PASS Information

Title	Burden of serious infection in patients with rheumatoid arthritis (RA) treated with biologics and Prolia observed in a clinical setting
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Joint PASS	No
Research Question and Objectives	Primary objectives within a rheumatoid arthritis cohort: 1) Estimate the frequency of serious infections among patients treated concomitantly with an immunosuppressive biologic and Prolia 2) Estimate the frequency of serious infections among patients treated with a single immunosuppressive biologic (without Prolia) Secondary objectives within a rheumatoid arthritis cohort: 1) Estimate the frequency of opportunistic infections among patients treated concomitantly with an immunosuppressive biologic and Prolia 2) Estimate the frequency of opportunistic infection among patients treated with a single immunosuppressive biologic (without Prolia)
Country of Study	Canada
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2. List of Abbreviations

Abbreviation	Definition
BMI	Body mass index
CRP	C-Reactive Protein
DMARD	Disease -modifying antirheumatic drugs
eGFR	Estimated glomerular filtration rate
EMR	Electronic medical record
EOI	Event of Interest
ER	Emergency room
ESR	Erythrocyte sedimentation rate
GC	Glucocorticoid
IV	Intravenous
RA	Rheumatoid arthritis
TNF	Tumor necrosis factor

3. Responsible Parties

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4. Abstract

Title: Burden of serious infection in patients with rheumatoid arthritis treated with immunosuppressive biologics and Prolia observed in a clinical setting

- Version: 1.0
- Date: 28 July 2014

- Authors: Jonathan (Rick) Adachi, McMaster University, Canada
  Mary Anthony, Amgen, Inc.

Rationale and Background: Rheumatoid arthritis (RA) has long been understood to contribute to the risk of osteoporosis and fracture. While oral bisphosphonates have been the mainstay of treatment of osteoporosis, denosumab (Prolia), a fully human monoclonal antibody that binds the receptor activator of nuclear- κ B ligand (RANKL) is a valuable treatment option for appropriate patients with rheumatoid arthritis. RA itself, and many of its treatments, predispose patients to serious infection, particularly of the pulmonary system and skin or soft tissues. While the etiology of increased infection risk in RA remains unknown, immune dysregulation, cartilage and other connective tissue damage, functional status impairment, and the inflammatory milieu may all contribute. Immune suppressants used in the treatment of RA can also contribute to risk of infection, including opportunistic infections. In the pivotal phase 3 study for Prolia, there was no overall increased risk of infection relative to placebo [FREEDOM]. However, limited studies to-date have looked at possible increased risk of infection with concomitant use of Prolia and immunosuppressive biologics used for the treatment of RA. This is an important question given that RA is an independent risk factor for fracture and that management of osteoporotic RA patients who are at high risk for fracture may warrant the use of denosumab along with immunosuppressive biologic therapy for RA disease control. Therefore, we propose an observational study to describe the occurrence of serious infections in RA patients with osteoporosis treated concomitantly with Prolia and immunosuppressive biologics in a Canadian medical practice.

- Research Question and Objectives
  - Primary Objectives
    1. Estimate the frequency of serious infections among patients treated concomitantly with an immunosuppressive biologic and Prolia
    2. Estimate the frequency of serious infections among patients treated with a single immunosuppressive biologic (without Prolia)
  - Secondary Objectives
    1. Estimate the frequency of opportunistic infections among patients treated concomitantly with an immunosuppressive biologic and Prolia
    2. Estimate the frequency of opportunistic infection among patients treated with a single immunosuppressive biologic (without Prolia)
- Study Design: Retrospective cohort

- Population: Adult patients age 18 or older with rheumatoid arthritis and osteoporosis who were receiving medical care at the Hamilton Rheumatology medical practice in Ontario, Canada, between 01 July 2010 and 31 July 2014.
- Variables
  - The primary endpoint is serious infection which is defined as an infection leading to hospitalization or an emergency room visit with intravenous antibiotics.
  - The secondary endpoint is opportunistic infection, including infection with the following pathogens, (e.g.: *Mycobacterium tuberculosis, Mycobacterium avium,* cytomegalovirus, varicella zoster, herpes simplex, *Cryptosporidium*, *Toxoplasma gondii*, *Crypotoccus neoformans*, *Pneumocystis carinii*, *Histoplasma capsulatum*, or other invasive fungi).
- Outcome Variables
  - Objective 1: The outcome will be the frequency of serious infections among patients treated concomitantly with an immunosuppressive biologic and Prolia in an RA cohort.
  - Objective 2: The outcome will be the frequency of serious infections among patients treated concomitantly with a single immunosuppressive biologic (without Prolia) in an RA cohort.
  - Objective 3: The outcome will be the frequency of opportunistic infections among patients treated concomitantly with an immunosuppressive biologic and Prolia an RA cohort.
  - Objective 4: The outcome will be the frequency of opportunistic infection amont patients treated with a single immunosuppressive biologic (without Prolia) in an RA cohort
- Data Sources: The Hamilton Rheumatology medical practice electronic medical records (EMR) database and Pharmaca Health records.
- Study Size: approximately100 Prolia-exposed patients and approximately1000 Prolia-unexposed patients

Data Analysis: Characteristics of the Prolia-exposed patients and Prolia-unexposed patients will be assessed descriptively. Cumulative incidence of infection (incidence proportion) will be calculated for both the Prolia and non-Prolia exposed cohorts. The incidence proportion will be assessed separately over a 6-month and a 12-month follow-up period. The incidence rate is calculated as the total number of patients with an infection divided by the summation of patient-days of applicable time at risk from all patients, where the time at risk is censored at the first occurrence of the event for patients experiencing an infection and not censored for those patients who do not experience an infection. Sensitivity analyses will be conducted using different measures of exposure time at risk. Subgroup analyses will be conducted to determine the influence of potential confounders on infection incidence proportions. For a full description of statistical analysis methods, refer to Section 9.7.

- Milestones

  Start of data collection: 01 November 2014

  End of data collection: 12 January 2015

  Final report of study results: 30 August 2015

5. Amendments and Updates

No amendments or updates.

6. Milestones

Milestone	Planned date
Start of secondary data collection	01 November 2014
End of secondary data collection	12 January 2015
Final report of study results	30 August 2015

7. Rationale and Background

Rheumatoid arthritis (RA) has long been understood to contribute to the risk of osteoporosis and fracture [1-3]. This increased risk is likely multifactorial in nature, due to the inflammatory state of RA, treatment with glucocorticoids, and other factors. While oral bisphosphonates have been the mainstay of treatment of osteoporosis, the newer biologic agent denosumab (Prolia) was approved for the treatment of post-menopausal osteoporosis in women at high risk for fracture in 2010, and subsequently approved for men with osteoporosis. Denosumab is a fully human monoclonal antibody that binds the receptor activator of nuclear- κ B ligand (RANKL) and prevents it from interacting with its receptor RANK, inhibiting the differentiation, survival, and activation of osteoclasts, thus reducing bone resorption. Prolia (Denosumab) stands as a valuable treatment option for appropriate patients with rheumatoid arthritis. However, co-morbidities and concomitant treatment modalities used in RA pose unique dilemmas for the treating physician. In particular, the possibility of increased risk of infection in RA patients receiving denosumab in combination with an immunosuppressive biologic has not been directly examined in clinical trials.

RA itself, and many of its treatments, predispose patients to serious infection, particularly of the pulmonary system and skin or soft tissues [4,5]. While the etiology of increased infection risk in RA remains unknown, immune dysregulation, cartilage and other connective tissue damage, functional status impairment, and the inflammatory

milieu may all contribute. Immune suppressants used in the treatment of RA can also contribute to risk of infection, including opportunistic infections. Numerous studies have demonstrated an increased risk of serious infection in RA patients treated with glucocorticoids, with risk increasing along with the prednisone dose [6,5].

Biologic therapy for RA, such as with tumor necrosis factor (TNF) inhibition, has been widely adopted over the past decade and further raises concerns regarding infection risk. While there are some divergent reports in the literature regarding the extent of infection risk from immunosuppressive biologic therapy, several studies have indicated that TNF inhibitors increase the risk of tuberculosis, other opportunisitic infections, serious bacterial infections, and overall infections in the RA population [7-9]. Concomitant use of immunosuppressive biologics and non-biologic disease modifying anti-rheumatic drugs (e.g. methotrexate) is common in clinical practice. However, dual treatment with TNF inhibitors and both abatacept (T-cell co-stimulation inhibitor) or anakinra (interleukin-1 receptor anagonist) raised infection risk beyond single biologic therapy without a significant increase in clinical efficacy. Thus, dual immunosuppressive biologic therapy for RA is not recommended by the American College of Rheumatology [10-13].

In the pivotal phase 3 study for Prolia, there was no overall increased risk of infection relative to placebo [FREEDOM]. Early studies of denosumab also showed no significant changes in white blood cell counts,overall lymphocyte counts, or lymphocyte subsets counts in patients receiving the agent, and animal models suggest immune function remains intact in the presence of RANKL inhibition [14]. However, limited studies to-date have looked at possible increased risk of infection with concomitant use of Prolia and immunosuppressive biologics used for the treatment of RA [15] This is an important question, RA is an independent risk factor for fracture and management of RA patients with osteoporosis at high risk for fracture may warrant treatment with denosumab along with immunosuppressive biologic therapy for RA disease control. We propose an observational study to describe the occurrence of serious infections in RA patients with osteoporosis treated concomitantly with Prolia and immunosuppressive biologics in a Canadian medical practice.

8. Research Question and Objectives

The research question is to describe the frequency of serious infection and opportunistic infection in a cohort of patients with rheumatoid arthritis using immunosuppressive

biologics for RA treatment by with results provided by Prolia exposure status. This study has 4 objectives:

1. To estimate the frequency of serious infections among patients treated concomitantly with an immunosuppressive biologic and Prolia in an RA cohort,
2. To estimate the frequency of serious infections among patients treated concomitantly with a single immunosuppressive biologic (without Prolia) in an RA cohort,
3. To estimate the frequency of opportunistic infections among patients treated concomitantly with an immunosuppressive biologic and Prolia an RA cohort,
4. To estimate the frequency of opportunistic infection amont patients treated with a single immunosuppressive biologic (without Prolia) in an RA cohort.

9. Research Methods

This pilot study focuses exclusively on data from a single rheumatology infusion clinic. Formal hypotheses will not be tested.

This study will estimate:

Objective 1: the frequency of serious infections among patients treated concomitantly with an immunosuppressive biologic and Prolia in an RA cohort,
Objective 2: the frequency of serious infections among patients treated concomitantly with a single immunosuppressive biologic (without Prolia) in an RA cohort,
Objective 3: the frequency of opportunistic infections among patients treated concomitantly with an immunosuppressive biologic and Prolia an RA cohort,

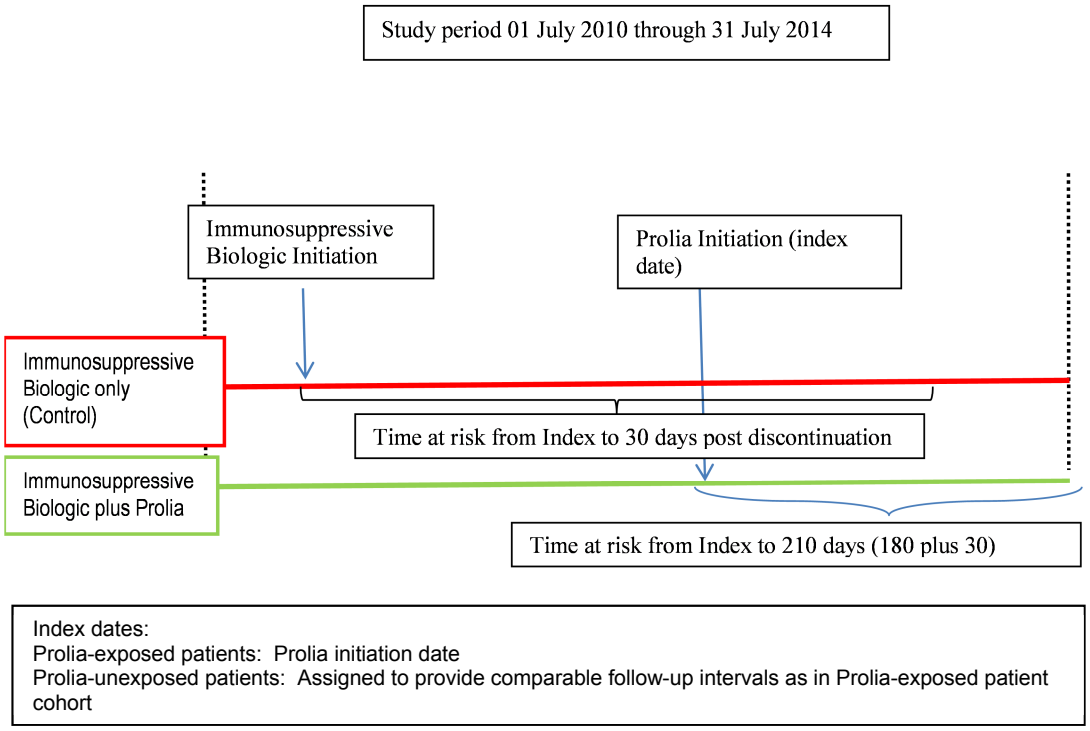
Objective 4: the frequency of opportunistic infection amont patients treated with a single immunosuppressive biologic (without Prolia) in an RA cohort

9.1 Study Design

We will use a retrospective cohort design to identify infection in biologic-exposed patients with rheumatoid arthritis and describe the frequency of infection by Prolia-exposure status. The primary endpoint is serious infection which is defined as an infection leading to hospitalization or an emergency room visit with intravenous antibiotics. The secondary endpoint is opportunistic infection, including infection with the following pathogens, (e.g.: *Mycobacterium tuberculosis, Mycobacterium avium,*

cytomegalovirus, varicella zoster, herpes simplex, *Cryptosporidium*, *Toxoplasma gondii*, *Crypotoccus neoformans*, *Pneumocystis carinii*, *Histoplasma capsulatum*, or other invasive fungi).

Figure 1. Study Schema



9.2 Setting

9.2.1 Study Population

The study population will be derived from a source population of adult patients with rheumatoid arthritis and osteoporosis who were receiving medical care at the Hamilton Rheumatology medical practice in Ontario, Canada, between 01 July 2010 and 31 July 2014.

9.2.2 Eligibility Criteria

9.2.2.1 Inclusion Criteria

We will include male and female patients in this study if they meet the following criteria:

- Men and women ≥ 18 years old with a diagnosis of rheumatoid arthritis.
- Registration in the Hamilton Rheumatology medical practice at least 3 months before and 3 months after index date (i.e., For Prolia-exposed patients the index date is the Prolia initiation date. For Prolia-unexposed patients, the index date will be assigned to each patient in order to provide comparable follow-up intervals as in Prolia-exposed patient cohort.)

- Received at least one injection, infusion or filled a prescription for an immunosuppressive biologic therapy for RA during the study period with Pharmaca Health (source population)
    - The Prolia cohort will be drawn from the source population with the added eligibility criteria of exposure to Prolia.

9.2.2.2 Exclusion Criteria

We will exclude subjects with:

- Evidence of HIV or AIDS
- Prevalent cancers that are being treated; history of cancer is not a reason for exclusion
- Patients on immunosuppressive therapies for conditions other than RA (e.g., organ transplant)
- Evidence of nursing home stay or residence

9.2.3 Definition of Time Periods

9.2.3.1 Study Period

The study period will be 01 July 2010 through 31 July 2014**.**

9.2.3.2 Baseline Visit

The baseline visit is the initial medical encounter during the study period 01 July 2010 through 31 July 2014.

9.2.3.3 Study Follow-up Period

Follow-up will begin at the first dose during the study period of an immunosuppressive biologic and continue until the end of study (31 July 2014) or disenrollment from the Hamilton Rheumatology medical practice, whichever comes first.

9.2.3.4 Time at Risk

The time at risk will be person-time in days, beginning at the day of the first immunosuppressive biologic exposure during the study period. The primary analysis will use a 30-day window of risk (i.e. 30 days following treatment discontinuation) while sensitivity analyses will use the active measure (i.e. end follow-up at treatment discontinuation), and the 3- month measure (i.e. 90 days following treatment discontinuation).

Time at risk will be calculated different ways:

- Active treatment measure: This measure counts the duration of time on an immunosuppressive biologic from the date of administration for the dosing interval specific to that immunosuppressive biologic. For example, Etanercept is a weekly dose so active treatment will be 7 days for each injection. Golimumab is dosed monthly so active treatment will be defined as 30 days for each injection.

- 30-day measure: This will be measured as the duration of time on that immunosuppressive biologic (active treatment) plus a 30-day risk window after each dosing period. It is the active treatment measure up through 30 days post last prescription day. The 30-day risk window will allow for of the prolonged immunosuppressive effects of the biologics and allow for variation in adherence [16].

- 3- month measure: This will be measured as the duration of time on that immunosuppressive biologic (active treatment) plus a 3- month risk window after each dosing period. The 3-month risk window allows for a longer period of prolonged immunosuppression than the 30-day measure.

9.2.3.5 Endpoints Assessment

Objectives 1 and 2: The endpoint will be evidence of serious infection defined as either

- hospitalization associated with a primary diagnosis of infection or
- ER visit with use of IV antibiotics associated with a primary diagnosis of infection.

Objectives 3 and 4: The endpoint will be evidence of opportunistic infection including infection with the following pathogens, (e.g.: *Mycobacterium tuberculosis*, *Mycobacterium avium,* cytomegalovirus, varicella zoster, herpes simplex, *Cryptosporidium*, *Toxoplasma gondii*, *Crypotoccus neoformans*, *Pneumocystis carinii*, *Histoplasma capsulatum*, or other invasive fungi).

Since ICD-9 diagnosis codes are not routinely captured in the electronic medical records (EMR), reference to these specific conditions of interest that appear in either the clinical notes or in the hospital discharge summaries will constitute evidence of serious infection.

9.3 Variables

9.3.1 Exposure variables

The exposure variables include immunosuppressive biologic medications for treatment of RA and Prolia for treatment of osteoporosis at high risk of fracture. These are listed in Table 1.

Table 1: Immunosuppressive biologic medications for treatment of RA and osteoporosis

Biologic Anti-TNF therapy for RA	Other Biologic therapy for RA	Biologic therapy for osteoporosis
Adalimumab	Abatacept	Prollia
Certolizumab	Rituximab	
Etanercept	Tocilizumab	
Golimumab	Ustekinumab	
Infliximab	Anakinra	

9.3.2 Covariates

We will evaluate the following covariates (Table 2) at baseline and assessed over the three months prior to each patient's index date. They will be derived from the Hamilton Rheumatology medical practice EMR database and Pharmaca Health records.

Table 2: Covariates

Variable	Operational definition
Patient age	Age groups will be based on the distribution of the data
Patient sex	Indicator for female sex
Smoking status	Past, current, never
BMI	Body mass index
History of hospitalization in 12 months pre-index	Yes/no
Duration of RA	Time since diagnosis, in months
RA disease severity	Joint count closest to index date. Pre-index data is preferred, but post-index data will be allowed if needed. Data on Clinical Disease Activity Index will also be collected if available.
Prior serious infection in 12 months pre-index	Hospitalization or emergency room visit with intravenous antibiotics and infection diagnosis
Non-biologic osteoporosis medication at baseline	Yes/no
Diabetes	Yes/No
Liver disease	Yes/No

Chronic renal failure	Yes/No
Chronic obstructive pulmonary disease	Yes/No
Cardiovascular disease	Yes/No, includes angina,arrhythmias,coronary artery disease, hypertension, myocardial infarction
CRP	C-Reactive Protein, a non-specific measure of inflammation
ESR	Erythrocyte sedimentation rate, a non-specific measure of inflammation
eGFR	Estimated glomerular filtration rate, a measure of renal function, calculated by the Cockcroft Gault method
History of use of biologic used at index	Use (duration in weeks) of the biologic used on the index date (history) Weeks of use at medication possession ratio of 80% or greater
Systemic GC use	Yes/No indicator for oral and/or inhaled steroids
GC duration in 3 months prior to index	Average daily dose as a continuous measure
Methotrexate use in 2 months prior to and including index	Yes/No indicator for any use of oral and/or subcutaneous methotrexate
Methotrexate dose at index	Actual dose will be recorded. Expected range of values is 7.5 to 25 mg per week
Hydroxychloroquine use in 2 months prior to and including index	Yes/No
Leflunomide use in 2 months prior to and including index	Yes/No
Minocycline use in 2 months prior to and including index	Yes/No
Sulfasalazine use in 2 months prior to and including index	Yes/No
Cyclosporine use in 2 months prior to and including index	Yes/No
Tofacitinib (Xeljanz) use in 2 months prior to and including index	Yes/No
Azathioprine use in 2 months prior to and including index	Yes/No
Gold sodium thiomalate, Auranofin use in 2 months prior to and including index	Yes/No
Cyclophosphamide use in 2 months prior to and including index	Yes/No
Mycophenolate mofetil use in 2 months prior to and including index	Yes/No

Other immunosuppressive medications used in 2 months prior to and including index	Yes/No

9.4 Data Sources

This study will use the Hamilton rheumatology medical practice EMR database which is a fully integrated EMR system that documents all patient care contacts. The EMR has been used since 2010 and includes the medical records for around 3000 patients on immunosuppressive biologic therapy approximately 130 of whom use denosumab. Data are entered in to the EMR as part of routine patient care and include diagnoses, procedures, laboratory and test results, medication orders as well as narrative descriptions of patient care. At each visit, patients are queried for signs of infection and hospitalizations that may have occurred since the last visit. Hospitalization and pharmacy data are sent directly to the Hamilton practice and entered into the medical record. Hospitalization data are shared through two routine procedures. First, the hospital notifies the practice when a patient is admitted to the hospital so the Hamilton physican can provide care for the patient. Second, a discharge summary of the patient's hospitalization experience is forwarded to the Hamilton practice. These two procedures will capture the outcome of hospitalization for serious infection. It is unlikely but possible that a patient could be hospitalized outside the Hamilton region and the physician may not be notified by the distant hospital. To address this possibility, patients are routinely asked if they have been hospitalized at each Hamilton clinic visit and by the pharmacy at the time of medication fill. Medication exposure is confirmed at Pharmaca Health Inc. which is the pharmacy that provides the patient with both oral and injectable biologics. Pharmaca Health Inc. provides documentation (i.e., medication fill note) for biologic infusions and Prolia injections including date of administration, dose, quantity, and a summary of any patient reaction(s) to the injection/infusion. At the time of receipt of all biologics, the pharmacy further queries the patient on signs of infection and these data are transmitted by electronic fax to the Hamilton clinic on the medication fill note. While both the exposure and outcome are systematically captured in standardized reporting procedures from the hospital and pharmacy, this is further confirmed through routine querying the patient at each office visit. Any discordancies between patient report and hospital or pharmacy notifications are investigated.

9.5 Study Size

Preliminary analysis of the dataset shows that between July 2010 and July 2014 there will be approximately 100 patients exposed concomitantly to a immunosuppressive biologic and Prolia. The intention of this study is to describe the frequency of infections in these patients. To provide context to the findings in the Prolia-exposed patients, we will describe the infection experience in approximately 1,000 Prolia-unexposed patients This is a pilot estimation study and is not designed to test significant differences in infection incidence proportions or rates. Table 3 provides precision estimates of the maximum 95% confidence interval around various assumed proportions of patients with infections. A sample size of 100 individuals (our planned Prolia-exposed cohort) produces a two-sided 95% confidence interval with a half-width equal to 0.046 when the incident infection proportion is 0.060. We believe we will have adequate precision to identify serious infections at an infection incidence proportion of 0.06 (comparable to incidence in other reports of RA patients exposed to anti-TNF) [16,18].

Table 3. Precision of 95% confidence interval of hypothetical proportions[19,20]

Numeric Results for Two-Sided Confidence Intervals for One Proportion
Confidence Interval Formula: Simple Asymptotic

Sample						
Confidence Level	**Size (N)**	**Actual Width**	**Proportion (P)**	**Lower Limit**	**Upper Limit**	**Width if P = 0.5**
0.950	100	0.047	0.020	0.000	0.047	0.196
0.950	100	0.063	0.030	0.000	0.063	0.196
0.950	100	0.077	0.040	0.002	0.078	0.196
0.950	100	0.085	0.050	0.007	0.093	0.196
0.950	100	0.093	0.060	0.013	0.107	0.196
0.950	100	0.100	0.070	0.020	0.120	0.196
0.950	200	0.039	0.020	0.001	0.039	0.139
0.950	200	0.047	0.030	0.006	0.054	0.139
0.950	200	0.054	0.040	0.013	0.067	0.139
0.950	200	0.060	0.050	0.020	0.080	0.139
0.950	200	0.066	0.060	0.027	0.093	0.139
0.950	200	0.071	0.070	0.035	0.105	0.139

Summary Statements
A sample size of 100 individuals produces a two-sided 95% confidence interval with a width equal to 0.0963 when the incident infection proportion is 0.060.

Definitions
Confidence level is the proportion of confidence intervals (constructed with this same confidence level, sample size, etc.) that would contain the population proportion.
N is the size of the sample drawn from the population.
Actual Width is the value of the width that is obtained from the procedure.
Incident Proportion (P) is the assumed sample incident proportion.
Lower Limit is the lower limit of the confidence interval.
Upper Limit is the upper limit of the confidence interval.

9.6 Data Management

A research coordinator at McMaster University will be responsible for all data preparation, collection, and entry with the guidance of the research statistician. All patient information will be collected using electronic medical records from the medical practice of the pricinpal investigator (JDA). The electronic medical records will be used to identify all research data prior to data collection. A data dictionary including research and administrative data will be created and include the following elements: variable name; variable definition; data type (continuous, categories); proposed possible values and decimals; units of measure; check or limits. An electronic case reporting form will be used for data collection. The form and database will be developed using Microsoft Access (version 2010). All data entry will have validation rules to prevent improper data entry. The number of subjects with missing information for each covariate in Table 2 will be described. If data on either exposure of outcome are missing, then that subject will be excluded from the study population. Missing data will not be imputed. The database will be encrypted and password protected.

All statistical analyses will be performed by the lead research statistician. The analyses will be conducted using the SAS/STAT (version 9.2; SAS Institute, Cary, NC, USA) software package running on Windows 7. Statistical analysis will be completed after all data have been entered, imported into and cleaned in SAS.

9.7 Data Analysis

Descriptive statistics will be used to describe patient characteristics in the Prolia-exposed and Prolia-unexposed patients. Mean and standard deviation, median and range will be reported for continuous variables, and frequency distributions will be reported for categorical variables. Cumulative incidence of infection (incidence proportion) will be calculated for both the Prolia and non-Prolia exposed cohorts. The incidence proportion will be assessed separately over a 6-month and a 12-month follow-up period. The incidence rate is calculated as the total number of patients with an infection divided by the summation of patient-days of applicable time at risk from all patients, where the time at risk is censored at the first occurrence of the event for patients experiencing an infection and not censored for those patients who do not experience an infection. Sensitivity analyses will be conducted using different measures of exposure time at risk, such as active and 3-month measures, described in Section 9.2.3.3.

Subgroup analyses will be conducted to determine the influence of GC use, methotrexate use, prior serious infection status and RA disease activity on infection incidence proportions.

9.8 Quality Control

The source data for this study come from the pharmacy and medical records of patients treated at the Hamilton Rheumatology clinic. These source documents are created in the course of routine patient care. The use of an EMR system and transcribed reports from the hospital and pharmacy eliminate legibility issues. These source documents will be used to create an analytic file for this study. Data collectors who will abstract from these source documents will be trained and a 5% sample of records will be re-abstracted for quality control and to determine whether there is a need for further training.

The abstracted data will be entered into an electronic study database and stored on secure servers operated and maintained by the Hamilton Rheumatology clinic. The server is located in a secure facility and access to the data is password-protected with access restricted on a 'need to know' basis. Back-ups are done daily, and a full backup is done weekly for each server. All data for this study are housed at the Hamilton Rheumatology clinic and will not be accessed remotely by Amgen.

9.9 Limitations of the Research Methods

9.9.1 Internal Validity of Study Design

Possible threats to internal validity include misclassification of the exposure (medication use) and the outcome (infection). While we have confirmatory processes for both exposure and outcome assessment, there is always a minimal possibility of misclassification. The impact of the 3- month requirement for study inclusion may result in a survival bias.

9.9.2 Measurement Error(s)/Misclassification(s)

GC use is an established risk factor for infection and oral GCs are often used by patients with RA. Although we will be controlling for the influence of GCs through stratification, there is the possibility of misclassification as we do not have firm evidence that the patient actually took the medications and in the dose and manner prescribed. We will acknowledge this as a limitation.

9.9.3 Information Bias

Considering the study design and study objectives, information bias is not a likely source of bias in this study. Outcome and exposure assessment data collection does not differ by cohort status.

9.9.4 Selection Bias

Although the study will not include all immunosuppressive biologic users, we will compare demographic and clinical characteristics of excluded patients to those of the selected study population to examine potential biases.

Patient selection for Prolia treatment also creates the possibility for bias in this retrospective study, as it is possible that the addition of Prolia to an immunosuppressive biologic therapy was preferentially chosen for patients who seem more reliable or have other specific intangible or unmeasured characteristics including socioeconomic status. In Canada, Prolia and immunosuppressive biologics for RA are covered by public insurance for individuals over age 65 years and private insurance covers these agents as well. Since the majority of study patients will be over age 65, we expect minimal impact from any potential prescribing bias.

In addition, patients with a history of infection or considered to be at high risk for serious infection may be less likely to receive Prolia. This type of differential prescribing could bias against demonstrating a greater incidence of serious infections in the Prolia group. In order to mitigate this potential bias, data will be collected on potential confounders (i.e., patient characteristics that might shape infection risk and incidence) and results stratified on those characteristics.

9.9.5 Confounding

Differences in clinical and demographic characteristics between patient groups will be evaluated and described in publications. Analyses will be stratified by GC use, age group, time on biologic therapy, methotrexate use, prior serious infection status and RA disease activity to further minimize the potential for confounding. It is possible that GC use will be differential in the two groups, but it is unclear in which direction. Individuals taking GCs for treatment of their RA are more likely to develop glucocorticoid-induced osteoporosis and therefore might be more likely to be prescribed Prolia. On the other hand, GCs are well-known to increase the risk of infections, so if the physician is concerned that Prolia, when added to immunosuppressive biologics, would increase infection risk; then the physician might be less likely to prescribe Prolia. Regardless, we

will quantify GC use in both groups and stratify or adjust for this exposure. The presence of osteoporosis may also potentially confound the results since patients with osteoporosis may be more frail and potentially more predisposed to infection. As noted in Section 9.9.4, stratified analyses will be conducted to assess potential confounders.

9.9.6 External Validity of Study Design

This study uses data from a Canadian rhematology practice. Therefore, these results may not be generalizable to patients with RA and osteoporosis in other practice settings, especially if the demographic and clinical characteristics of patients, RA treatment patterns, or the background infection rates differ in those other settings.

9.10 Other Aspects

The data source used for this study provides richly detailed, reliable clinical data on exposures, covariates and outcomes of interest. However, we also acknowledge that the sample sizes that can be obtained from this data source may limit the precision of the estimates derived from this study. As noted in section 9.5, feasibility work suggests 100 patients will meet the entry critiera for the immunosuppressive biologics plus Prolia cohort (Prolia-exposed). The incidence of serious infections in patients with co-administration of Proila and an immunosuppressive biologic is unknown so our precision calculations assume an incidence similar to that in Prolia-unexposed group (6%). If the true infection rate in the Prolia-exposed cohort is considerably lower than this, the confidence interval could be quite wide.

Results from this single-site pilot study can also be used to inform the design of larger, multi-site studies of infection in RA patients. In particular, this pilot will provide new data on the real-world prevalence of serious infections in patients using immunosuppressive biologics for RA stratified by Prolia exposure status (yes/no). In addition, results for this pilot will stratified by patient characteristics that are potential confounders for the risk of infection, and this information can be used to develop matching or stratification strategies to address confounding in future studies.

10. Protection of Human Subjects

This study will comply with all applicable laws, regulations, and guidance regarding patient protection including patient privacy. Informed consent will not be required, however, the protocol will be approved by the Institutional Review Board at McMaster University prior to study implementation.

11. Management and Reporting of Adverse Events/Adverse Reactions

General information regarding reporting of AEs/ADRs and/or SAEs/SADRs:

- Report only AEs/ADRs and/or SAEs/SADRs, other safety findings, or product complaints involving Amgen products
- Do not report AEs/ADRs and/or SAEs/SADRs, other safety findings, or product complaints that occurred prior to a patient taking an Amgen product

11.1 Safety Event Definitions

11.1.1 Definition of Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject/patient administered a pharmaceutical product(s) and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a product(s), whether or not considered related to the product(s). The definition of an AE includes:

- Worsening of a pre-existing condition
- Events occurring from a medication error or overdose of a product(s), whether accidental or intentional
- Events occurring from abuse of a product(s)
- Events associated with the discontinuation of the use of a product(s), (eg, appearance of new symptoms)
- Any lack or loss of intended effect of the product(s)

An adverse device effect is any adverse event related to the use of a medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

11.1.2 Adverse Drug Reactions (ADRs)

AEs that are explicitly stated in the medical record to be related to an Amgen product are classified as adverse drug reactions (ADRs).

11.2 Definition of Serious Adverse Events

A serious adverse event (SAE) is any AE as defined above that also:

- is fatal
- is life threatening (places the subject/patient at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization

- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an "other significant medical hazard" that does not meet any of the above criteria

A hospitalization meeting the regulatory definition for "serious" is any in-patient hospital admission that includes a minimum of an overnight stay in a healthcare facility.

"Other significant medical hazards" refer to important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject/patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

11.2.1 Serious Adverse Drug Reactions (SADRs)

SAEs that are explicitly stated in the medical record to be related to an Amgen product are classified as serious adverse drug reactions (SADRs).

11.2.2 Definition of Other Safety Findings

Other Safety Findings include:

- Medication errors, overdose, misuse, or abuse, whether accidental or intentional, involving an Amgen product, regardless of whether associated with an AE and/or ADR and/or SAE and/or SADR
- Pregnancy and lactation exposure regardless of whether associated with an AE and/or ADR and/or SAE and/or SADR
- Transmission of infectious agents regardless of whether associated with an AE and/or ADR and/or SAE and/or SADR
- Reports of uses outside the terms for authorized use of the product including off label use when associated with an AE and/or ADR and/or SAE and/or SADR

Note: Reports of unauthorized use that are NOT associated with an AE and/or ADR and/or SAE and/or SADR must be reported to the study database, but should not be reported to Amgen Safety.

11.2.3 Definition of Product Complaints

Product Complaints include any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product or device after it is released for distribution. This includes all

components distributed with the product(s) such as packaging, product containers, delivery system, labeling, inserts, etc.

Product Complaints may include but are not limited to issues related to:

- Appearance (eg, broken, cracks, color, particles, odor)
- Labeling (eg, missing, torn, smudged)
- Durability (eg, stability issues)
- Open packaging
- Device damage (eg, pre-filled syringe with bent needle)
- Inability of customer to understand product labeling
- Inability of customer to deliver the product successfully, including partial or incomplete delivery (eg, defective delivery system [syringe])

11.2.4 Reportable Events and Reporting Timeframes

The vendor/HCP is responsible for ensuring that all SADRs, product complaints and other safety findings for any Amgen product(s) are submitted to Amgen via the supplied Amgen Safety Reporting Forms. See Annex 3 for a sample Safety Reporting Form and Annex 4 for sample Pregnancy and Lactation Notification Woksheets.

All clearly documented SADRs, product complaints and other safety findings, including pregnancy and/or lactation, are to be reported to Amgen within 1 business day of the vendor's/HCP's date of awareness.

ADRs that do not meet serious criteria are to be collected in the study database and must be included in the final study report.

The vendor is to provide event listings to Amgen for purposes of reconciliation with the safety database per the contractual agreement.

Amgen will report adverse events as required to regulatory authorities in accordance with Pharmacovigilance guidelines and in compliance with local regulations.

12. Administrative and Legal Obligations

12.1 Study Amendments and Study Termination

Amendments to the study may be made upon agreement between Amgen and the vendor/HCP. When applicable, the IRB must be informed of all amendments and give approval. The vendor/HCP must send a copy of the approval letter from the IRB to Amgen.

Both Amgen and the vendor/HCP reserve the right to terminate participation in the study according to the study contract. The vendor/HCP should notify the IRB in writing of the study's completion or early termination and send a copy of the notification to Amgen.

12.2 Study Documentation and Archive

Retention of study-related documents is governed by Amgen Policy CCD024r03, "RECORDS AND INFORMATION MANAGEMENT POLICY".

13. Plans for Disseminating and Communicating Study Results

The protocol and final report of results will be posted to the European Medicines Agency and other appropriate entities according to the guidelines for post authorization safety studies.

Results generated from this analysis will be submitted for publication in relevant rheumatology, epidemiology, or general medicine journals. Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors), which states:

- Authorship credit will be based on (1) substantial contributions to: the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; (2) drafting the work or revising it critically for important intellectual content; (3) final approval of the version to be published; (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors will meet conditions 1, 2, 3, and 4.

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15. Annexes

Annex 1. List of Stand-alone Documents

Not Applicable.

Annex 2. ENCePP Checklist for Study Protocols

Study title:
Burden of serious infection in patients with rheumatoid arthritis treated with biologics and Prolia observed in a clinical setting

Study reference number:
N/A

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☐	☐	☒	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	
4.2 Is the planned study population defined in terms of:	☒	☐	☐	
4.2.1 Study time period?	☒	☐	☐	
4.2.2 Age and sex?	☒	☐	☐	
4.2.3 Country of origin?	☒	☐	☐	
4.2.4 Disease/indication?	☒	☐	☐	
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6 Seasonality?				
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	
5.4 Is exposure classified based on biological				

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

With regard to 5.2, the completeness of exposure data capture is described in Section 9.4, page 16.

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	

Comments:

With regard to 6.2, the completeness of exposure data capture is described in Section 9.4, page 16.

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	
	☒	☐	☐	

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1.3 Covariates?				
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☒	☐	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☒	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☒	☐	

Comments:

Section 9: Study size and precision	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical precision calculated?	☒	☐	☐	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	
10.3 Are descriptive analyses included?	☒	☐	☐	
10.4 Are stratified analyses included?	☒	☐	☐	
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	
11.3 Are methods of quality assurance described?	☒	☐	☐	
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	
12.3 Does the protocol address other limitations?	☒	☐	☐	

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	

Comments:

With regard to 13.2, any comments received from the IRB will be addressed.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	

Comments:

Name of the main author of the protocol: _____

Date: / /

Signature: _____

Annex 3. Sample Safety Reporting Form

AMGEN Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

US: +000 000 0000

1. Case Administrative Information

Protocol/Study Number: 20140127

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ Site # _____

Phone (____) _____ Fax (____) _____ Email _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Gender: ☐ Female ☐ Male Subject DOB: mm ▼ / dd ▼ / yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm▼/dd▼/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm▼/dd▼/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's LMP mm▼/dd▼/yyyy____ ☐ Unknown

Estimated date of delivery mm▼/dd▼/yyyy____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm▼/dd▼/yyyy____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm▼/dd▼/yyyy____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details: _____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Amgen maintains a Pregnancy Surveillance Program that collects data about pregnancy of women who have been exposed to an Amgen product directly or via male sexual partner. Information from this program and from other sources of information, will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during pregnancy.

Effective Date: March 27, 2011 Page 1 of 1

Annex 4. Pregnancy and Lactation Notification Worksheets

AMGEN Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

US: +888 814 8653

1. Case Administrative Information

Protocol/Study Number: 20140127

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ Site # _____

Phone (____) _____ Fax (____) _____ Email _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Gender: ☐ Female ☐ Male Subject DOB: mm___ / dd___ / yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm___/dd___/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm___/dd___/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's LMP mm___ / dd___ / yyyy____ ☐ Unknown

Estimated date of delivery mm___ / dd___ / yyyy____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm___ / dd___ / yyyy____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm___ / dd___ / yyyy____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details: _____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Amgen maintains a Pregnancy Surveillance Program that collects data about pregnancy of women who have been exposed to an Amgen product directly or via male sexual partner. Information from this program and from other sources of information, will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during pregnancy.

Effective Date: March 27, 2011 Page 1 of 1

Print Form

AMGEN™ Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# US: +888 814 8853

1. Case Administrative Information

Protocol/Study Number: 20140127

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ Site # _____

Phone (____)_____ Fax (____)_____ Email _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Date of Birth: mm____ / dd____ / yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details: _____

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Amgen maintains a Lactation Surveillance Program that collects data about women who have been exposed to an Amgen product while breastfeeding. Information from this program and from other sources of information will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during lactation.

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