analytic results	15 November 2019
Final study report	21 December 2019

10. RATIONALE AND BACKGROUND

Rheumatoid arthritis (RA) is an autoimmune, chronic, systemic disorder, which affects around 1% of world population. It is characterized by synovial membranes swelling, causes joints swelling, stiffness and pain, which lead to cartilage and bone tissue progressive erosion and destruction at the affected joints. Between 17.85%-40.9% of patients with RA may experience extra-articular manifestations which may involve skin, eye, respiratory, oral, cardiovascular, neurological, hematological, and/or vascular function (1–4). Patients with RA are also likely to experience depression, sexual dysfunction, and social relationships disruption.

In addition, RA represents an important burden for informal caregivers (spouse, relatives) who spend a lot of time helping patients with their daily activities, personal care, social activities and financial matters (12,13). This caregiver overload contributes substantially to loss of productivity and to the total disease burden.

There is no cure for RA, the treatment goals are to relieve disease signs and symptoms, control disease activity, improve physical function and patient's quality of life and inhibit structural-damage progression in the disease course. Treatment for RA is typically initiated with nonsteroidal anti-inflammatory drugs (NSAIDs) and/or low-dose glucocorticoids and conventional synthetic disease modifying anti-rheumatic drugs (DMARDs) (typically Methotrexate (MTX)) as soon as possible after diagnosis (14–16).

Biological therapies are drugs that emerged almost a decade ago for preventing or reducing the swelling caused by Rheumatoid Arthritis (RA) after failure from a conventional drug such as methotrexate. These are molecules consisting of proteins produced by living organisms that act on very specific mechanisms of a cell, organ or system (1–4) .

Furthermore, there are also chemically synthesized molecules produced from chemical precursors for the treatment of arthritis; tofacitinib is a chemically synthesized drug targeted to block the pathway of an enzyme called Janus kinase (JAK), involved in body's immune response, and fighting swelling from inside the cell.

Recently, American College of Rheumatology (ACR) recommended in established RA, if disease activity remains moderate or severe despite conventional DMARD monotherapy, the rheumatologist can use a combination of traditional DMARDs or add a Tumor Necrosis Factor (TNF) inhibitor or a non-TNF biological DMARD or tofacitinib (17). Also, ACR recommended tofacitinib in patients who remain moderate and severe despite use of at least a TNF inhibitor or non-TNF biologic agents (17). Within the group of biological DMARDs there are nine compounds identified (18), five TNF inhibitor agents: adalimumab,

certolizumab pegol, etanercept, golimumab and infliximab; abatacept, a selective T-cell co-stimulation modulator; rituximab, an anti-B cells monoclonal antibody; tocilizumab, a monoclonal antibody against the interleukin-6 receptor, and anakinra an interleukin-1 inhibitor.

Tofacitinib is an orally-administered chemically synthesized molecule that inhibits the enzymes Janus kinase 1 and 3, and therefore interferes with the Janus Kinase - Signal Transducer and Activator of Transcription (JAKSTAT) signaling pathway, thereby preventing replication of genetic information that leads to disease progression. It is used for treating moderate to severe RA when there is an inadequate response or intolerance to DMARDs.

Tofacitinib 5 mg twice daily (BID) and tofacitinib 10 mg BID have demonstrated consistent efficacy in reducing the signs and symptoms of RA, and showed improvements in the Patient-Reported Outcomes (PROs), with manageable safety profiles across six Phase 3 studies, either as monotherapy or in combination with conventional disease-modifying antirheumatic drugs (DMARDs) (5–10).

Tofacitinib belongs to the therapeutic group L04AA29, it may be administered in monotherapy or in combination with MTX or other DMARDs. The recommended dose is 5 mg twice daily, it should not be used in patients with serious liver failure; in case of lymphopenia, neutropenia or anemia it is recommended to suspend the treatment and the same applies if the patient develops a serious infection, until the infection is controlled (19).

In the United States, the Food and Drug Administration (FDA) approved the use of tofacitinib for the treatment of RA in 2012. In Colombia, the "*Instituto Nacional de Vigilancia de Medicamentos y Alimentos*" (INVIMA) approved the presentation of tofacitinib 5 mg under Health Registration No. 2013M-0014423 on July 26, 2013. In Chile, the *Instituto de Salud Pública* (ISP) approved the same presentation under Health Registration No. F-20759/14 on January 8, 2014. In Peru the "*Dirección General de Medicamentos e Insumos y Drogas*" (DIGEMID) approved tofacitinib 5 mg under the register EE-00112 on September 25, 2013. In Ecuador the *"Agencia Nacional de Regulación Control y Vigilancia Sanitaria"* (ARCSA) approved tofacitinib 5 mg under the register 172-MEE-0314 on March 25, 2014.

Six phase III randomized clinical trials have been conducted with tofacitinib in different stages of arthritis in which the drug is compared to placebo or methotrexate. These studies demonstrated good results related to efficacy and safety of tofacitinib (5–10). Currently, there are no data in real life conditions comparing tofacitinib with biological DMARDs

directly. This kind of studies has great importance for all stakeholders involved in the management of RA patients.

Although there are several studies for the assessment of efficacy (including patient reported outcomes) and safety of tofacitinib compared with placebo or methotrexate in the treatment of RA, there is limited information on its use in current practice in Latin America. Additionally, there are no data comparing tofacitinib with biological DMARDs directly in real conditions. Studies focusing on these comparisons are of great importance for all physicians involved in the management of RA patients.

On the other hand, being an oral therapy, tofacitinib can be advantageous in terms of work productivity and quality of life due to its easiness of administration in patients who have difficulties of mobility or movement to health care provider for the administration of the drug or patients with fear of needles.

Additionally, tofacitinib's safety profile has demonstrated to be consistent in extension clinical studies (11). In the indirect comparison, the analysis suggested that tofacitinib has similar safety profile to biological DMARDs. However, Latin-American data is scarce and there is no certainty among physicians that their patients have a similar behavior to published studies. Latin-American physicians expect to see similar results with their patients.

11. RESEARCH QUESTION AND OBJECTIVES

The objective of this study is to describe the outcomes related to physical activity, activity of disease, quality of life, work productivity and safety in Latin-American patients with RA treated with tofacitinib or biological DMARDs after failure of conventional DMARDs in real-life conditions.

Data from questionnaires self-administrated by patients (Patient Reported Outcomes [PRO]) will be used to achieve the objectives.

The scope is patients ≥ 18 years of age from Latin-America diagnosed with rheumatoid arthritis who failed to respond to conventional DMARDs. Patient Reported Outcomes (PROs) and adverse events will be measured. Questionnaires originally developed in English, validated in Spanish language will be used in order to measure the PROs, and are detailed in section 12.3.2.

Measurement of disease activity requiring a physician's intervention during the follow-up, such as the Clinical Disease Activity Index (CDAI) or the Simple Disease Activity Index (SDAI), will not be considered, only questionnaires that could be self-administered are included. The Disease Activity Score - DAS28 will be collected depending on the availability in the medical records.

11.1 Primary objective

The primary objective of this study is to compare the disease activity measured by RAPID3 at 0 and 6 months follow-up (±1 month), in adult Latin-American patients with rheumatoid arthritis who previously failed to respond to conventional DMARDs, and start treatment with tofacitinib, against those patients who start treatment with a biological DMARD.

11.2 Secondary objectives

The secondary objectives of this study are:

- To compare the functional status measured by adapted HAQ-DI at 0 and 6 months follow-up (±1 month), in adult Latin-American patients with rheumatoid arthritis who previously failed to respond to conventional DMARDs, and start treatment with tofacitinib, against those patients who start treatment with a biological DMARD.
- To compare the quality of life measured by EQ-5D at 0 and 6 months follow-up (±1 month), in adult Latin-American patients with rheumatoid arthritis treated who

previously failed to respond to conventional DMARDs, and start treatment with tofacitinib, against those patients who start treatment with a biological DMARD.

- To compare the work productivity measured by WPAI questionnaire at 0 and 6 months follow up (±1 month), in adult Latin-American patients with rheumatoid arthritis who previously failed to respond to conventional DMARDs, and start treatment with tofacitinib, against those patients who start treatment with a biological DMARD.
- To describe the activity of disease measured by DAS28 of adult Latin-American patients with rheumatoid arthritis who failed to respond to conventional DMARDs and start treatment with tofacitinib or biological DMARDs, since the beginning of the therapy.
- To describe the frequency of adverse events in adult Latin-American patients with rheumatoid arthritis who failed to respond to conventional DMARDs and start treatment with tofacitinib or biological DMARDs, during the period evaluated.

12. RESEARCH METHODS

In order to achieve the objectives proposed, presented in the above section, a group of patients who meet the inclusion and exclusion criteria will be recruited. Data collection will be conducted by the CRO, who will contact the arthritis sites or physicians from three Latin American countries (Colombia, Ecuador and Peru) who will facilitate identification of the patients from whom the information will be collected.

Arthritis sites and physicians that will be involved in the recruitment process will be selected based on the following criteria:

- There exist patients recently prescribed with tofacitinib or a biological DMARD,
- the required information is available and good quality,
- there exists an ethics committee registered with local regulatory agency, and
- There is willingness to participate in the clinical research.

Each one of the 15 sites will have a local investigator assigned by the site for reviewing and signing contracts, starting, follow-up and finish the data collection process.

The site will be responsible for recruiting the selected patients based on inclusion/exclusion criteria, contacting them and measuring outcomes to study at the time points stablished in this protocol. The CRO will create a database with the data collected, which must comply with the requirements for data protection and patient identification as set forth in Pfizer policies and regulations.

12.1 Study design

This is a non-interventional, hybrid study with two arms (patients treated with tofacitinib and patients treated with biological DMARDs) comparing tofacitinib to biologic DMARD treatments in patients with RA after failure of conventional DMARDs, in second line of therapy.

A 6-month follow-up of patients will be performed by interviewing patients at month 0, and at month 6 (±1 month), for measuring the outcomes defined through questionnaires previously validated in Spanish language and registering the information reported in the medical records. Changes to the treatment during the follow-up of the patients only could be done by the treating physician.

12.2 Setting

Sampling will be conducted at the main sites using tofacitinib in the participating countries. Convenience sampling will be performed in accordance with the study drugs' prescription process: tofacitinib or biological DMARDs due to the limited access to treatment for patients with RA. The number of patients on tofacitinib or on biological DMARDs must be the same in each cohort and site. According to this, all patients who meet the inclusion and exclusion criteria available at the time of recruitment will be invited to participate in the study. Identification process will last until approximately 160 patients are selected for each cohort: tofacitinib or biological DMARDs. The patients will be recruited in following countries: Colombia (11 sites), Ecuador (1 site) and Peru (4 sites).

The patient population is those patients with established rheumatoid arthritis who failed to respond to conventional DMARDs and the targeted population is patients in Latin-America with established rheumatoid arthritis who failed to respond to conventional DMARDs.

12.2.1 Inclusion criteria

- Patients ≥ 18 years of age at the time of recruitment
- Patient diagnosed with moderate to severe RA ≥ 6 months before enrollment
- Patients with DAS28 score ≥ 3.2
- Patients who have had an inadequate response to the continuous use of methotrexate or combination of conventional DMARDs for at least 12 weeks before the study without dose change within the last 8 weeks before enrollment in the study.
- Patients with no biological DMARDs use in patient history.
- Patients prescribed with tofacitinib or biological DMARDs in the last two weeks at doses established in ACR guidelines published in 2015 and following medical criteria.

- Acceptance for patients to participate in the study and signing of the informed consent.

12.2.2 Exclusion criteria

- Patients who do not have the ability to answer the questionnaires by themselves or who have any kind of mental disorder that may affect their answers.
- Patients diagnosed with autoimmune rheumatic diseases other than RA and Sjogren's syndrome.
- Patients treated with biological DMARDs in monotherapy.
- Participation in other studies involving investigational drug(s) (Phases 1-4) within 4 weeks or 5 half-lives (whichever is longer) after discontinuation of the investigational compound before the current study begins and/or during study participation.
- Pregnant or breastfeeding women.
- Patients with any current malignancy or a history of malignancy, with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ.
- Patients with lymphoproliferative disorders (e.g., Epstein Barr Virus (EBV) related lymphoproliferative disorder), a history of lymphoma, leukemia, or signs and symptoms suggestive of current lymphatic disease.

Observation unit will consist of patients with rheumatoid arthritis who failed to respond to conventional DMARDs.

12.2.3 Sampling process

Convenience sampling will be conducted due to the limited access to patients with tofacitinib. For patients using a biological DMARD, data will be collected randomly with replacement; for this purpose, at the beginning of the week patients from each site that had started treatment with biological DMARD the previous week will be listed consecutively following the order of visit and will be selected through random numbers generated by computer delivered by the CRO. The candidate patients will be contacted by phone and those who do not want to participate will be replaced by the next patient until completing the required number of patients.

The number of patients with tofacitinib and a biological DMARD must be the same in each arm for each site.

If sites do not meet the pre-specified sample size, more sites from the same country will be included. Similarly, if a country does not obtain together the planned number of patients

other countries can replace the missing patients until completing the pre-specified sample size.

12.3 Variables

12.3.1 Variables measured at the initial phase

At the initial phase the following data from the medical record will be collected:

Name of variable	Type of variable	Scale of measurement	Categorization
Date of birth	Quantitative	Nominal	
Residence country	Qualitative	Nominal	• Colombia • Ecuador • Perú
Gender	Qualitative	Dichotomous	Female Male
Ethnicity	Qualitative	Nominal	• African American / Black • White / Caucasian • Hispanic/ Latin American • Indigenous
Current treatment	Qualitative	Nominal	• Methotrexate • Leflunomide • Tofacitinib • Adalimumab • Etanercept • Certolizumab • Infliximab • Golimumab • Tocilizumab • Abatacept • Rituximab • Prednisolone • Deflazacort • NSAIDs
Years elapsed since the disease was diagnosed	Quantitative		
Prior anti-rheumatic treatment	Qualitative	Nominal	• Methotrexate • Leflunomide • Prednisolone • Sulfasalazine • Deflazacort • Hydroxychloroquine
Duration of prior treatments (months)	Quantitative		
DAS28 score before the	Quantitative	Ordinal	

initiation of the evaluated treatment			
HAQ-DI score before the initiation of the treatment to evaluate	Quantitative	Ordinal	
Erosion score before the initiation of the evaluated treatment	Quantitative	Ordinal	
Number of tender joints before the initiation of the treatment to evaluate	Quantitative	Ordinal	
Number of swollen joints before the initiation of the evaluated treatment	Quantitative	Ordinal	
Lymphocytes count before the initiation of the evaluated treatment	Quantitative	Ordinal	
Neutrophils count before the initiation of the evaluated treatment	Quantitative	Ordinal	
Comorbidities (Non-exhaustive) (Charlson score)	Qualitative	Nominal	• Myocardial infarction • Cardiac failure congestive • Peripheral disease • Stroke • Dementia • Chronic lung disease • Connective Tissue Disease • Peptic Ulcer Disease • Mild hepatic disease • Diabetes without organ damage • Hemiplegia • Severe or moderate kidney disease • Diabetes with organ damage. • Tumor without metastasis • Leukemia • Lymphoma • Severe liver disease • Metastatic solid tumor • HIV •

The completeness of the information collected will depend on the quality of medical records. In order to ensure the entirety of the information to record, the investigator physician will collect the data related to the clinical variables based on source documents and will be verified by the monitor.

12.3.2 Effectiveness variables

Outcomes that will be assessed at day 1, and 6 months (approximately day 180) follow-up are described below:

- Functional status: it will be evaluated through the Health Assessment Questionnaire – Disability Index (HAQ-DI) adapted since the 8 questions included in the RAPID Questionnaire will not be included in this questionnaire section in CRF (Annex 2), the disability assessment component of the HAQ, that assesses a patient's level of functional ability and includes questions of fine movements of the upper extremity, locomotors activities of the lower extremity, and activities that involve both upper and lower extremities(20,21), which consists of 8 categories: dressing, arising, eating, walking, hygiene, reach, grip, reaching and common daily activities. Each category consists of 2-3 items. Each item evaluates the functional status using the same equipment the patient used the week before the questionnaire. Functional status levels go from zero (0) to three (3), being zero (0) without any difficulty, one (1) with some difficulty, two (2) with much difficulty and three (3) unable to do. In case of requiring assistance from other person or device the patient must select a score of two (2). The questionnaire HAQ-DI has been validated in Spanish by diverse Spanish-speaking populations (22) and by Argentina (23) and must be completed entirely by the patient.
- Quality of life: it will be evaluated through the Health Assessment Questionnaire EQ-5D (Annex 3), a standardized instrument for use as a measure of health outcome that consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The scoring range goes from zero (0) to one hundred (100), being one hundred the best quality of life (24). Official Spanish versions of EQ-5D-3L are available at EuroQol webpage and must be licensed for this study (25). The questionnaire must be completed by the patient.
- Work productivity: it will be assessed through the Work Productivity and Activity Impairment Questionnaire for Rheumatoid Arthritis (WPAI-AR) (Annex 4), that was created as a Patient-Reported quantitative assessment of the amount of absenteeism, presenteeism and daily activity impairment attributable to general health (WPAI:GH) or a specific health problem (WPAI:SHP). The WPAI:GH and the WPAI:SHP were created simultaneously and use the same template, but in the GH version the subject is instructed to respond with reference to general health status while in the SHP version,

the subject responds with reference to a specified health problem, disease or condition(26). It consist of six questions that evaluate how many hours the person miss from work, how many hours the person actually work, loss of work productivity and daily activities. Some of these questions require specifying a number of hours and other use a score from zero (0) to ten (10), being ten the maximum level of work impairment. Spanish versions of WPAI for Rheumatoid Arthritis are available at Reilly Associates webpage(27). Written permission is neither required nor provided to investigators using the WPAI; there are no fees to use the WPAI or the translations from the website. The questionnaire must be completed by the patient.

- Disease activity: it will be evaluated through the RAPID3 (Annex 5), it is a questionnaire derived from the three core data set PRO measures, physical function (1 – FN), pain (2 – PN), and patient global estimate (4 – PTGL) taken from Multidimensional Health Assessment Questionnaire (MDHAQ). RAPID3 score goes from 0 to 30, as the result of the addition of each subscale score, which goes from 0 to 10. Final result may be expressed into a scale of 0 to 10, if divided in 3; it contains severity categories of high (> 4), moderate (2.01–4), low (1.01–2), and near-remission (≤ 1)(28). This questionnaire has been validated in Spanish with Argentinian population (29) and must be licensed for this study.
- Activity disease. Disease activity score using 28 tender and swollen joint counts (Disease Activity Score - DAS28) will be collected only if it is reported in the medical records. DAS28 is a composite index that includes variables such as number of joints for swelling and tenderness, patient global health (0 represents best and 100 represents worst) and erythrocyte sedimentation rate (ESR)(30,31),

12.3.3 Safety variables

- Incidence and severity of adverse events

Adverse events that occur from the prescription of therapies under evaluation during 6 month follow-up will be considered.

From the information on the medical record, the investigator will identify possible adverse events from the initiation of the evaluated treatment to the end of the follow-up. In addition, patients may report adverse events spontaneously during the follow-up period.

Serious and non-serious adverse events will be classified. It will be considered as serious adverse events as defined in the Guide to Good Clinical Practice of the International Conference on Harmonization (ICH) (32). The guide defines it as any unfavorable occurrence that at any dose: results in death, life-threatening; requires inpatient

hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity.

Additionally, the adverse events will be evaluated by a committee composed by two investigators/ rheumatologist defined by the CRO that will verify the causality and severity of the adverse event based on World Health Organization (WHO) criteria (33) and Common Terminology Criteria for Adverse Events (CTCAE)v 4.03 from National Institutes of Health United States (34), respectively.

The WHO classifies causality in various categories such as probable, possible, unlikely, conditional and unassessable (32).

According to the CTCAE the severity of adverse events is classified in grade one (1) to grade five (5). Each grade is defined as (34):

- Grade 1: Mild; asymptomatic or mild symptoms, diagnostic or clinical observations only; intervention not indicated.
- Grade 2: Moderate; Minimal, non-invasive or local interventions indicated, limitation in the appropriate daily activities for the age.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization; disability; limitations for self-care.
- Grade 4: Life-threatening consequences: requires urgent intervention.
- Grade 5: Death related to adverse event

12.4 Data sources

The study information will be collected from three sources: medical records, questionnaires, and spontaneous report of adverse events by patients.

After verifying that the patient meets the inclusion criteria and accepts to participate, medical records will be reviewed at time of recruitment and 6 months (± 1 month) follow-up. In the case that any patient decides to dropout the study or the drug is discontinued the medical record will be reviewed.

At the moment of the recruitment, patients' baseline data will be collected since prescription of the treatments to evaluate. Data will correspond to the patient's demographic and clinical characteristics regarding the rheumatoid arthritis status and comorbidities study (See variables at section 12.3.1). In addition, the medical records will be reviewed for searching adverse events that the patient has reported to the physician

within the time of recruitment and the 6 months follow-up (retrospectively). Safety management and reporting of adverse events/adverse reactions related to extraction of data from medical record is detailed in Section 14.1. This information will be collected by the investigator(s) assigned to the site or someone from the site's medical staff, as agreed with the site.

Data collection will be performed through a data collection instrument (explained on Section 12.6.4) previously developed. The CRO will monitor the collection process. Pfizer's staff will conduct audits of this process as well, in order to guarantee the quality of the information collected.

The second source of data is questionnaires previously validated in Spanish (Described in section 12.3.2). The site will train the patients – since the beginning of the study, once the informed consent is signed – on how to complete the questionnaires in order to avoid bias of misclassification. Patients will complete the questionnaires personally without help from the research team in order to avoid bias interviewer (all questionnaires are designed for self-administration). The patient will only get help for any questions once completed.

While completing the questionnaires or during the contact to follow-up during medical attention, the patient – as a third source – may report adverse events spontaneously; in this case, the research group will collect the information reported by the patient in pre-designed forms. Safety management and reporting of adverse events/adverse reactions related to spontaneous reports by patients is detailed in Section 14.2

Each investigator or delegated will pay close attention that the patients complete the questionnaires entirely. The questionnaires will be verified as soon as they are received.

12.5 Study size of the study

Sample size was estimated based on the primary objective that is to compare the disease activity as measured by the RAPID3 scale. Taking into account the results obtained in prior studies with biological drugs, a difference of 2 points in the RAPID3 scale, with a standard deviation of 6 in both arms, a confidence level of 95% (type I error), and one-sided testing, and a statistical power of 80% (type II error) is expected between the arm with tofacitinib and the arm with biological DMARDs. In this scenario, approximately 142 patients are required in each arm. With a correction factor of 15% considering the proportion of patients that can dropout during the study, the number of patients required as minimum is approximately 160 per arm.

The enrollment process will last until approximately 160 patients in each arm. Every month, the CRO will attend meetings with Pfizer in order to evaluate the enrollment process and the need for increasing the number of sites. An enrollment period of 10 months is estimated.

The time when the patient starts receiving study drugs is defined as the zero time point. Then, a 6-months follow-up from the zero time point will be conducted; measurements will be made at day 1 and 6-months (approximately day 180).

12.6 Data management

12.6.1 Patients selection

Patients will be identified with the help of rheumatologists or preferably identified from rheumatology sites.

Each site's investigator will verify that patients with rheumatoid arthritis are prescribed during the last two week with tofacitinib or biological DMARDs at the time of the enrollment, then, the inclusion and exclusion criteria will be verified in a checklist by the investigator to identify eligible patients. Patients that meet the criteria will be contacted by phone or personally, to explain to them the objective of the study, describe the methods and the implications of the study, in order that the patients make a decision whether participate or not in the study. All the information of the study will be available in the informed consent.

Before enrolling in the study, patients must sign the informed consent. The investigator will guaranty that all patients included in the study have signed the informed consent document and the Clinical Research Associate (CRA) will verify this process through monitoring.

12.6.2 Collection of information at the initial phase

In order to achieve the objectives of the study, validated questionnaires in Spanish language will be given to patients diagnosed with RA who are treated with tofacitinib or a biological DMARD after they failed to respond to conventional DMARDs.

The information may only be collected once the protocol has been approved by Pfizer and the Ethics Committee of the sites, training on AE reporting has been provided, and the informed consent form has been signed by the parts. After the potential patients to be included in the study are identified, the investigator/ treating physician (rheumatologist) will verify the inclusion/exclusion criteria for determining the patient eligibility and will complete the baseline information.

The investigators s will apply health assessment questionnaires at the beginning of recruitment (day 1) and month 6 (approximately day 180) of follow-up. Before sending the information to the sponsor in a standard form for subsequent analysis, data from patients must be codified and verified by the CRO to assure that we will receive complete information and that patients would not be identified by the sponsor.

In order to collect data at the zero time point, the medical records retained in the sites of those patients enrolled in the study will be reviewed; the site's investigators (or treating physician) will be in charge of this review, as agreed with the site.

Forms verified by the sponsor for collecting the information will be used to collect the data.

The coding of each patient will be composed with the number assigned to each participating center which can be from 01 to 15, followed by the consecutive number of the patient that is formed by two digits.

12.6.3 Patients follow-up

Due to the characteristics of the disease, patients need periodical follow-up visits with their rheumatologists. For patients' convenience, the questionnaires will be applied at the time of the visits at day 1 and 6 months (±1 month).

Each site's investigator will be in charge of collecting information and will decide the way for identifying and addressing patients the place for completing the questionnaires and collecting the forms.

In order to reduce the risk of losing patients due to administrative matters or due to changes of address or site, each patient will be asked for contact information which will be kept confidential to the site (not accessible to Pfizer).

12.6.4 Case report form

The case report form (CRF), for the purposes of this study, will be a paper data register form, according to method of data selection. A CRF should exist and be completed for each patient enrolled, and must not include information that could lead to the identification of the patient.

Pfizer owns all CRFs and they must not be available for third parties not authorized by Pfizer or by requirement of the regulatory authorities.

The investigators are responsible for measuring and reporting all the effectiveness and safety outcomes planned in this protocol on the CRFs, guaranteeing that the report is accurate, authentic, consistent, legible, complete, opportune and available as needed.

Data must be reported within a week after contacting the patient.

In case of adverse events, the report must be done in the timelines specified in the section 14 and using specific CRF for the adverse event report, taking into account if it is an active report based on clinical record review (Annex 6) or a spontaneous report from patients (Annex 7). If any pregnancy occurs during the follow-up period of the study, it should be reported using the appropriated form (Annex 8)

Each CRF must be signed by the investigator, who guarantees that the report contains true data. Any amendment to the CRF must be signed by the person who did it, with his/her name initials and the date. The amendment should be done by crossing out the information to amend.

In order to guarantee the protection of patients' personal data and maintain high confidentiality and patients' personal data protection standards, under the corporate policy 404 *Protecting the Privacy of personal information*, the CRO will not transfer data that could lead to patients' identification or any kind of traceability to Pfizer. The CRO will provide Pfizer a database with CFRs' information, where patients are codified. This database will not include the Identification Document (ID) card number, address, phone number or e-mail.

Pfizer will monitor the CRO in order to guarantee the protection of patients' personal data.

12.6.5 Records retention

The site will retain the records, signed informed consents, serious adverse events reports and relevant correspondence in case that Pfizer or regulatory agencies conduct audits.

The records must be retained in accordance with local regulations or as specified in the Clinical Study Agreements.

In case that the site cannot retain the records any longer, must notify Pfizer for its relocation. The site cannot dispose of them without prior notice and a written permit from Pfizer.

12.6.6 Endpoint and covariates

12.6.6.1 Effectiveness endpoint

For this study the change of disease activity measured by RAPID3 change from the baseline to the 6 months of treatment is considered to be the efficacy's primary endpoint.

Secondary endpoints are:

- Physical function measured by HAQ-DI adapted at approximately 6 months follow-up, as well as the change from the baseline.
- Different dimensions of quality of life, measured by EQ-5D at approximately 6 months follow-up, as well as the change from the baseline.
- Work productivity measured by WPAI at approximately 6 months follow-up, as well as the change from the baseline.
- DAS28 will be described according to the information available in the medical records every three months since the prescription of the observed treatment.

12.6.6.2 Safety endpoint

The following endpoints will be considered to describe safety events:

- Incidence of serious adverse events
- Incidence of serious infections
- Incidence of non-serious adverse events
- Withdrawals due to all causes
- Withdrawals due to adverse events

12.6.6.3 Covariates

For effectiveness analysis the following aspects will be considered as covariates:

- Age
- Disease duration
- Severity of the disease at the treatment initiation
- Type of previous treatments for RA (Glucocorticoid (yes/no); methotrexate (yes/no); leflunomide (yes/no))
- Patients with doses over methotrexate 15 mg per week
- Place of origin
- Gender
- Number of swollen joints at the initiation of the treatment
- Number of tender joints at the initiation of the treatment
- Score of erosion at the initiation of the treatment
- DAS28 score at the initiation of the treatment under evaluation
- Concomitant medication (Glucocorticoid (yes/no); methotrexate (yes/no); leflunomide (yes/no))
- Comorbidities

12.7 Data analysis

The information collected by the CRO will be analyzed by Pfizer through a statistical management plan. Initially, the sample will be matched using propensity score calculated from baseline variables. For effectiveness outcomes, a descriptive analysis will be performed for all variables.

12.7.1 Working hypothesis

This protocol was developed based on the hypothesis that there are differences between patients with rheumatoid arthritis treated with tofacitinib and those treated with biological DMARDs regarding the disease activity, quality of life, functional status and work productivity. Null hypothesis is that there are no differences between tofacitinib and biological DMARDs. The alternative hypothesis is that there are significant differences between the study treatments.

12.7.2 Propensity score

The descriptive summary of continuous variables will be reported as number of patients, means, standard deviation, minimum, first quartile, medians, third quartile, and maximum. For dichotomous variables, the number and percentage will be reported.

Continuous variables and categorical variables will be compared between treatment groups using the standard t test and chi-square test. A difference will be considered as significant if p value < 0.05.

Propensity score analysis will be used to reduce potential confounding and selection bias. Propensity score will be estimated using logistic regression including baseline variables associated with the activity of disease or recommendation of physicians. The variable with a significant value below 0.2 will be kept in the model. A goodness of fit measures will be performed.

A bivariate analysis will be performed to identify the association between the baseline variables and the activity of disease. Pearson or Spearman correlation and Mann-Whitney test will be used in order to evaluate the association between the continuous and categorical variables with the activity of disease, respectively.

Patients treated with tofacitinib and biological DMARDs will be matched on the propensity score. Each patient treated tofacitinib will be matched with one patient treated with biological DMARDs. The matching will be used a caliper of width equal to 0.2 of the standard deviation of the logit of the estimated propensity score. This value has been recommended by previous studies (35).

Balance diagnostic will allow assessing if the propensity score is true. The means and prevalence of continuous and dichotomous baseline variables in both groups will be compared from matched sample. The standardized difference will be used to quantify the differences. Additionally, cumulative density plots and quantile plots will be used to compare the distribution of the continuous baseline variables in both groups. If there are important differences the initial propensity score model will be modified adding additional covariates, and interactions between covariates.

12.7.3 Analysis of effectiveness

Functional status (adapted HAQ-DI), Quality of life (EQ-5D) and Disease activity (RAPID3) will be analyzed by direct estimating the difference in means between patients treated with tofacitinib and patients treated with biological DMARDs in matched sample. Paired t test or Wilcoxon test will be used to compare functional status, quality of life and disease activity between both groups.

Additionally, generalized linear mixed model will used to compare the same analysis adjusted by potential confounding covariables. The structured covariance will be pre-specifying by the condition of the model.

DAS28 will be compared in both treatment groups according to an exploratory analysis. Paired t test or Wilcoxon test will be performed to compare the behavior in patients treated with tofacitinib and patients treated with biological DMARDs.

12.7.4 Analysis of safety

Information related to safety will be used only for descriptive purposes.

Safety will be assessed from the adverse events spontaneously reported by patients when filling out the questionnaires and medical record revision from the enrollment initiation to the end of the study.

Due to the nature of this study, patients will not be subject to clinical follow-up, which will be limited to reports by patients related with adverse events symptoms. Moreover, the

medical record will be verified in order to find out changes evaluated by the physician (signs and symptoms).

All the safety data will be summarized through appropriate data tabulations, descriptive statistics, and graphical presentations. The frequency, type of adverse events, and the severity will be involved in the summary.

The incidence will be estimated by the number of patient with adverse events divided per the number of patient–years exposure.

For safety results, two types of outcomes will be presented: serious adverse events (grade 3-5 according to CTCAE (34)) and non-serious adverse events (grade 1 and 2 according to CTCAE (34)).

12.7.4.1 Safety outcomes report monitoring team

A team of two physicians designed by the CRO will analyze the adverse events reported during the study to develop the analysis related to severity and causality. To establish the causality between the adverse event and study drug Bradford Hill and WHO criteria will be used. To establish the severity of the event Common Terminology for Adverse Events criteria will be used.

This team will be created by the CRO and can ask for further information if required during the adverse events analysis. However, the team is not responsible for reporting the adverse events.

The investigator is solely responsible for reporting adverse events to Pfizer, ethics committees and regulatory agencies that require it, as indicated in section 14.

12.7.4.2 Missing data management

Missing values from different components of the scales used will be imputed if loss percentage > 15%. If needed, multiple imputations will be conducted through the program STATA® with an m of 20 that is related to numbers of imputation. This value is selected because reduces the sampling error and allows obtaining valid inferences. If the variable with missing data is continuous, it will be used linear regression. In the case of dichotomous variables, it will be used logistic regression. All predictors relevant to missing data mechanism will be associated.

12.8 Quality control

During the study Pfizer will conduct four audits to the CRA and the sites randomly selected for verifying the compliance with the protocol. In these audits the following aspects will be verified:

- Review of illogical data or outliers
- Review for detecting false answers, such as scale scores out of the limit.
- Review of very high percentage of answers such as "Not known" or "data not available"
- Verify that the data extracted are truthful by comparing them with the source documents.
- Verification of informed consent.
- Reporting of adverse events
- Documentation file

CRO and healthcare sites will allow Pfizer and the appropriate health authorities to conduct this type of follow-up. The main staff will have to dedicate enough time when Pfizer or the health authorities conduct these audits.

12.9 Limitations of the research methods

The study has the following general limitations:

- Patients selected for enrollment in the study represent a "convenience sample", ensuring that the records will be obtained from physicians willing to be involved in the study. Therefore, the results of the study may not be applicable to the general RA population or to physicians treating RA in the countries included.
- All the data collected on the CRF will be those available in questionnaires (PRO) used.
- Quality of data in the medical records can be different between countries and sites. For that reason, there are specific criteria in the selection of sites.
- The characteristics of the patients who accept to participate in the study can be different of the population of study.
- There is probability to find heterogeneity among patients which will be controlled as much as possible with propensity score matching.

12.10 Other aspects

Definition of study completion

Study completion in each country will be defined as the last visit of the last patient.

The study may end early by decision of the regulatory agencies, Ethics committees, safety issues or Pfizer decision. If this happens, Pfizer must notify CRO's monitors to inform to the investigators, who will contact the patients for communicating them the decision.

13. PROTECTION OF HUMAN SUBJECTS

13.1 Patient information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

The informed consent form must be in compliance with local regulatory requirements and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) and Pfizer before use.

The investigator must ensure that each study patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent form.

The investigator must ensure that every patient is fully informed on the nature of the study, its objectives and the possible risks for participating.

Before the study initiation patients must sign the informed consents. The investigator will retain the original informed consent.

The parties will guarantee the patients' personal data protection by maintaining high confidentiality and data protection standards. When the CRO provides the database to Pfizer, will not provide data such as name, phone number, address or any other information that could lead to patients' identification should be encoded.

The CRO will protect the patients' data following the most stringent guidelines.

Publications, reports or informative documents will not include the patients' names.

13.2 Patient withdrawal

Patients may be withdrawn from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved adverse events.

Reasons why patients may discontinue or be withdrawn from the protocol may include one of the following:
• Patient is lost to follow-up;
• Death;
• Study terminated by sponsor;
• Withdrawal of consent;

If any patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. Pfizer may retain and continue to use any data collected before such withdrawal of consent.

13.3 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, (e.g., recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The investigator is responsible for protocol, informed consent and report forms approval from ethics committee. Ethics Committees must comply with each country laws and be in a position to protect all patients included in the research.

Ethics Committee communications will be recorded in the investigator's record. The approval copy should be sent to Pfizer.

If amendments are required to the protocol, the investigator must notify the ethics committee, obtain re-approval and send a copy to Pfizer.

13.4 Ethical conduct of the study

This study will be conducted under the legal requirements as well as the International Ethical Guidelines for Biomedical Research principles (Council for International Organizations of Medical Sciences 2002), the Good Clinical Practice guidelines (International Conference on Harmonization 1996) and the Helsinki Statement (World Medical Association 2008).

In addition, the study will meet the local regulatory requirements.

14. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

14.1 Secondary Data Collection Study - Includes Protocol-Required Human Review of Unstructured Data

REQUIREMENTS

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report adverse events (AE) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to any Pfizer drug that appear in the reviewed information must be recorded on the data collection tool and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form, as well as ethics committees and regulatory agencies that require it.
- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form, as well as ethics committees and regulatory agencies that require it..

For these safety events with an explicit attribution to or associated with use of, respectively, a Pfizer product, the data captured in the medical record will constitute all clinical information known regarding these adverse events. No follow-up on related adverse events will be conducted.

All research staff members will complete the Pfizer requirements regarding training on the following: "*Your Reporting Responsibilities: Monitoring the Safety, Performance and Quality of Pfizer Products (Multiple Languages)"* and any relevant Your Reporting Responsibilities supplemental training. This training will be provided to all research staff members prior to study start. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the

training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

14.2 Other Primary Data Collection Study

REQUIREMENTS

This study does not involve data collection on clinical endpoints on individual patients. However, safety information may be identified during the course of data collection. Any safety information for an individual patient that is volunteered by a study participant (e.g., health care professional, lay person) during the course of this research must be reported as described below.

The following safety events must be reported on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form: serious and non-serious AEs when associated with the use of the Pfizer product, and scenarios involving exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure **(all reportable, regardless of whether associated with an AE)**, when associated with the use of a Pfizer product.

All Programme staff will complete the Pfizer requirements regarding training on the following: "*Your Reporting Responsibilities: Monitoring the Safety, Performance and Quality of Pfizer Products (Multiple Languages)"* and any relevant Your Reporting Responsibilities supplemental training. This training will be provided to the Programme staff prior to commencement of the study. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. The study CRO will also provide copies of all signed training certificates to Pfizer.

Study participants will complete the PROs questionnaires on paper. The questionnaires do not include questions that could potentially identify a safety event, and does provide an opportunity (e.g., free text field, blank margins on a paper survey) where study participants could provide information that may constitute a safety event. Further, routine communication with participants via email or phone with the Programme staff may not be expected during the conduct of the survey. However, it is possible that a study participant may provide information that could constitute a safety event (e.g., serious and non-serious AEs and/or scenarios involving exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure) to the Programme staff while in conversation about the survey for any reason (e.g., seeking information about the purpose of the

survey). Programme staff will be trained to identify safety event information. In the event that a study participant reports a safety event associated with a Pfizer product, the Programme staff will complete the NIS AEM Report Form and submit to Pfizer within 24 hours of becoming aware of the safety event. Included in the completion of the NIS AEM Report Form is the study participant's contact information as the reporter; complete contact information should be obtained so that, once the NIS AEM Report Form is transferred to Pfizer, the NIS AEM Report Form can be assessed and processed according to Pfizer's standard operating procedures, including requests for follow-up to the study participant.

14.3 Single reference safety document

The Product Label for each included country will serve as the single reference safety document during the course of the study, which will be used by Pfizer safety to assess any safety events reported to Pfizer Safety by the investigator during the course of this study.

The Product Label should continue to be used by the investigator for prescribing purposes and guidance.

The Single Reference Safety Document (SRSD) should be used by the investigator for prescribing purposes and guidance.

15. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Pfizer will post results within one year after study completion, defined as Last Subject, Last Visit (LSLV).

For all publications relating to the Study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship established by the International Committee of Medical Journal Editors.

COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new

information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

16. REFERENCES

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17. LIST OF TABLES

Not applicable

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Number	Document reference number	Date	Title
1		NA	Data Collection Form

ANNEX 2. Adapted HAQ-DI (English version)

The STANFORD HEALTH ASSESSMENT QUESTIONNAIRE©
Stanford University School of Medicine, Division of Immunology & Rheumatology

HAQ Disability Index:
In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page.

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY difficulty [0]	With SOME difficulty [1]	With MUCH difficulty [2]	UNABLE to do [3]
DRESSING & GROOMING Are you able to: -Shampoo your hair?	☐	☐	☐	☐
ARISING Are you able to: -Stand up from a straight chair?	☐	☐	☐	☐
EATING Are you able to: -Cut your meat?	☐	☐	☐	☐
-Open a new milk carton?	☐	☐	☐	☐
WALKING Are you able to: -Climb up five steps?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of these activities:

- ☐ Cane
- ☐ Walker
- ☐ Crutches
- ☐ Wheelchair
- ☐ Devices used for dressing (button hook, zipper pul
  long-handled shoe horn, etc.)
- ☐ Built up or special utensils
- ☐ Special or built up chair
- ☐ Other (Specify:_____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

- ☐ Dressing and Grooming
- ☐ Arising
- ☐ Eating
- ☐ Walking

Please check the response which best describes your usual abilities **OVER THE PAST WEEK:**

	Without ANY difficulty [0]	With SOME difficulty [1]	With MUCH difficulty [2]	UNABLE to do [3]
HYGIENE				
Are you able to:				
-Take a tub bath?	☐	☐	☐	☐
-Get on and off the toilet?	☐	☐	☐	☐
REACH				
Are you able to:				
-Reach and get down a 5-pound object (such as a bag of sugar) from just above your head?	☐	☐	☐	☐
GRIP				
Are you able to:				
-Open car doors?	☐	☐	☐	☐
-Open jars which have been previously opened?	☐	☐	☐	☐
ACTIVITIES				
Are you able to:				
-Run errands and shop?	☐	☐	☐	☐
-Do chores such as vacuuming or yardwork	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of these activities:

- ☐ Raised toilet seat
- ☐ Bathtub seat
- ☐ Jar opener (for jars previously opened)
- ☐ Bathtub bar
- ☐ Long-handled appliances for reach
- ☐ Long-handled appliances in bathroom
- ☐ Other (Specify:_____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

- ☐ Hygiene
- ☐ Reach
- ☐ Gripping and opening things
- ☐ Errands and chores

We are also interested in learning whether or not you are affected by pain because of your illness.
How much pain have you had because of your illness IN THE PAST WEEK:

PLACE A VERTICAL (|) MARK ON THE LINE TO INDICATE THE SEVERITY OF THE PAIN

No Pain — **Severe Pain**

0 — **100**

Considering all the ways that your arthritis affects you, rate how you are doing on the following scale by placing a vertical mark on the line.

Very Well — **Very Poor**

0 — **100**

ANNEX 3. EQ-5D-3L (English version)

EQ-5D-3L (UK English sample version)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

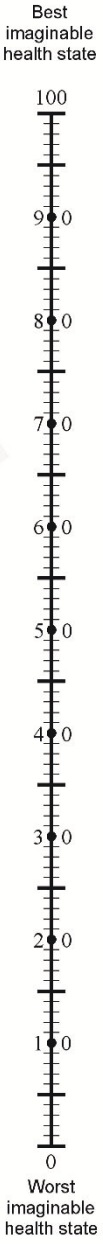
Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked **100** and the worst state you can imagine is marked **0**.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



ANNEX 4. WPAI (English version)

Work Productivity and Activity Impairment Questionnaire:
General Health V2.0 (WPAI:GH)

The following questions ask about the effect of your health problems on your ability to work and perform regular activities. By health problems we mean any physical or emotional problem or symptom. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? ____ NO ____ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of your health problems? *Include hours you missed on sick days, times you went in late, left early, etc., because of your health problems. Do not include time you missed to participate in this study.*

   _____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

WPAI:GH V2.0 (US English) 1

5. During the past seven days, how much did your health problems affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If health problems affected your work only a little, choose a low number. Choose a high number if health problems affected your work a great deal.

Consider only how much health problems affected productivity while you were working.

Health problems had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Health problems completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your health problems affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If health problems affected your activities only a little, choose a low number. Choose a high number if health problems affected your activities a great deal.

Consider only how much health problems affected your ability to do your regular daily activities, other than work at a job.

Health problems had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Health problems completely prevented me from doing my daily activities

CIRCLE A NUMBER

ANNEX 5. RAPID3 (English version)

Multi-Dimensional Health Assessment Questionnaire (R808-NP2)

This questionnaire includes information not available from blood tests, X-rays, or any source other than you. Please try to answer each question, even if you do not think it is related to you at this time. Try to complete as much as you can yourself, but if you need help, please ask. There are no right or wrong answers. Please answer exactly as you think or feel. Thank you.

1. Please check (√) the ONE best answer for your abilities at this time:

OVER THE LAST WEEK, were you able to:	Without **ANY** Difficulty	With **SOME** Difficulty	With **MUCH** Difficulty	**UNABLE** To Do
a. Dress yourself, including tying shoelaces and doing buttons?	0	1	2	3
b. Get in and out of bed?	0	1	2	3
c. Lift a full cup or glass to your mouth?	0	1	2	3
d. Walk outdoors on flat ground?	0	1	2	3
e. Wash and dry your entire body?	0	1	2	3
f. Bend down to pick up clothing from the floor?	0	1	2	3
g. Turn regular faucets on and off?	0	1	2	3
h. Get in and out of a car, bus, train, or airplane?	0	1	2	3
i. Walk two miles or three kilometers, if you wish?	0	1	2	3
j. Participate in recreational activities and sports as you would like, if you wish?	0	1	2	3
k. Get a good night's sleep?	0	1.1	2.2	3.3
l. Deal with feelings of anxiety or being nervous?	0	1.1	2.2	3.3
m. Deal with feelings of depression or feeling blue?	0	1.1	2.2	3.3

FOR OFFICE USE ONLY

1.a-j FN (0-10):

1=0.3 16=5.3
2=0.7 17=5.7
3=1.0 18=6.0
4=1.3 19=6.3
5=1.7 20=6.7
6=2.0 21=7.0
7=2.3 22=7.3
8=2.7 23=7.7
9=3.0 24=8.0
10=3.3 25=8.3
11=3.7 26=8.7
12=4.0 27=9.0
13=4.3 28=9.3
14=4.7 29=9.7
15=5.0 30=10

2.PN (0-10):

4.PTGL (0-10):

RAPID 3 (0-30)

Cat:
HS = >12
MS = 6.1-12
LS = 3.1-6
R = ≤3

2. How much pain have you had because of your condition OVER THE PAST WEEK? Please indicate below how severe your pain has been:

NO PAIN 0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10 PAIN AS BAD AS IT COULD BE

3. Please place a check (√) in the appropriate spot to indicate the amount of pain you are having today in each of the joint areas listed below:

	None	Mild	Moderate	Severe		None	Mild	Moderate	Severe
a. LEFT FINGERS	☐ 0	☐ 1	☐ 2	☐ 3	i. RIGHT FINGERS	☐ 0	☐ 1	☐ 2	☐ 3
b. LEFT WRIST	☐ 0	☐ 1	☐ 2	☐ 3	j. RIGHT WRIST	☐ 0	☐ 1	☐ 2	☐ 3
c. LEFT ELBOW	☐ 0	☐ 1	☐ 2	☐ 3	k. RIGHT ELBOW	☐ 0	☐ 1	☐ 2	☐ 3
d. LEFT SHOULDER	☐ 0	☐ 1	☐ 2	☐ 3	l. RIGHT SHOULDER	☐ 0	☐ 1	☐ 2	☐ 3
e. LEFT HIP	☐ 0	☐ 1	☐ 2	☐ 3	m. RIGHT HIP	☐ 0	☐ 1	☐ 2	☐ 3
f. LEFT KNEE	☐ 0	☐ 1	☐ 2	☐ 3	n. RIGHT KNEE	☐ 0	☐ 1	☐ 2	☐ 3
g. LEFT ANKLE	☐ 0	☐ 1	☐ 2	☐ 3	o. RIGHT ANKLE	☐ 0	☐ 1	☐ 2	☐ 3
h. LEFT TOES	☐ 0	☐ 1	☐ 2	☐ 3	p. RIGHT TOES	☐ 0	☐ 1	☐ 2	☐ 3
q. NECK	☐ 0	☐ 1	☐ 2	☐ 3	r. BACK	☐ 0	☐ 1	☐ 2	☐ 3

4. Considering all the ways in which illness and health conditions may affect you at this time, please indicate below how you are doing:

VERY WELL 0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10 VERY POORLY

Please turn to the other side

ANNEX 6. NIS AEM Report Form 1 (Active Collection)

Non-Interventional Study Adverse Event Report Form
For Protocols with Stipulated Active Collection of Adverse Events
(Including Pragmatic Clinical Studies [Non-Medicinal Intervention])

For Pfizer internal use only	
Local #	Date Reported to Pfizer

AER # (*insert when known*)

PROTOCOL # **SUBJECT #**

Protocol Title:

☐ Initial Report ☐ Follow Up Report — **Country where event occurred:**

Patient Data | Date of Birth ☐ Male ☐ Female | Height ☐ in ☐ cm Weight ☐ lb ☐ kg

Patient's Race:

☐ Asian ☐ Black or African American ☐ Native Hawaiian or other Pacific Islander ☐ American Indian or Alaska Native
☐ White ☐ Unknown ☐ Cannot ask per local regulations , Other (specify)

Patient's Ethnicity: ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Unknown

If patient has died: | Date of Death | Cause(s) of Death | Determined by Autopsy: Y ☐ N ☐ Unknown ☐ *If yes, what was the autopsy determined cause of Death:*

Patient History ☐ None ☐ Unknown — *Provide relevant medical history below Include other illnesses present at time of event and pre-existing medical conditions. If additional space is necessary, use addiitonal copies of this page.*

Illness (specify)	Onset Date	Stop Date	*Check box if Ongoing*	Pertinent Details *Include surgical procedures and dates*
			☐	
			☐	
			☐	
			☐	

Study Drug (Trade and Generic), Formulation, Route, Indication	*Check box if Pfizer Drug*	Dose	Units	Frequency	Start Date	Stop Date	*Check box if Ongoing*
	☐						☐
	☐						☐
	☐						☐
	☐						☐

Concomitant Drugs ☐ None ☐ Unknown — *List below concomitant drugs taken within two weeks before the event onset. Exclude all drugs only administered more than two weeks before the event, and any drug used to treat the event or taken after event onset. If additional space is necessary, use additional copies of this page.*

Drug Name (Trade and Generic)	Reason for Use	Route	Start Date	Stop Date	*Check box if Ongoing*
					☐
					☐
					☐
					☐

Relevant Tests — *List only relevant confirmatory test results for adverse event(s), for example, from blood tests, diagnostic imaging. If additional space is necessary, use additional copies of this page.*

Test	Date	Result	Units	Normal Range Low	Normal Range High	Comments

Version 5.0, Effective August 2016 **Page _____ of _____** **Pfizer Confidential**

Non-Interventional Study Adverse Event Report Form
For Protocols with Stipulated Active Collection of Adverse Events
(Including Pragmatic Clinical Studies [Non-Medicinal Intervention])

For Pfizer internal use only	
Local #	Date Reported to Pfizer

AER # (*insert when known*)

PROTOCOL # **SUBJECT #**

ADVERSE EVENTS *(if more than two, use additional copies of this page)*
Specify diagnosis if known, rather than symptoms or signs

Adverse Event Term	**Adverse Event Term**
Onset Date:	Onset Date:
Is the event serious? ☐ **Yes** ☐ **No** **If yes, identify seriousness criteria below:**	**Is the event serious?** ☐ **Yes** ☐ **No** **If yes, identify seriousness criteria below:**
Seriousness Criteria (Check all that apply): ☐ Resulted in death ☐ Life-threatening ☐ Hospitalization/Prolongation of hospitalization ☐ Persistent/Significant disability/Incapacity ☐ Congenital anomaly/Birth defect ☐ Important medical event	**Seriousness Criteria (Check all that apply):** ☐ Resulted in death ☐ Life-threatening ☐ Hospitalization/Prolongation of hospitalization ☐ Persistent/Significant disability/Incapacity ☐ Congenital anomaly/Birth defect ☐ Important medical event
Status at date of report or at death: ☐ Recovered } Date of Recovery: _____ ☐ Recovered with sequelae } ☐ Recovering ☐ Not Recovered ☐ Unknown	**Status at date of report or at death:** ☐ Recovered } Date of Recovery: _____ ☐ Recovered with sequelae } ☐ Recovering ☐ Not Recovered ☐ Unknown
Is there a reasonable possibility that the event is related to Study Drug? ☐ **Yes** ☐ **No**	**Is there a reasonable possibility that the event is related to Study Drug?** ☐ **Yes** ☐ **No**
If yes, specify Study Drug:	**If yes, specify Study Drug:**
Is there a reasonable possibility that the event is related to Concomitant Drug? ☐ **Yes** ☐ **No**	**Is there a reasonable possibility that the event is related to Concomitant Drug?** ☐ **Yes** ☐ **No**
If yes, specify Concomitant Drug:	**If yes, specify Concomitant Drug:**
Last Action Taken In Response to Event(s); specify drug name:	**Last Action Taken In Response to Event(s); specify drug name:**
☐ Withdrawn (temporarily or permanently, or delayed) ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable	☐ Withdrawn (temporarily or permanently or delayed) ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable
☐ Withdrawn (temporarily or permanently, or delayed) ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable	☐ Withdrawn (temporarily or permanently or delayed) ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable
Did an SAE/AE recur with re-administration of drug? ☐ Yes ☐ No ☐ Unknown ☐ Not Applicable If yes, which drug?:	Did an SAE/AE recur with re-administration of drug? ☐ Yes ☐ No ☐ Unknown ☐ Not Applicable If yes, which drug?:

Non-Interventional Study Adverse Event Report Form
For Protocols with Stipulated Active Collection of Adverse Events
(Including Pragmatic Clinical Studies [Non-Medicinal Intervention])

For Pfizer internal use only	
Local #	Date Reported to Pfizer

AER # (*insert when known*)									

PROTOCOL # **SUBJECT #**

Event Narrative

Provide any information regarding the circumstances, sequence, diagnosis and treatment of the event(s) not otherwise reported on this form. If additional space is necessary, use additional copies of this page.

Reporter Comments:

Reporter: - -

First Name | Last Name (*Please* PRINT) | Date: DD-MMM-YYYY

Address: /

Street | City / State | Zip Code | Country

Telephone: Fax: Email:

Investigator's Name: _____ **Investigator/Designee Signature:**

Investigator/Designee Awareness Date: - - DD-MMM-YYYY

Report this form to Pfizer within 24 hours of awareness or immediately in case of death and life-threatening SAEs.

RECORD ALL PERTINENT INFORMATION ON THE FORM. DO NOT ATTACH SOURCE DOCUMENTS.

ANNEX 7. NIS AEM Report Form 2 (Spontaneous Report)

Non-Interventional Study Adverse Event Report Form
For Protocols without Stipulated Active Collection of Adverse Events (Including Pragmatic Clinical Studies [Non-Medicinal Intervention])

For Pfizer internal use only	
Case #	Date Reported to Pfizer
	- -

AER # (*insert when known*)

PROTOCOL # **SUBJECT #**

Protocol Title:

☐ Initial Report ☐ Follow-Up Report	Indicate any supplemental form(s) used by selecting the appropriate box: ☐ Exposure During Pregnancy ☐ Vaccine ☐ Medical Device	**Country where event occurred:**

Patient Data	Date of Birth: - - DD-MMM-YYYY ☐ Male ☐ Female	Height: ☐ in ☐ cm Weight: ☐ lb ☐ kg

Patient's Race:

☐ Asian ☐ Black or African American ☐ Native Hawaiian or other Pacific Islander ☐ American Indian or Alaska Native
☐ White ☐ Unknown ☐ Cannot ask per local regulations, Other (specify):

Patient's Ethnicity: ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Unknown

If patient has died:	Date of Death: - - DD-MMM-YYYY	Cause(s) of death:	Was an autopsy performed? ☐ Yes ☐ No ☐ Unknown If yes, what was the autopsy determined cause of death?

ADVERSE EVENTS *(If more than two, use additional copies of this page.)*
Specify diagnosis if known, rather than symptoms or signs.

Adverse Event Term:	Date of Onset: - - DD-MMM-YYYY	**Is the event serious? ☐ Yes ☐ No** **If yes, identify seriousness criteria below:**

Seriousness Criteria (check ***ALL*** that apply)

☐ Resulted in death ☐ Life-threatening ☐ Hospitalization/Prolongation of hospitalization ☐ Persistent/Significant disability/incapacity
☐ Congenital anomaly/Birth defect ☐ Important medical event

Status at date of report or at death ☐ Recovered ☐ Recovered with sequelae ☐ Recovering ☐ Not Recovered ☐ Unknown
*(check **ONE**)*:
If Recovered, or Recovered with sequelae, enter date: - - DD-MMM-YYYY
NOTE: Does the reporter believe this AE may be related to a Suspect Product? ☐ Yes ☐ No
If Yes, which Suspect Product(s)?

Adverse Event Term:	Date of Onset: - - DD-MMM-YYYY	**Is the event serious? ☐ Yes ☐ No** **If yes, identify seriousness criteria below:**

Seriousness Criteria (check ***ALL*** that apply)

☐ Resulted in death ☐ Life-threatening ☐ Hospitalization/Prolongation of hospitalization ☐ Persistent/Significant disability/incapacity
☐ Congenital anomaly/Birth defect ☐ Important medical event

Status at date of report or at death ☐ Recovered ☐ Recovered with sequelae ☐ Recovering ☐ Not Recovered ☐ Unknown
*(check **ONE**)*:
If Recovered, or Recovered with sequelae, enter date: - - DD-MMM-YYYY
NOTE: Does the reporter believe this AE may be related to a Suspect Product? ☐ Yes ☐ No
If Yes, which Suspect Product(s)?

Version 2.0, Effective August 2016 **Page _____ of _____** **Pfizer Confidential**

Non-Interventional Study Adverse Event Report Form
For Protocols without Stipulated Active Collection of Adverse Events (Including Pragmatic Clinical Studies [Non-Medicinal Intervention])

For Pfizer internal use only	
Case #	Date Reported to Pfizer
	- -

AER # (*insert when known*)

PROTOCOL # **SUBJECT #**

Suspect Pfizer Product *If more space is needed, use additional copies of this page.*

Trade Name:		Generic Name:	
Lot Number	Expiration Date	☐ Interacting Product Name of Product:	☐ AE involves a product problem NDC Number or PCR Number *(For US Only)*
	- - DD-MMM-YYYY		

INDICATION:

Dose	Units	Formulation	Route	Frequency	Start Date	Stop Date
					- - DD-MMM-YYYY	- - DD-MMM-YYYY

If no stop date, check box if administration was ongoing during the event(s): ☐

Last Action Taken with Suspect Product in Response to Event(s): ☐ Withdrawn Permanently ☐ Dose Reduced ☐ Dose Not Changed ☐ Unknown ☐ Withdrawn Temporarily ☐ Dose Increased ☐ Not Applicable

Did an AE recur with re-administration of product? ☐ Yes ☐ No ☐ Unknown ☐ Not Applicable
If Yes, which AE?

Concomitant Drugs ☐ None ☐ Unknown
Include all concomitant products taken before the date of onset of the first event. Do not include products taken more than 2 weeks before the event, used to treat the event, or taken only after event onset.
If more space is needed, use additional copies of this page.

Trade Name	Indication	Dose	Units	Formulation	Route	Frequency	Start Date \ Stop Date
							- -
Generic Name							DD-MMM-YYYY
							- -
							DD-MMM-YYYY

If no stop date, check box if administration was ongoing during the event(s): ☐

Trade Name							
							- -
Generic Name							DD-MMM-YYYY
							- -
							DD-MMM-YYYY

If no stop date, check box if administration was ongoing during the event(s): ☐

Patient History ☐ None ☐ Unknown
Provide relevant medical history below. Include other illnesses present at time of event and pre-existing medical conditions (e.g. allergies, previous drug reactions, alcohol/drug abuse,). If more space is needed, use additional copies of this page.

Illness	Start Date \ Stop Date	If no stop date, check box if history/illness was ongoing during the event(s)	Pertinent Details (include procedures and dates)
	- - DD-MMM-YYYY - - DD-MMM-YYYY	☐	
	- - DD-MMM-YYYY - - DD-MMM-YYYY	☐	

Non-Interventional Study Adverse Event Report Form
For Protocols without Stipulated Active Collection of Adverse Events (Including Pragmatic Clinical Studies [Non-Medicinal Intervention])

For Pfizer internal use only	
Case #	Date Reported to Pfizer
	- -

AER # (*insert when known*)

PROTOCOL # **SUBJECT #**

Relevant Tests
☐ None
☐ Unknown

List only relevant confirmatory and diagnostic test results for event(s), for example, from blood tests, diagnostic imaging, etc. If more space is needed, use additional copies of this page

Test	Date	Result	Units	Normal Range Low	Normal Range High	Comments
	- - DD-MMM-YYYY					
	- - DD-MMM-YYYY					
	- - DD-MMM-YYYY					
	- - DD-MMM-YYYY					

Event Narrative

Provide clear narrative description of the sequence of event(s), diagnosis, treatment, and any other relevant details. If more space is needed, use additional copies of this page.

Non-Interventional Study Adverse Event Report Form
For Protocols without Stipulated Active Collection of Adverse Events (Including Pragmatic Clinical Studies [Non-Medicinal Intervention])

For Pfizer internal use only	
Case #	Date Reported to Pfizer
	- -

AER # (*insert when known*)

PROTOCOL # **SUBJECT #**

Reported By: (*PRINT*)

Last Name First Name Healthcare Professional? ☐ Yes ☐ No ☐ Unknown

Address: City: Postal Code: Telephone:
State/Province: Country: Fax:

Date: - - DD-MMM-YYYY Email Address:

☐ Check if reporter grants permission to be contacted by the Company for additional information if needed.

Reporter Occupation:
☐ Physician ☐ Pharmacist ☐ Nurse ☐ Other Healthcare Professional
☐ Consumer\Other Non-HCP ☐ Lawyer

Name of Patient's Prescribing/Primary Physician (if known, PRINT):

Last Name First Name

Address: City: Postal Code: Telephone:
State/Province: Country:

Email Address:

☐ Check if reporter grants permission to contact his/her physician for additional information if needed.

Prepared By: (*PRINT*)

Last Name First Name

Vendor/ Program Staff Telephone: City: Country:

Comments:

ANNEX 8. NIS AEM Report Form 3 (Pregnancy)

Exposure During Pregnancy (EDP) Supplemental Form

AER # (*insert when known*)	*For Pfizer internal use only*	
	Local #	Date Reported to Pfizer

PROTOCOL # **SUBJECT #**

Complete whenever an embryo or fetus has been exposed to study drug. Send as soon as EDP has been diagnosed, together with the SAE Report Form with the appropriate fields completed. If more space is needed, use additional copies of this page.

Pregnancy

First Day of Last Menstrual Period DD-MMM-YYYY

Estimated Date of Conception DD-MMM-YYYY

Gestation at time of initial exposure weeks **Or, if number of weeks unknown:** ☐ First trimester? ☐ Second trimester? ☐ Third trimester?

Relevant History/Exposure to Products

Risk factors for adverse pregnancy outcomes including environmental or occupational exposures, e.g. hypertension, diabetes, etc. Family history of congenital abnormality/genetic diseases, consanguinity (or any family relation or lineage) between parents (specify degree):

1) Did the mother smoke during this pregnancy? ☐ No ☐ Yes: Number per day?

2) Did the mother drink alcohol during this pregnancy? ☐ No ☐ Yes : Frequency?

3) Did the mother use illicit drugs during this pregnancy? ☐ No ☐ Yes : Frequency?

Obstetrical History *(Check the box if not applicable)*

☐ Not Applicable: No previous pregnancy

Number of previous pregnancies Number of other children

Outcome of previous pregnancies (live birth, miscarriage, elective termination, late fetal death, ectopic pregnancy, molar pregnancy). Previous maternal pregnancy complications. Previous fetal/neonatal abnormalities and type. History of sub-fertility.

OUTCOME OF PREGNANCY

Complete and send after the end of pregnancy in all cases when an embryo or fetus has been exposed to study drug

Date of outcome of pregnancy DD-MMM-YYYY

Pregnancy outcome

Check one ☐ Full term live birth ☐ Preterm live birth ☐ Stillbirth* ☐ Spontaneous abortion/miscarriage* ☐ Induced abortion ☐ Unknown

Gestational age at birth in weeks, (if known):

Complete also the Serious Adverse Event section of the report

Infant

Check one ☐ Normal ☐ Congenital Malformation/Anomaly** ☐ Other neonatal problem** ☐ Unknown

Other neonatal problem/abnormality (include dysmaturity, neonatal illness, hospitalization, drug therapies) Specify:

Apgar Score 1min 5min

☐ Male ☐ Female Birthweight grams ***Or, if birthweight in grams unknown:*** Birthweight ☐ lb ☐ oz

Length at birth: ☐ in ☐ cm Head Circumference at birth: ☐ in ☐ cm

****Complete also the Serious Adverse Event section of the report, specifying the diagnosis as the Serious Adverse Event***

Exposure During Pregnancy (EDP) Supplemental Form

AER # (*insert when known*)	*For Pfizer internal use only*	
	Local #	Date Reported to Pfizer

PROTOCOL # **SUBJECT #**

Paternal Information *(Check the box if not applicable)*

☐ Not Applicable

Age (years) **Date of Birth** DD-MMM-YYYY **Occupation**

Relevant History

Risk factors including environmental or occupational exposures, e.g. AIDS, toxins. Family history of congenital abnormality/genetic diseases, consanguinity (or any family relation or lineage) between parents (specify degree):

Exposure to Products

Where any drugs (e.g., OTC, medical prescription) taken by the father during the mother's pregnancy? ☐ No ☐ Yes, *please specify*

Product	Indication	Start Date \ Stop Date	Reason for stopping	Dose	Formulation	Frequency
		DD-MMM-YYYY DD-MMM-YYYY				
		DD-MMM-YYYY DD-MMM-YYYY				
		DD-MMM-YYYY DD-MMM-YYYY				
		DD-MMM-YYYY DD-MMM-YYYY				

Exposure to Products - Recreational Drug Use

1) Did the father smoke during the mother's pregnancy? ☐ No ☐ Yes: Number per day?

2) Did the father drink alcohol during the mother's pregnancy? ☐ No ☐ Yes : Frequency?

3) Did the father use illicit drugs during the mother's pregnancy? ☐ No ☐ Yes : Frequency?