Summary Table of Study Protocol

Title	A Prospective Observational Study to Evaluate Long-term Safety of AMGEVITA™ in Patients With Rheumatoid Arthritis
Protocol version identifier	20160264 Version **2.0**
Date of last version of the protocol	**10 January 2019**
EU Post Authorization Study (PAS) Register No	Registration occurs after Amgen internal approval of the protocol; must be prior to commencement of first data capture.
Active Substance	AMGEVITA (ABP 501; Amgen adalimumab biosimilar)
Medicinal Product	AMGEVITA
Product Reference	H0004212
Procedure Number	EMEA/H/C/004212
Joint PASS	No
Research Question and Objectives	What is the long-term safety of AMGEVITA in patients with moderate to severe rheumatoid arthritis (RA) in a real-world setting? The primary objective is to estimate the incidence rates of the safety concerns (identified risks of adalimumab) serious infections in patients with RA exposed to AMGEVITA. The secondary objectives are to estimate the incidence rates of **serious hypersensitivity reactions and** other serious adverse events (safety concerns) in patients with RA exposed to AMGEVITA, and to estimate the incidence rates for the same outcomes from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA) anti-tumor necrosis factor (TNF) comparison cohort **and a non-biologic disease-modifying antirheumatic drug (nbDMARD) comparison cohort**, as defined in Section 9.7.2.
Country of Study	United Kingdom
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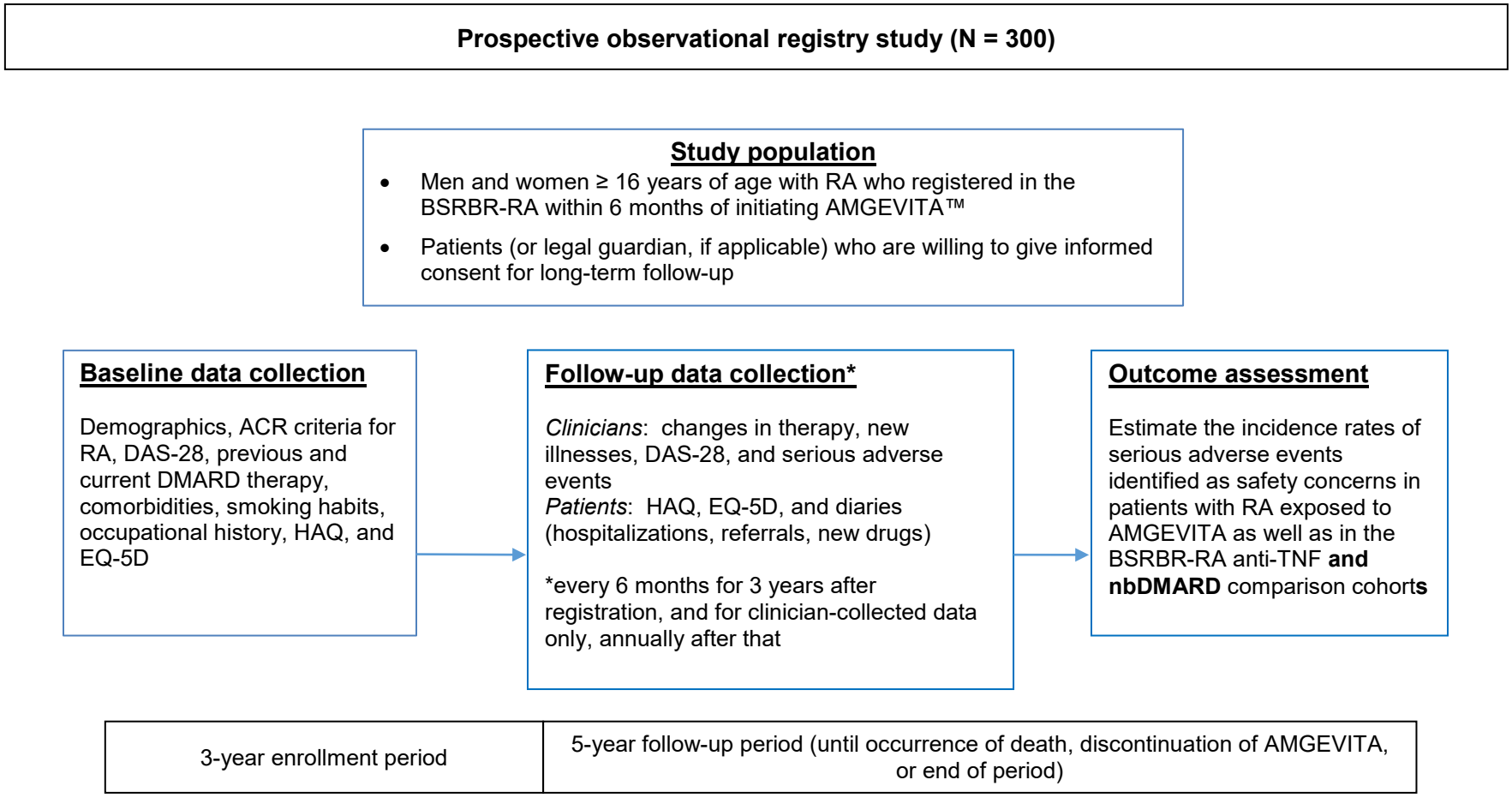
Study Design Schema



ACR = American College of Rheumatology; BSRBR-RA = British Society for Rheumatology Biologics Register for Rheumatoid Arthritis; DAS-28 = Disease Activity Score; DMARD = disease-modifying antirheumatic drug; EQ-5D = Euro quality-of-life 5-dimension scale; HAQ = Health Assessment Questionnaire; **nbDMARD = non-biologic disease-modifying antirheumatic drug**; RA = rheumatoid arthritis; TNF = tumor necrosis factor

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2. List of Abbreviations

Abbreviation or Term	Definition/Explanation
ACR	American College of Rheumatology
ACR20	20% improvement in ACR Core Set Measurement
BSRBR-RA	British Society for Rheumatology Biologics Register for Rheumatoid Arthritis
CCP	cyclic citrullinated peptide
CRF	case report form
CRP	C-reactive protein
DAS-28	Disease Activity Score
DMARD	disease-modifying antirheumatic drug
DMEC	Data Monitoring and Ethics Committee
EQ-5D	Euro quality-of-life 5-dimension scale
ESR	erythrocyte sedimentation rate
HAQ	Health Assessment Questionnaire
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MMP	matrix metalloproteinase
nbDMARD	**non-biologic disease-modifying antirheumatic drug**
NHS	National Health Service
NSAID	nonsteroidal anti-inflammatory drug
OLE	open-label extension
ORSR	observational research study report
PASI	Psoriasis Area and Severity Index
PASI 50	50% or better improvement in PASI response
PASS	post-authorization safety study
PK	pharmacokinetic
PSUR	periodic safety update report
PY	person-years
RA	rheumatoid arthritis
SAP	statistical analysis plan
SmPC	Summary of Product Characteristics
TB	**tuberculosis**
TIMP	tissue inhibitor of metalloproteinase
TNF	tumor necrosis factor
UK	United Kingdom

3. Responsible Parties

Amgen Inc., is the study sponsor and responsible for authoring the protocol and final observational research study report (ORSR). This study will be conducted in the United Kingdom (UK) using data from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA), who is responsible for writing the statistical analysis plan (SAP), conducting all data analyses, and providing interim analysis reports and the final report to Amgen. The main responsible parties are listed below.

No clinical sites will be recruited.

Name	Title and Affiliation
PPD PhD	Director, Center for Observational Research, Amgen
PPD, MD, **MPH**	Executive Medical Director, Biosimilars Global Development, Amgen
PPD MD	Medical Director, Global Safety, Amgen
PPD PhD	Manager of Pharmacovigilance Studies, BSRBR-RA

4. Abstract

- A Prospective Observational Study to Evaluate Long-term Safety of AMGEVITA™ in Patients With Rheumatoid Arthritis
- Study Background and Rationale

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology in which patients exhibit systemic features such as fatigue, swollen joints, low grade fever, weight loss, anemia, and increased systemic levels of acute phase reactants such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) (Aletaha et al, 2010). Tumor necrosis factor α (TNFα) has multiple roles in the development of RA and is one of the key cytokines that drives the inflammatory process in this disease (Smolen et al, 2018; Brennan and McInnes, 2008). TNFα promotes joint damage by increasing the release of matrix metalloproteinases (MMPs), particularly MMP-3 (Carrasco and Barton, 2010), which is involved in the breakdown of the connective tissue matrix, and by decreasing production of tissue inhibitor of MMP (TIMP) (Shingu et al, 1993). TNFα also plays a role in the bone damage seen in RA by promoting the development of osteoclasts.

AMGEVITA is a biosimilar of Humira® (adalimumab), an anti-TNFα monoclonal antibody. AMGEVITA is approved for the treatment of moderately to severely active RA, in addition to other approved indications (AMGEVITA Summary of Product Characteristics

[SmPC]). The active ingredient of AMGEVITA is an anti-TNFα monoclonal antibody which has the same amino acid sequence as adalimumab.

In previous studies, AMGEVITA has been shown to have similar pharmacokinetic (PK), safety, and efficacy profiles as adalimumab and overall, treatment with AMGEVITA was safe and well tolerated (Cohen et al, 2017a; Cohen et al, 2017b; Cohen et al, 2016; Kaur et al, 2017). The immunogenicity rates for AMGEVITA and adalimumab were also similar.

The current study is designed to fulfill a post-authorization commitment to evaluate long-term safety of AMGEVITA and utilizes an existing registry, the BSRBR-RA. This method supports the collection of long-term safety data for new, similar biological product treatments in the postmarketing setting and is an efficient approach for conducting post-authorization safety studies (PASS).

- Research Question and Objectives
  - Research Question
    What is the long-term safety of AMGEVITA in patients with moderate to severe RA in a real-world setting?
  - Primary Objective
    Estimate the incidence rates of the following safety concerns (identified risks of adalimumab) in patients with RA exposed to AMGEVITA: serious infections (ie, infectious events which require intravenous [IV] antibiotics, hospitalization, or meet other criteria for a serious adverse event).
  - Secondary Objectives
    Estimate the incidence rates of other serious adverse events (safety concerns) in patients with RA exposed to AMGEVITA, including: **serious hypersensitivity reactions,** opportunistic infections (a subset of serious infections); **tuberculosis (TB); malignancy (overall),** nonmelanoma skin cancer; melanoma; lymphoma; congestive heart failure; myocardial infarction; cerebrovascular accident; interstitial lung disease; cutaneous vasculitis; hematologic disorders; elevated alanine aminotransferase levels, liver failure and other liver events; demyelination disorders; and pregnancy exposure.

    Estimate the incidence rates of the above listed safety concerns from **both** the BSRBR-RA anti-TNF **and the non-biologic disease-modifying antirheumatic drug (nbDMARD)** comparison cohort**s**, which **are** defined in Section 9.7.2.
  - Hypothesis/Estimation
    This is an estimation study providing a descriptive analysis on incidence rates. No formal hypothesis testing will be performed.
- Study Design/Type

  This is a long-term, noninterventional, prospective, observational, registry study.

- Study Population or Data Resource

  Approximately 300 patients with RA initiating AMGEVITA will be enrolled. This study will be conducted over a total of 8 years using data from the BSRBR-RA in the UK.

- Summary of Patient Eligibility Criteria
  - men and women ≥ 16 years of age with RA who registered in the BSRBR-RA within 6 months of initiating AMGEVITA
  - patients (or legal guardian, if applicable) who are willing to give informed consent for long-term follow-up

- Follow-up

  Follow-up of patients will start from the date patients are registered in the study and end with occurrence of death, discontinuation of AMGEVITA, or the end of 5-year follow-up period. Patients will be considered at risk of serious events, malignancy, and death according to the risk windows defined in Section 9.3.1.

- Variables
  - Outcome Variables
    The primary outcome measures are incidence of serious infections (ie, infectious events which require IV antibiotics, hospitalization, or meet other criteria for a serious adverse event). The secondary outcome measure is incidence of **serious hypersensitivity reactions and** other serious adverse events.
  - Exposure Variables
    All patients enrolled in the study will be exposed to AMGEVITA. A patient's exposure status will be assessed from the data provided by the BSRBR-RA. Analyses will be stratified based on biologic-experienced and biologic-naïve status. Patients **with prior use of** adalimumab **(reference product or biosimilar)** will be a subset of the biologic-experienced stratum and, where possible, will be identified as adalimumab patients.
  - Other Covariates
    Both the primary and secondary outcome measures will be stratified by prior biologic status (ie, biologic-naïve or biologic-experienced, as defined in Section 9.3.3.1). Other covariates include demographic and clinical characteristics that are part of BSRBR-RA case report form (CRF).

- Study Sample Size

  This study will enroll approximately 300 patients. The estimated precision of this study was based on different estimates of average enrollment rates and an expected serious infection incidence rate of 4.2 per 100 person-years (PY).

- Data Analysis

  Incidence of primary and secondary outcomes (ie, serious infections, hypersensitivity reactions, and other serious adverse events [safety concerns]) will be estimated as cumulative incidence rates (95% CI). For the purposes of context, current incidence rates will also be calculated from **both of** the **following** BSRBR-RA **comparison cohorts:**

  - anti-TNF comparison cohort, which is a cohort of patients receiving an established anti-TNF drug (adalimumab, etanercept, or infliximab) who were recruited within 6 months of first exposure.
  - **nbDMARD comparison cohort, which is a cohort of patients with similar disease activity receiving conventional systemic DMARDs who have never been exposed to biologic therapy. The cohort was recruited from selected sites across the UK between 2002 and 2008 and continues to be followed up. In total, 3774 patients were recruited to this cohort.**

This is an observational study and the approach to the statistical analysis will be generally descriptive. No formal hypotheses will be tested. For categorical variables, the frequency and percentage, with 95% CI where appropriate, will be provided. Summary statistics for continuous variables will include the number of patients, mean, median, SD or standard error, minimum, and maximum. Interim analyses will be provided every 6 months by the BSRBR-RA. The primary analysis will be focused on incidence rates of serious adverse events as described in Section 8.1 and will occur when the last patient has completed 5 years of follow-up. We do not expect any differences between the AMGEVITA cohort and the BSRBR-RA anti-TNF comparison cohort because AMGEVITA has been shown to be similar to the reference product, adalimumab. **A historical RA cohort of patients treated with nbDMARDs recruited to the BSRBR-RA from a select number of sites within the UK (recruited between 2002 and 2008) is being included as a second comparator cohort. As this cohort is not contemporaneous to either of the other cohorts and may have differences in underlying disease severity, the anti-TNF cohort will be considered the primary comparison cohort of interest.** If any differences are noted between the cohorts based on evaluation of incidence rates, modifications to the analyses (eg, regression modelling) could be made and would be reflected in a protocol amendment.

5. Amendments and Updates

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
1	**13 June 2019**	**See Summary of Changes**	**To reorder the primary and secondary objectives, as well as to add a new comparison cohort**	**See Summary of Changes**

6. Milestones

Milestone	Planned date
EU PAS registration	2019 2Q
Start of data collection	2019 **3**Q
BSRBR-RA 6-month reports[a]	Every 6 months (January and July)[b]
End of data collection	2027 2Q
BSRBR-RA final report	2027 4Q[c]
Final ORSR (primary analysis)	2028 2Q

BSRBR-RA = British Society for Rheumatology Biologics Register for Rheumatoid Arthritis; EU = European Union; ORSR = observational research study report; PAS = post-authorization study; PSUR = periodic safety update report

[a] Includes the following 3 sections: Manchester template, PSUR line listing of all events, and an adverse drug reaction PSUR-style line listing. These reports will be submitted to the European Medicines Agency on an annual basis.

[b] Beginning from study start date.

[c] Final report will be provided 6 months after the end of data collection.

7. Rationale and Background

7.1 Diseases and Therapeutic Area

Rheumatoid arthritis is a chronic inflammatory disease of unknown etiology in which patients exhibit systemic features such as fatigue, swollen joints, low grade fever, weight loss, anemia, and increased systemic levels of acute phase reactants (eg, ESR and CRP) (Aletaha et al, 2010). Although the disease is systemic in nature, the primary target tissues are the synovial membrane, cartilage, and bone (McInnes and Schett, 2007), which exhibit uncontrolled synovium/pannus proliferation and excess fluid production, and ultimately undergo progressive destructive arthropathy (Aletaha et al, 2010; Choy and Panayi, 2001).

Tumor necrosis factor α has multiple roles in the development of RA and is one of the key cytokines that drives the inflammatory process in this disease (Smolen et al, 2018; Brennan and McInnes, 2008). TNFα promotes joint damage by increasing release of MMPs, particularly MMP-3 (Carrasco and Barton, 2010), which is involved in the breakdown of the connective tissue matrix, and by decreasing production of TIMP

(Shingu et al, 1993). TNFα also has a role in the bone damage seen in RA by promoting development of osteoclasts.

7.2 Product Background

AMGEVITA is a biosimilar of adalimumab (Humira®), an anti-TNFα monoclonal antibody. AMGEVITA is approved for the treatment of moderately to severely active RA, in addition to other approved indications (AMGEVITA SmPC). The active ingredient of AMGEVITA is an anti-TNFα monoclonal antibody which has the same amino acid sequence as adalimumab.

In previous studies, AMGEVITA has been shown to have similar PK, safety, and efficacy profiles as adalimumab. A PK equivalence study (Study 20110217) comparing AMGEVITA with adalimumab was conducted in healthy adult men and women (Kaur et al, 2017). The primary endpoints, maximum observed concentration and area under the concentration-time curve from 0 to infinite time, demonstrated PK equivalence according to protocol-specified criteria. Overall, both treatments were safe and well tolerated. The immunogenicity rates for AMGEVITA and adalimumab were similar.

A randomized, double-blind, active comparator-controlled study (Study 20120262) was conducted in adult subjects with moderate to severe RA who had an inadequate response to methotrexate to compare the efficacy, safety, and immunogenicity of AMGEVITA with adalimumab (Cohen et al, 2017a). A total of 526 patients were randomized (264 to AMGEVITA and 262 to adalimumab). The primary efficacy endpoint was the risk ratio of at least 20% improvement from baseline in American College of Rheumatology (ACR) Core Set Measurement (ACR20) response at week 24. The 90% CI for the risk ratio of ACR20 for AMGEVITA versus adalimumab was contained within the predefined equivalence margin of (0.738, 1.355), thus clinical equivalence of AMGEVITA and adalimumab in terms of efficacy was demonstrated. Additionally, similarity in terms of safety and immunogenicity were demonstrated. The most frequently reported adverse events were nasopharyngitis (36 of 526 subjects, 6.8%), headache (23 of 526 subjects, 4.4%), arthralgia (17 of 526 subjects, 3.2%), cough (15 of 526 subjects, 2.9%), and upper respiratory tract infection (14 of 526 subjects, 2.7%). The adverse events were similar between AMGEVITA and adalimumab. The overall incidence of patients developing binding antidrug antibodies was 38.2% and was similar between groups.

Study 20130258 was a single-arm, open-label extension (OLE) study of the parent Study 20120262 in adult patients with moderate to severe RA (Cohen et al, 2017b;

Cohen et al, 2016). A total of 467 patients were enrolled and 466 patients were treated with investigational product. Results of the long-term safety data and immunogenicity observed in the OLE study were consistent with the known safety profile for adalimumab, and efficacy was also maintained. No new safety signals were identified throughout the study.

In addition to the RA population, AMGEVITA has been studied in patients with psoriasis. A randomized, double-blind, active-controlled study (Study 20120263) was conducted in adult patients with moderate to severe psoriasis not treated with concomitant methotrexate to compare the efficacy, safety, and immunogenicity of AMGEVITA with adalimumab (Papp et al, 2017a; Papp et al, 2017b). A total of 350 patients were randomized and 347 patients were treated with investigational product. The primary efficacy endpoint was Psoriasis Area and Severity Index (PASI) percent improvement from baseline at week 16. The 95% CI for treatment difference for AMGEVITA versus adalimumab fell within the predefined equivalence margin of ± 15; thus, efficacy clinical equivalence of AMGEVITA to adalimumab was demonstrated. At week 16, patients with a 50% or better improvement in PASI response (PASI 50) continued on study up to week 52. Eligible patients were rerandomized in a blinded fashion such that all patients initially randomized to AMGEVITA continued treatment with AMGEVITA, and patients initially randomized to adalimumab either continued treatment with adalimumab or underwent a single transition to AMGEVITA in a 1:1 ratio. Over the entire study, the most frequently reported adverse events were nasopharyngitis (26.5%), headache (11.0%), upper respiratory tract infection (10.7%), arthralgia (6.6%), and psoriasis (6.6%).

Based on the demonstration of the quality, nonclinical, PK, and clinical similarity of AMGEVITA and adalimumab, the clinical efficacy and safety information for adalimumab, as described in the product labeling for adalimumab (Humira SmPC), is considered relevant to predicting the effects of AMGEVITA in humans.

7.3 Rationale

The purpose of this noninterventional, observational registry study is to evaluate the long-term safety of AMGEVITA in patients with moderate to severe RA in a real-world setting.

The post-authorization safety of the reference product, adalimumab, is already being extensively investigated in a range of indications and covering a wide range of potential and identified risks; all known and new identified risks for adalimumab will be applicable

to AMGEVITA. For the current study to be feasible and generate relevant data on the Amgen biosimilar product, it will focus on several important identified risks (safety concerns) of AMGEVITA in patients with RA.

The primary outcome of interest **is** the incidence of serious infections. The incidence of **serious hypersensitivity reactions and** other serious adverse events (safety concerns) will also be examined. The data collected by this registry study will provide information to further characterize the long-term safety of AMGEVITA.

Use of existing registries, such as the BSRBR-RA, supports the collection of long-term safety data for new, similar biological product treatments in the postmarketing setting and is an efficient approach for conducting a PASS.

The BSRBR-RA recruits patients from rheumatology departments in National Health Service (NHS) hospitals who are prescribed biologics and similar biological products in the UK with 5 years follow-up (if patient remains on drug and stays enrolled in the registry). All serious adverse events are captured during this period using standardized methods in addition to linking with the national UK cancer and death registers providing additional follow-up data on these patients for these 2 outcomes.

7.4 Statistical Hypothesis

This is an estimation study providing a descriptive analysis on incidence rates. No formal hypothesis testing will be performed.

8. Research Question and Objectives

What is the long-term safety of AMGEVITA in patients with moderate to severe RA in a real-world setting?

8.1 Primary Objective

The primary objective of this study is to estimate the incidence rates of the following safety concerns (identified risks of adalimumab) in patients with RA exposed to AMGEVITA:

- serious infections (ie, infectious events which require IV antibiotics, hospitalization, or meet other criteria for a serious adverse event)

8.2 Secondary Objectives

The secondary objectives of this study are to:

- estimate the incidence rates of other serious adverse events (safety concerns) in patients with RA exposed to AMGEVITA, including:
  - **serious hypersensitivity reactions**

- opportunistic infections (a subset of serious infections)
- **TB**
- **malignancy (overall)**
- nonmelanoma skin cancer
- melanoma
- lymphoma
- congestive heart failure
- myocardial infarction
- cerebrovascular accident
- interstitial lung disease
- cutaneous vasculitis
- hematologic disorders
- elevated alanine aminotransferase levels, liver failure, and other liver events
- demyelination disorders
- pregnancy exposure

- estimate the incidence rates of the above listed safety concerns from **both** the BSRBR-RA anti-TNF **and nbDMARD** comparison cohort**s**, which **are** defined in Section 9.7.2

9. Research Methods

9.1 Study Design

This study is a long-term, noninterventional, prospective, observational, registry PASS of patients with RA who initiated AMGEVITA; this study is designed to fulfill a post-authorization commitment. The study will use data from the BSRBR-RA to estimate the incidence rates of serious adverse events (safety concerns). No product will be provided by Amgen. The BSRBR-RA will generate reports every 6 months on all registered patients who have initiated AMGEVITA and will distribute these reports to Amgen. These reports will be used to monitor the incidence of several important identified risks (eg, serious infections, serious hypersensitivity reactions, and other serious adverse events [safety concerns]) as well as the incidence of serious hypersensitivity events for patients **with no prior biologic use and patients with prior use of a different anti-TNF before initiating** AMGEVITA (as part of the stratified analysis of the biologic-experienced group, as defined in Section 9.3.3.1). Current estimated incidence rates will also be calculated from the BSRBR-RA anti-TNF **and nbDMARD** comparison cohort**s**. A study design schema is provided at the beginning of the protocol.

Approximately 300 patients will be enrolled into this study over a 3-year period. If enrollment accrual is less than expected, an extension of enrollment time will be evaluated after the first year. Additional details are provided in Section 9.5.

All data collected for this study will be extracted from the BSRBR-RA. Start of data collection for patients will begin as soon as possible after marketing authorization of AMGEVITA and follow-up will continue for up to 5 years per patient after that date. Cumulative data will be analyzed every 6 months for interim analyses (as described in Section 11) and a final report will be generated at 5 years. This observational study is not intended to alter the clinical management of patients.

9.2 Setting and Study Population

9.2.1 Study Period

The total study duration is approximately 8 years, which includes a 3-year enrollment period and an individual patient observation period of up to 5 years.

9.2.2 Patient Eligibility

9.2.2.1 Inclusion Criteria

- men and women ≥ 16 years of age with RA who registered in the BSRBR-RA within 6 months of initiating AMGEVITA
- patients (or legal guardian, if applicable) who are willing to give informed consent for long-term follow-up

9.2.2.2 Exclusion Criteria

There are no exclusion criteria.

9.2.3 Matching

Not applicable.

9.2.4 Baseline Period

Patients with RA commencing therapy with a biological agent, including AMGEVITA, are asked to consent to participate in the BSRBR-RA. Data collected in the registry at baseline includes demographics, the 1987 ACR criteria for RA, the individual components of the Disease Activity Score (DAS-28, which can provided using either the ESR or CRP modifications depending on local practice), details of all previous and current disease-modifying antirheumatic drugs (DMARDs), comorbidities, smoking habits, occupational history, Health Assessment Questionnaire (HAQ), and the Euro quality-of-life 5-dimension scale (EQ-5D). Outcomes of interest identified during the baseline period will be excluded from incidence analyses.

9.2.5 Study Follow-up

Each enrolled patient will be followed for up to 5 years. Data collected by clinicians and patients during follow-up includes changes in therapy, new illnesses, DAS-28, and serious adverse events; data will be collected from the hospital every 6 months for 3 years after registration and annually after that. Data collected from patients during follow-up include HAQ, EQ-5D, and diaries (hospitalizations, referrals, new drugs); data will be collected from patients every 6 months for 3 years after registration and annually after that.

Follow-up of patients will start from the date patients are registered in the study and end with occurrence of discontinuation of AMGEVITA, death, or the end of the 5-year follow-up period, whichever comes first. Patients will be considered at risk of serious events, malignancy, and death according to the risk windows defined in Section 9.3.1.

9.3 Variables

9.3.1 Exposure Assessment

The exposed cohort will include patients receiving AMGEVITA for RA. A patient's exposure status will be assessed from the data provided by the BSRBR-RA. The following definitions of risk windows will be used:

- For all adverse events (including pregnancy) except malignancy or death, the risk window begins with the start of the index biologic agent and continues until 90 days after the end of therapy, death, or end of data collection, whichever comes first. Serious adverse events which occur beyond this risk window will not count for purposes of incidence rate estimation. However, where a patient starts a second biologic agent within 90 days after discontinuing a first one, the risk windows will overlap and both agents will get credit for the serious adverse event.
- For analyses of risk of death, the risk window begins with the start of the index biologic agent and continues until 90 days after the end of therapy, death or the cutoff date for the report, whichever comes first. Deaths which occur beyond this risk window will not count for purposes of incidence rate estimation.
- For analyses of risk of malignancy, the risk window includes all person-time in the register (since starting that biologic therapy) and extends until the cutoff date for the report or the date of death, whichever occurs sooner, even in the case of subsequent switching to another biologic agent. Where a malignancy is diagnosed after a second agent has begun, both agents will receive credit in the incidence rate estimations.

9.3.2 Outcome Assessment

9.3.2.1 Primary Outcome Measures

The primary outcome measures are:

- incidence of serious infections (ie, infectious events which require IV antibiotics, hospitalization, or meet other criteria for a serious adverse event) in patients with RA exposed to AMGEVITA

9.3.2.2 Secondary Outcome Measures

The secondary outcome measures are:

- **Incidence of serious hypersensitivity reactions in patients with RA exposed to AMGEVITA**
- incidence of other serious adverse events (safety concerns) in patients with RA exposed to AMGEVITA, including:
  - opportunistic infections (a subset of serious infections)
  - **TB**
  - **malignancy (overall)**
  - nonmelanoma skin cancer
  - melanoma
  - lymphoma
  - congestive heart failure
  - myocardial infarction
  - cerebrovascular accident
  - interstitial lung disease
  - cutaneous vasculitis
  - hematologic disorders
  - elevated alanine aminotransferase levels, liver failure, and other liver events
  - demyelination disorders
  - pregnancy exposure
- incidence rates of above listed safety concerns from **both** the BSRBR-RA anti-TNF **and nbDMARD** comparison cohort**s**, which **are** defined in Section 9.7.2

9.3.3 Covariate Assessment

Covariates will be analyzed in the primary analysis report and include the following demographic and clinical characteristics, which are part of the BSRBR-RA CRF:

- age (years)
- gender (male/female)
- disease duration (years)

- rheumatoid factor status (positive/negative)
- number of previous DMARDs
- concomitant methotrexate (yes/no)
- concomitant steroids (yes/no)
- **prior use of adalimumab (reference product or biosimilar)**
- **prior use of other biologics/anti-TNF**
- baseline anti-cyclic citrullinated peptide (CCP) status (yes/no)
- baseline nonsteroidal anti-inflammatory drug (NSAID) use (yes/no)
- smoking status (current/former/never)
- tender joint count
- swollen joint count
- patient global assessment
- ESR
- CRP
- DAS-28
- HAQ
- number of comorbidities (0/1/2/3+): hypertension, ischemic heart disease (myocardial infarction and/or angina), stroke, epilepsy, asthma, chronic bronchitis or emphysema, peptic ulcer, liver disease, renal disease, **TB**, demyelination, diabetes, hyperthyroidism, depression, cancer, other
- comorbidity (yes/no): hypertension, ischemic heart disease (myocardial infarction and/or angina), stroke, epilepsy, asthma, chronic bronchitis or emphysema, peptic ulcer, liver disease, renal disease, **TB**, demyelination, diabetes, hyperthyroidism, depression, cancer, other
- registration year (ie, in BSRBR-RA)
- weight, height, and body mass index

9.3.3.1 Stratified Analyses

Both the primary and secondary outcome measures will be stratified by prior biologic status. Patients will be defined as either:

- biologic-naïve: no prior biologic use before initiating AMGEVITA, or
- biologic-experienced: prior use of a different **anti-TNF** before initiating AMGEVITA

Patients with prior exposure to adalimumab will be part of the biologic-experienced stratum and will be of interest for the hypersensitivity-reactions outcome.

9.3.4 Validity and Reliability

The data collected for this study will be extracted from the BSRBR-RA, which derives its data from medical records that are kept per routine clinical practice in the UK for the documentation and decision-making for a patient's care.

A detailed data management plan will be implemented to ensure the quality of the collected data.

9.4 Data Sources

This study utilizes an existing registry in the UK, the BSRBR-RA, as its exclusive data source. This registry was set up and is currently managed by the University of Manchester, Manchester, England (Watson et al, 2005).

Data in the BSRBR-RA are collected via links to NHS databases, from rheumatology healthcare professionals, and directly from patients. All adverse events in the BSRBR-RA are coded using the Medical Dictionary for Regulatory Activities (MedDRA) schema (BSRBR-RA Study, 2018).

9.5 Study Size

This study will enroll approximately 300 patients.

Table 1 provides the estimated precision of this study based upon different estimates of average enrollment rates and on a serious infection incidence rate of 4.2 per 100 PY. This rate was based on a BSRBR-RA registry study, which reported a serious infection rate of 42 per 1000 PY of patients who received TNFα-inhibitor medication (Galloway et al, 2011). Based on these assumptions, the expected rates can be estimated with a high degree of precision in this study if predicted enrollment rates are achieved.

Table 1. Estimated Precision of Study Based on Enrollment Rates

Serious Infection Incidence Rate (per 100 PY)	Enrollment Duration	Follow-up Duration	Average Enrollment Rate	Total Follow-up Time (PY)	Maximum half-width of 95% CI (100 PY)[a]
4.2	3 years	5 years/ patient	50/year	750	1.74
			100/year	1500	1.17
			150/year	2250	0.94

CI = confidence interval; PY = person-years
[a] Based on Exact method

If enrollment accrual is less than expected, an extension of enrollment time will be evaluated after the first year. Based on the enrollment rate after year 1, Amgen will extend enrollment for either 1 year (if enrollment rate is approximately 80 patients/year) or 2 years (if enrollment rate is approximately 60 patients/year) to ensure that enrollment reaches the target of 300 patients.

9.6 Data Management

As specified in Section 9.4, study data will be collected in in the existing BSRBR-RA registry via paper forms completed by health professionals and patients. An online portal for data to be entered directly to the study is being developed with anticipated availability by the end of 2019.

9.6.1 Obtaining Data Files

Study reports and datasets will be encrypted and sent via the University of Manchester Zendto service.

9.6.2 Linking Data Files

Not applicable.

9.6.3 Review and Verification of Data Quality

All information received on a serious adverse event is reviewed by 1 of 2 trained registered nurses prior to coding. Reports can be sent from hospitals treating the patient, the patients themselves, or the national registers. Reporting malignancies to the national cancer registries is mandatory by law in the UK. To allow serious adverse events to be processed, the following information is required as a minimum:

- a legible and recognized disorder/sign/symptom
- the date of event
- which targeted therapy drug(s) the patient was on at the time of the event

Where information is missing, the BSRBR-RA pharmacovigilance team contacts the hospital to validate and confirm the details around the serious adverse event. Where a serious adverse event is patient reported, a request for information is always sent to the hospital for validation. Events that do not fall under the definition of a serious adverse event are not subject to validation. The data undergo regular validation checks both manually and automatically.

9.7 Data Analysis

9.7.1 Planned Analyses

9.7.1.1 Interim Analyses

Interim reports will be generated every 6 months by the BSRBR-RA, with delivery in January and July. These reports will include recruitment details, baseline characteristics, and crude non-adjusted rates of events and can act as a guide to recruitment and level of follow-up required.

9.7.1.2 Primary Analysis

The primary analysis will be the final analysis. This analysis will be focused on incidence rates of serious adverse events as described in Section 8.1 and will occur when the last patient has completed 5 years of follow-up.

9.7.2 Planned Method of Analysis

All analyses will be descriptive. For categorical variables, the frequency and percentage, with 95% CI where appropriate, will be provided. Summary statistics for continuous variables will include the number of patients, mean, median, SD or standard error, minimum, and maximum.

Follow-up among the AMGEVITA-treated patients will start from initiation of the drug and end with the occurrence of death, discontinuation of AMGEVITA, or the end of the 5-year follow-up period, whichever comes first.

For the purposes of context, current incidence rates will also be calculated from **both of** the **following** BSRBR-RA **comparison cohorts:**

- anti-TNF comparison cohort, which is a cohort of patients receiving an established anti-TNF drug (adalimumab, etanercept, or infliximab) who were recruited within 6 months of first exposure. Recruitment of this cohort began in 2010 and over 2000 patients have been recruited; BSRBR-RA plans to recruit over 4000 patients over the coming years if prescribing patterns in the UK allow.
- **nbDMARD comparison cohort, which is a cohort of patients with similar disease activity receiving conventional systemic DMARDs who have never been exposed to biologic therapy. The cohort was recruited from selected sites across the UK between 2002 and 2008 and continues to be followed up. In total, 3774 patients were recruited to this cohort.**

All statistical analysis will be performed in Stata. Detailed methodology for summary statistics and analyses of data captured within the study are documented in a SAP which will be filed, dated and maintained by BSRBR-RA. The SAP may modify the plans outlined in the protocol, and any modifications to major endpoints or analyses would be reflected in a protocol amendment.

9.7.2.1 General Considerations

This is an observational study and the approach to the statistical analysis will be generally descriptive. No formal hypotheses will be tested.

9.7.2.2 Missing or Incomplete Data and Lost to Follow-up

Missing data are expected in real-world clinical research. Efforts are made to capture missing data on subsequent follow-up forms if available but not recorded.

9.7.2.3 Descriptive Analysis

9.7.2.3.1 Description of Study Enrollment

Annual enrollment into the registry and cumulative PYs accrued will be described. All patients enrolled into the study who meet the eligibility criteria will be included in the full analysis set.

9.7.2.3.2 Description of Patient Characteristics

Baseline demographic and clinical characteristics including those described in Section 9.2.4 will be summarized descriptively.

9.7.2.4 Analysis of the Primary and Secondary Endpoints

The most recent version of MedDRA (current version is 21.0) will be used to code all adverse events.

Incidence of primary and secondary outcomes (ie, serious infections, hypersensitivity reactions, and other serious adverse events [safety concerns]) will be estimated as cumulative incidence rates per 1000 PY (95% CI). Incidence rates are based on the different definitions of the risk window for different outcomes of interest as defined in Section 9.3.1. For crude incidence event rates, patients will not be censored with the occurrence of the event, and multiple events can be counted per patient. Outcomes of interest identified during the baseline period will be excluded from the incidence of primary and secondary outcomes.

Initial analyses, carried out when sufficient numbers of AMGEVITA patients (so they cannot be identified due to small numbers) have reached 6 months of follow-up, will consist of evaluation of baseline characteristics of AMGEVITA-treated patients and of the BSRBR-RA anti-TNF **and nbDMARD** comparison cohort**s**, which **are** defined in Section 9.7.2. The primary/final analysis of endpoints at 5 years will describe rates of events overall and, as sample size allows, within relevant subgroups as determined by patient characteristics such as treatment history.

At the conclusion of the study, incidence rates will be recalculated with complete data and will reflect the appropriate risk windows. Event rates per 1000 PY (95% CI) will be presented for each cohort separately, as well as for men and women within each cohort separately. We do not expect any differences between the AMGEVITA cohort and the BSRBR-RA anti-TNF comparison cohort because AMGEVITA has been shown to be similar to the reference product, adalimumab. **The nbDMARD cohort may be different than the other 2 cohorts for several reasons. This cohort was enrolled between**

2002 and 2008, and therefore there may be differences related to data collection and reporting as well as changes in treatment paradigms. Additionally, the nbDMARD cohort may have differences in disease severity as RA patients tend to initiate therapy on nbDMARD and then only progress to anti-TNF if disease worsens. For these reasons, the anti-TNF cohort is considered the primary comparison cohort of interest. If any differences are noted between the cohorts based on evaluation of incidence rates, modifications to the analyses (eg, regression modelling) could be made and would be reflected in a protocol amendment. Cancer incidence rates will also be calculated at the end of the study to reflect the experience of patients who have and have not switched therapies.

9.7.2.5 Sensitivity Analysis

No sensitivity analyses are planned. If any differences are noted between the AMGEVITA cohort and the comparison cohort**s** based on evaluation of incidence rates, modifications to the analyses (eg, regression modelling) could be made and would be reflected in a protocol amendment.

9.7.2.5.1 Subgroup Analysis

Not applicable.

9.7.2.5.2 Stratified Analysis

Analyses of incidence rates will be stratified by patients who are biologic-experienced and biologic-naïve. Where possible, patients **with prior use of** adalimumab **(reference product or biosimilar) and other biologics** will be a subset of the biologic-experienced stratum and will be of specific interest for the hypersensitivity-reactions outcome.

Analyses of incidence rates may also be stratified by the covariates listed in Section 9.3.3.

9.7.3 Analysis of Safety Endpoints/Outcomes

The current version of MedDRA (version 21.0) will be used to code all adverse events.

9.8 Quality Control

Please refer to Section 9.6.3 for details.

9.9 Limitations of the Research Methods

This study will be subject to the common limitations of observational studies, as the patients are not randomly placed in the treatment groups. Thus, the risk of selection bias may be present, particularly in the form of channeling bias. Confounding,

particularly residual confounding, may be a concern with regard to interpretation of event rates, but as formal comparisons are not included, the impact should be minimal.

9.9.1 Internal Validity of Study Design

9.9.1.1 Measurement Errors/Misclassifications

Given that patients are classified into therapy cohorts based on drug status (initiation or current use of biologic) at enrollment, there may be risk of bias resulting from misclassification of treatment status. It is possible, although not likely based on the prospective nature of the data collection, that patients may be erroneously captured in an incorrect therapy cohort.

9.9.1.2 Information Bias

Because the registry is not based on an inception cohort and patients can enter at any time during disease duration, there is an inherent risk of misclassification which may be a result of recall bias, such as misclassification of biologic-naïve versus biologic experienced. However, this potential bias is limited by the fact that this information is taken from the medical records and shared accordingly with the registry medical personnel. It does not rely on patient recall.

9.9.1.3 Selection Bias

Selection bias is known to be less of a problem in cohort studies; however, bias may still be introduced during the process of enrolling patients into registries. Proper patient selection is important as bias may be introduced if certain subgroups of patients are routinely included or excluded from the registry. For example, patients who are currently failing or have previously failed the reference product may be forced to switch to AMGEVITA for formulary/tender reasons; inclusion of these patients in the study cohort could bias study results. Additionally, certain groups may be channeled to or away from certain treatments introducing a channeling bias. However, the BSRBR-RA registry makes efforts to recruit all eligible patients (there are no specific inclusion/exclusion criteria) which will help to minimize selection bias.

9.9.1.4 Confounding

Confounding, particularly residual confounding, may be a concern with regard to interpretation of event rates, but as formal comparisons are not included, the impact should be minimal.

9.9.2 External Validity of Study Design

The study explores serious adverse event rates in RA patients enrolled in a UK Biologics registry and may not be generalizable to regions outside of the UK.

9.9.3 Analysis Limitations

Study sample size may limit our ability to provide reliable estimates in the stratified analysis or for rare outcomes. Accurate and timely recording of the outcomes may be a concern as the study only captures data every 6 or 12 months and not in real time.

9.9.4 Limitations Due to Missing Data and/or Incomplete Data

Missing data are expected in real-world clinical research. Efforts are made to capture missing data on subsequent follow-up forms if available but not recorded.

9.10 Other Aspects

Not applicable.

10. Protection of Human Patients

This study will comply with all applicable laws, regulations, and guidance regarding patient protection, including data privacy. Additional details are available on the BSRBR-RA Study website (BSRBR-RA Study, 2018).

10.1 Informed Consent

The BSRBR-RA provides an informed consent form that patients must review and sign before enrolling into the registry. A written patient information sheet is available on the BSRBR-RA Study website explaining the purpose of the study, the risks and benefits of participation, and the informed consent process (BSRBR-RA Study, 2018).

10.2 Institutional Review Board/Independent Ethics Committee

The study protocol will be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for review.

10.3 Patient Confidentiality

The BSRBR-RA will ensure that the patient's confidentiality is maintained for documents submitted to Amgen.

- Patients are to be identified by a BSRBR-RA unique patient identification number, date of birth, and initials.
- In the 6-month reports, patient demographics should include the age at time of enrollment, in addition to the unique patient identification number.

- For serious adverse events reported to Amgen, patients are to be identified by their unique patient identification number, initials, and date of birth in accordance with local laws and regulations. The brand name and batch number (if possible) will be provided on the serious adverse event forms to ensure traceability of the product used.
- Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the BSRBR-RA.

10.4 Patients' Decision to Withdraw

Patients have the right to withdraw from the BSRBR-RA at any time after giving signed consent. Withdrawal of consent means that the patient does not wish to or is unable to continue further study participation. The BSRBR-RA is to discuss with the patient appropriate steps for withdrawal of their consent based upon the patient's desired level of withdrawal (no further participant contact, no further participant or hospital contact, or complete withdrawal). Patient data up to withdrawal of consent will be included in the analysis of the study.

11. Collection, Recording, and Reporting of Safety Information and Product Complaints

The BSRBR-RA collects systematic data on serious adverse events. Serious adverse events are reported to the BSRBR-RA registry on the CRF and then reported to the sponsor via the Biologic Studies Group Harmonized Serious Adverse Event Report Form (Appendix C). Events can also be picked up by the BSRBR-RA team via patient diaries and by the Health and Social Care Information Center (in some cases the BSRBR-RA will go back to the clinician/nurse for further information when required). All serious adverse events **that occurred in patients receiving Amgevita** will be reported by BSRBR-RA to Amgen. This will be carried out in 2 ways:

- 24-hour **reports for** serious adverse event**s related to Amgevita**: the BSRBR-RA is required to report all medically confirmed serious adverse events **related to Amgevita** to Amgen within 24 hours of the BSRBR-RA becoming aware of such an event. The 24-hour reporting rule starts from the moment that the BSRBR-RA becomes aware of a medically confirmed serious adverse event. Serious adverse events are classified as medically confirmed if they have been reported to the BSRBR-RA via the consultant/nurse. When available, key information regarding non-medically confirmed serious adverse events **related to Amgevita** will also be reported within 24 hours of being aware. All serious adverse events **related to Amgevita** reported by the patient during the first 3 years of follow-up are classified as non-medically confirmed serious adverse events and are reported to the BSRBR-RA on the 6-monthly patient diary. The clinical team are then contacted by the BSRBR-RA to see whether the patient reported event can be medically confirmed.

- Aggregated data reports will be generated every 6 months by the BSRBR-RA. These reports will include the Manchester Template report, which provides demographic data, cumulative follow-up time, and number and rates of serious adverse events, a PSUR (Periodic Safety Update Report) cumulative line listing of events, and an adverse drug reaction PSUR-style line listing of events that were thought to be related to the biologic drug. Adverse drug reactions will not be used in the study analysis.

If the BSRBR-RA receives further information regarding a serious adverse event which has already been reported to Amgen using the 24-hour system, then a follow-up report is sent. These follow-up reports are sent when any further clinically relevant information relating to the original event has been clinically reviewed by the pharmacovigilance team and within 24 hours of being clinically reviewed.

11.1 Definition of Safety Events

11.1.1 Adverse Events

An adverse event is any untoward medical occurrence in a patient/patient administered a pharmaceutical product irrespective of a causal relationship with this treatment.

An adverse event 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, whether or not considered related to the product. The definition of an adverse event includes:

- worsening of a pre-existing condition or underlying disease
- events associated with the discontinuation of the use of a product, (eg, appearance of new symptoms)

11.1.2 Serious Adverse Events

A serious adverse event is any adverse event as defined above that is considered to represent a significant hazard to the patient and includes events that meet at least 1 of the following criteria:

- is fatal
- is life-threatening (places the patient at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- requires an IV antibiotic, antiviral, or antifungal drug (BSRBR-RA Study, 2018)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an “other medically important serious event” 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 medically important serious events" refer to important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the 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.

11.1.3 Other Safety Findings

Other safety findings (regardless of association with an adverse event) will be captured when the event is considered serious, including:

- medication errors, overdose, whether accidental or intentional, misuse, or abuse involving an Amgen product,
- pregnancy and lactation exposure,
- transmission of infectious agents,
- reports of uses outside the terms for authorized use of the product including off-label use,
- occupational exposure,
- any lack or loss of intended effect of the product.

11.1.4 Adverse Drug Reactions

BSRBR-RA will provide a PSUR-style line listing of adverse drug reactions, which are nonserious events that were thought to be related to the biologic drug used to treat RA. Adverse drug reactions will not be used in the study analysis. It is the treating physician's responsibility to evaluate whether an adverse event is related to AMGEVITA.

11.1.5 Product Complaints

BSRBR-RA does not collect reports 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 to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

11.2 Safety Collection, Recording and Submission to Amgen Requirements

This study is collecting information from the BSRBR-RA, which is a prospective registry of patients in the UK with RA who are treated with biologic agents. The following safety

events considered to have occurred following patient exposure to AMGEVITA will be collected from the date patients are registered in the study to final study contact:

- serious adverse events (defined in Section 11.1.2) which are reported to the study on the clinical follow-up form, the patient diaries and via cancer/death data linkage
- adverse drug reactions (defined in Section 11.1.4) which are reported via the clinical data collection form

The BSRBR-RA is responsible for ensuring that all safety events they become aware of during study period are recorded in the patients' appropriate study documentation. Serious adverse events **in patients receiving Amgevita** must be submitted to Amgen Safety using the BSRBR-RA Harmonized Serious Adverse Event Reporting Form within 24 hours of the BSRBR-RA's awareness of the event; a sample of this form is provided in Appendix C. The BSRBR-RA will provide a list of adverse drug reactions every 6 months, however these events will not be used in the study analysis.

11.2.1 Safety Reporting Requirement to Regulatory Bodies

Amgen will report safety data as required in accordance with local requirements to regulatory authorities, IRBs/IECs, or other relevant ethical review board(s) in accordance with pharmacovigilance guidelines and in compliance with local regulations.

The BSRBR-RA is to notify the Data Monitoring and Ethics Committee (DMEC) or other relevant ethical review board of serious adverse events in accordance with local procedures and statutes. The DMEC has been established by the BSRBR-RA and includes at least 1 epidemiologist and 1 statistician. The DMEC is analogous to a Data Safety and Monitoring Board established for major clinical trials and is independent of the principal investigators and any of the pharmaceutical companies involved; as such, the DMEC oversees the entire BSRBR-RA study. The DMEC has the power to request interim analyses.

12. Administrative and Legal Obligations

12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. Amgen reserves the right to terminate the study at any time.

13. Plans for Disseminating and Communicating Study Results

An ORSR or ORSR abstract will be prepared for this study. The results of the study will also be communicated to health authorities.

13.1 Publication Policy

The results of this study will be submitted for publication. Authorship of any publications resulting from this study will be determined based on the International Committee of Medical Journal Editors Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (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 should meet conditions 1, 2, and 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group alone does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The vendor agreement will detail the procedures for, and timing of, Amgen's review of publications.

14. References

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15. Appendices

Appendix A. List of Stand-alone Documents

No.	Document Reference Number	Date	Title
1	Not applicable	03 January 2017	British Society for Rheumatology Biologics Register – Rheumatoid Arthritis (BSRBR-RA): Standard Operating Procedure Pharmacovigilance and Reporting

Appendix B. ENCePP Checklist for Study Protocols

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: A Prospective Observational Study to Evaluate Long-term Safety of AMGEVITA™ in Patients With Rheumatoid Arthritis

EU PAS Register® number: Registration occurs after Amgen internal approval of the protocol; must be prior to commencement of first data capture.
Study reference number (if applicable): 20160264

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6

[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.

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Section 1: Milestones	Yes	No	N/A	Section Number
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	Yes	No	N/A	Section Number
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)	☒	☐	☐	7.3
2.1.2 The objective(s) of the study?	☒	☐	☐	8.1/8.2
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7.3/9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	7.4

Comments:

This is an estimation study, no hypothesis is being tested.

Section 3: Study design	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.2.7
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

This is an estimation study, no measures of association are planned.

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	9.3
4.2 Is the planned study population defined in terms of:				Study schema
4.2.1 Study time period	☒	☐	☐	

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.2.2 Age and sex	☒	☐	☐	9.2.2.1
4.2.3 Country of origin	☒	☐	☐	7.3/9.4
4.2.4 Disease/indication	☒	☐	☐	9.2.2.1
4.2.5 Duration of follow-up	☒	☐	☐	9.2.5
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2.1

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3.4
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.3.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.7.2

Comments:

Drug PK/PD not applicable for this analysis.

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.3.4
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

This is a Safety study, other outcomes will not be analyzed.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.9.1.4
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9.1.3
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9.1.2

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

There are no subgroup or comparative analyses planned.

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4/9.6
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4/9.6
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4/9.6
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.7.2.4
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.3.3

Section 9: Data sources	Yes	No	N/A	Section Number
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

All variables will come directly from Medical chart. There is no planned linkage to other data source.

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7.2
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5/Table 1
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.2
10.4 Are stratified analyses included?	☒	☐	☐	9.7.2.5.2
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.2.2
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

This is an estimation study, no comparative analyses requiring control of confounding, misclassification are planned. As stated in Section 9.7.2.5, no sensitivity analyses are planned.

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.6
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.6

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9.1.3
12.1.2 Information bias?	☒	☐	☐	9.9.1.2

Section 12: Limitations	Yes	No	N/A	Section Number
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9.1.4
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5

Comments:

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.2
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10
13.3 Have data protection requirements been described?	☒	☐	☐	9.6.1/10.3

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	13
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	13

Comments:

Name of the main author of the protocol: PPD [redacted]

Date: 09/January/2019 PPD [redacted]

Signature: PPD [redacted]

Appendix C. Sample Biologic Studies Group Harmonized Serious Adverse Event Form

Biologic Studies Group Serious Adverse Event Report Form

British Society for Rheumatology

Rheumatoid Arthritis Register

This event been medically confirmed

Serious Adverse Event Awareness Date/ Date of report:	

REPORTER DETAILS: BSRBR-RA			
Name:		**Address: BSRBR-RA** The University of Manchester Rutherford House (Unit 4) Manchester Science Park 40 Pencroft Way, Manchester, M15 6SZ	
Email: bsgpharmacovigilance@manchester.ac.uk			
Phone: 0161 275 1613			
Country of Report: UK		**Fax:** 0161 275 1640	
PATIENT DETAILS			
Pt Study/Id number: **«studyno»**		Patient Initials: **«Initials»**	
Sex:	Date of Birth:	Height (cm):	Weight (kg):
COMORBIDITIES/ MEDICAL HISTORY/YEAR OF ONSET			**Ongoing?**
			☒
			Unknown (for all comorbidities)

Lifestyle Factors	Yes	No	Unknown	Start Date	Stop Date
Smoking	☐	☐	☒		
Alcohol	☐	☐	☒		

Concomitant Medications	Start date	Stop date/ongoing	Indication

BIOLOGIC/ BIOSIMILAR DRUG INFORMATION

Start Date	Dose(mg)	Route/ Frequency	Start Date	Stop Date	Indication

Lot/ batch no:	**Not Available** ☒
Notes (e.g. any further relevant info re drug):	

SERIOUS ADVERSE EVENT DETAILS		
Start Date:	Stop Date:	Event ongoing ☐
Description of Serious Adverse Event		
Further information / ESI attached: ☐ (Number of pages:)		
Seriousness criteria (check all that apply):		
Death		☐
Life-threatening (Immediately)		☐
Overnight Hospitalisation (initial or prolonged) :		☐
IV antibiotics/ IV anti-viral or IV anti-fungal drugs required		☐
Significant loss of function or disability		☐
Congenital malformation /birth defect		☐
Other medically important event*		☐

**Including pregnancy and malignancy*

"Do you believe there is a possibility this adverse event was related to the biologic/biosimilar drug used to treat «IndicLongDesc»?" *(Question asked of clinicians completing register data.)*		
Answer supplied by clinician (Yes/No/Don't know/Not available):		
Was biologic drug stopped due to this event?		
Yes (permanently): ☐*	Yes (temporarily): ☐*	* *See details on page 1 for biologic/biosimilar drug information*
No: ☐	Unknown: ☐	Not applicable (stopped prior to event): ☐
Was the patient hospitalised due to this event?		
Date of admittance:	Date of discharge:	Dates unknown: ☐
What was the outcome of the event?		
Recovered: ☐	Not Recovered: ☐	Recovered with Sequelae: ☐
Fatal ☐ Date:		Outcome unknown: ☐
All currently available information has been provided in this report and is correct at the time of reporting. Should further information become available this will be forwarded as follow up information. Please confirm receipt of this report, failure to do so will result in you being contacted to confirm. If you have queries about this report please contact the reporter (see page 1).		

Version #2

Protocol Title: A Prospective Observational Study to Evaluate Long-term Safety of AMGEVITA™ in Patients With Rheumatoid Arthritis

Amgen Protocol Number ABP 501 20160264

Amendment Date: 13 June 2019

Rationale:

This protocol is being amended as a response to questions from the European Medicines Agency's Pharmacovigilance Risk Assessment Committee.

These changes include:

- Moving "serious hypersensitivity reaction" as a primary objective to a secondary objective while maintaining serious infections as a primary endpoint
- Adding a non-biologic disease-modifying antirheumatic drug (nbDMARD) comparison cohort
- Adding the estimate of rates of any malignancy and tuberculosis to align with current important identified risks for the adalimumab reference product
- Updated the stratification of analyses to state that patients with prior use of adalimumab (reference product or biosimilar) will be a subset of the biologic experienced stratum and, where possible, will be identified as adalimumab patients

Description of Changes

Section: Global

Change: The Amgen version date was changed from 10 January 2019 to **13 June 2019**

Section: Global

Change: Editorial, typographical, and formatting changes were made throughout the document.

Section: Summary Table of Study Protocol

Replace:

Title	A Prospective Observational Study to Evaluate Long-term Safety of AMGEVITA™ in Patients With Rheumatoid Arthritis
Protocol version identifier	20160264 Version 1.0
Date of last version of the protocol	NA

With:

Title	A Prospective Observational Study to Evaluate Long-term Safety of AMGEVITA™ in Patients With Rheumatoid Arthritis
Protocol version identifier	20160264 Version **2.0**
Date of last version of the protocol	**10 January 2019**

Section: Summary Table of Study Protocol, Objectives

Delete:

Research Question and Objectives	What is the long-term safety of AMGEVITA in patients with moderate to severe rheumatoid arthritis (RA) in a real-world setting? The primary objective is to estimate the incidence rates of the safety concerns (identified risks of adalimumab) serious infections ~~and serious hypersensitivity reactions~~ in patients with RA exposed to AMGEVITA.

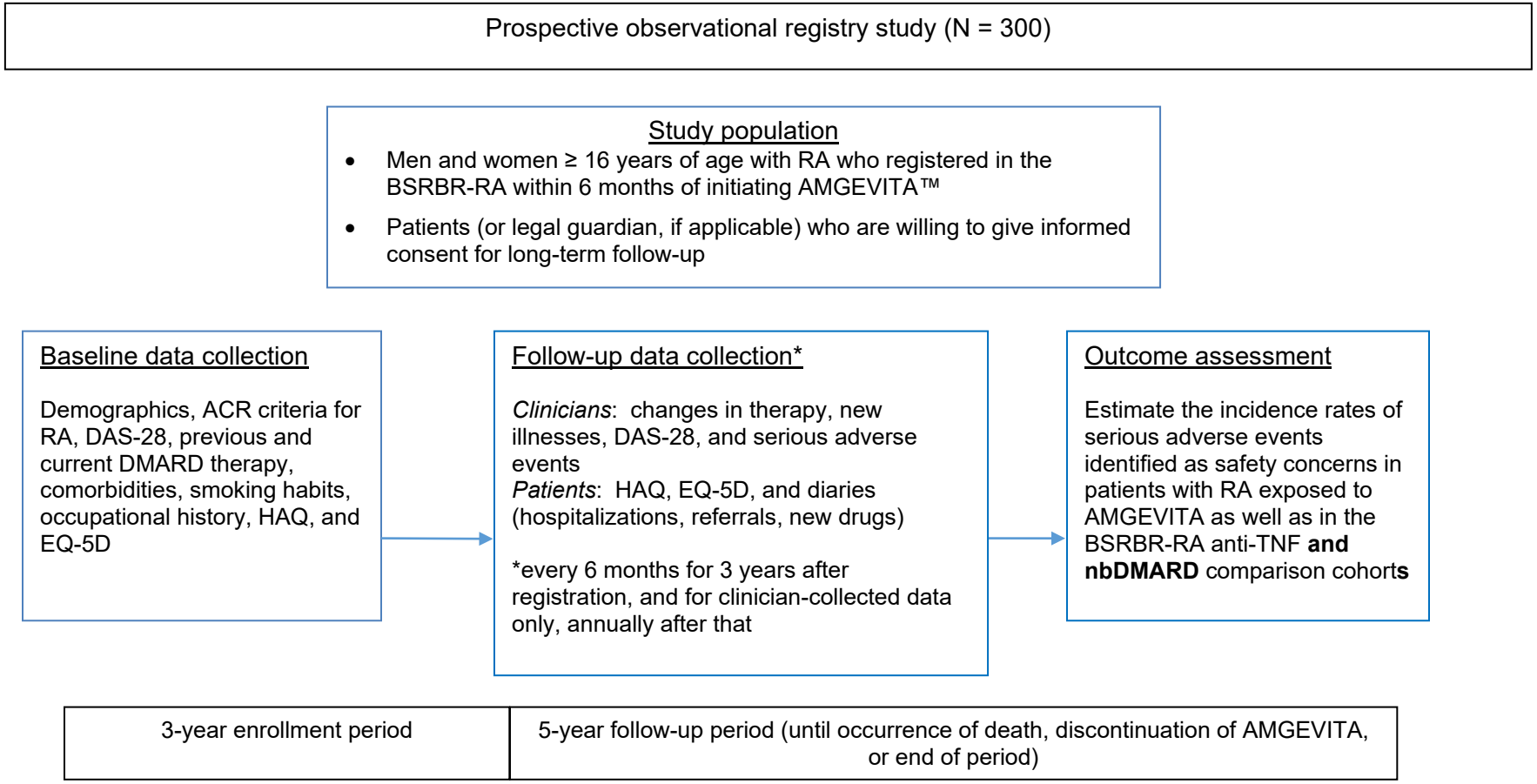
Section: Summary Table of Study Protocol, Objectives

Add:

Research Question and Objectives	The secondary objectives are to estimate the incidence rates of **serious hypersensitivity reactions and** other serious adverse events (safety concerns) in patients with RA exposed to AMGEVITA, and to estimate the incidence rates for the same outcomes from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA) anti-tumor necrosis factor (TNF) comparison cohort **and a non-biologic disease-modifying antirheumatic drug (nbDMARD) comparison cohort**, as defined in Section 9.7.2.

Section: Study Design Schema

Add:



Section: Study Design Schema, footnotes

Add:

ACR = American College of Rheumatology; BSRBR-RA = British Society for Rheumatology Biologics Register for Rheumatoid Arthritis; DAS-28 = Disease Activity Score; DMARD = disease-modifying antirheumatic drug; EQ-5D = Euro quality-of-life 5-dimension scale; HAQ = Health Assessment Questionnaire; **nbDMARD = non-biologic disease-modifying antirheumatic drug**; RA = rheumatoid arthritis; TNF = tumor necrosis factor

Section: 2, List of Abbreviations

Add:

Abbreviation or Term	Definition/Explanation
nbDMARD	**non-biologic disease-modifying antirheumatic drug**
TB	**tuberculosis**

Section: 3, Responsible Parties

Replace:

Name	Title and Affiliation
PPD, PhD	Director, Center for Observational Research, Amgen
PPD, MD, MBA, MS	Executive Medical Director, Biosimilars Global Development, Amgen
PPD, MD	Medical Director, Global Safety, Amgen
PPD, PhD	Manager of Pharmacovigilance Studies, BSRBR-RA

With:

Name	Title and Affiliation
PPD, PhD	Director, Center for Observational Research, Amgen
PPD MD, **MPH**	Executive Medical Director, Biosimilars Global Development, Amgen
PPD, MD	Medical Director, Global Safety, Amgen
PPD, PhD	Manager of Pharmacovigilance Studies, BSRBR-RA

Section: 4, Abstract
Research question and objectives

Delete:

- Primary Objective
  Estimate the incidence rates of the following safety concerns (identified risks of adalimumab) in patients with RA exposed to AMGEVITA: serious infections (ie, infectious events which require intravenous [IV] antibiotics, hospitalization, or meet other criteria for a serious adverse event) ~~and serious hypersensitivity reactions~~.

Section: 4, Abstract
Research question and objectives

Add:

- Secondary Objectives
  Estimate the incidence rates of other serious adverse events (safety concerns) in patients with RA exposed to AMGEVITA, including: **serious hypersensitivity reactions,** opportunistic infections (a subset of serious infections); **tuberculosis (TB); malignancy (overall);** nonmelanoma skin cancer; melanoma; lymphoma; congestive heart failure; myocardial infarction; cerebrovascular accident; interstitial lung disease; cutaneous vasculitis; hematologic disorders; elevated alanine aminotransferase levels, liver failure and other liver events; demyelination disorders; and pregnancy exposure.
- Estimate the incidence rates of the above listed safety concerns from **both** the BSRBR-RA anti-TNF **and the non-biologic disease-modifying antirheumatic drug (nbDMARD)** comparison cohort**s**, which **are** defined in Section 9.7.2.

Section: 4, Abstract
Variables

Replace:

- Outcome Variables
  The primary outcome measures are incidence of serious infections (ie, infectious events which require IV antibiotics, hospitalization, or meet other criteria for a serious adverse event) and incidence of serious hypersensitivity reactions. The secondary outcome measure is incidence of other serious adverse events.
- Exposure Variables
  All patients enrolled in the study will be exposed to AMGEVITA. A patient's exposure status will be assessed from the data provided by the BSRBR-RA. Analyses will be stratified based on biologic-experienced and biologic-naïve status. Patients switching from adalimumab will be a subset of the biologic-experienced stratum and, where possible, will be identified as adalimumab patients.

With:

- Outcome Variables
  The primary outcome measures are incidence of serious infections (ie, infectious events which require IV antibiotics, hospitalization, or meet other criteria for a serious adverse event). The secondary outcome measure is incidence of **serious hypersensitivity reactions and** other serious adverse events.
- Exposure Variables
  All patients enrolled in the study will be exposed to AMGEVITA. A patient's exposure status will be assessed from the data provided by the BSRBR-RA. Analyses will be stratified based on biologic-experienced and biologic-naïve status. Patients **with prior use of** adalimumab **(reference product or biosimilar)** will be a subset of the biologic-experienced stratum and, where possible, will be identified as adalimumab patients.

Section: 4, Abstract
Data analysis

Add:

Incidence of primary and secondary outcomes (ie, serious infections, hypersensitivity reactions, and other serious adverse events [safety concerns]) will be estimated as cumulative incidence rates (95% CI). For the purposes of context, current incidence rates will also be calculated from **both of** the **following** BSRBR-RA **comparison cohorts:**

- anti-TNF comparison cohort, which is a cohort of patients receiving an established anti-TNF drug (adalimumab, etanercept, or infliximab) who were recruited within 6 months of first exposure.
- **nbDMARD comparison cohort, which is a cohort of patients with similar disease activity receiving conventional systemic DMARDs who have never been exposed to biologic therapy. The cohort was recruited from selected sites across the UK between 2002 and 2008 and continues to be followed up. In total, 3774 patients were recruited to this cohort.**

This is an observational study and the approach to the statistical analysis will be generally descriptive. No formal hypotheses will be tested. For categorical variables, the frequency and percentage, with 95% CI where appropriate, will be provided. Summary statistics for continuous variables will include the number of patients, mean, median, SD or standard error, minimum, and maximum. Interim analyses will be provided every 6 months by the BSRBR-RA. The primary analysis will be focused on incidence rates of serious adverse events as described in Section 8.1 and will occur when the last patient has completed 5 years of follow-up. We do not expect any differences between the AMGEVITA cohort and the BSRBR-RA anti-TNF comparison cohort because AMGEVITA has been shown to be similar to the reference product, adalimumab. **A historical RA cohort of patients treated with nbDMARDs recruited to the BSRBR-RA from a select number of sites within the UK (recruited between 2002 and 2008) is being included as a second comparator cohort. As this cohort is not contemporaneous to either of the other cohorts and may have differences in underlying disease severity, the anti-TNF cohort will be considered the primary comparison cohort of interest.** If any differences are noted between the cohorts

based on evaluation of incidence rates, modifications to the analyses (eg, regression modelling) could be made and would be reflected in a protocol amendment.

Section: 5, Amendments and Updates

Replace:

None.

With:

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
1	**13 June 2019**	**See Summary of Changes**	**To reorder the primary and secondary objectives, as well as to add a new comparison cohort**	**See Summary of Changes**

Section: 6, Milestones

Replace:

Milestone	Planned date
Start of data collection	2019 2Q

With:

Milestone	Planned date
Start of data collection	2019 **3**Q

Section: 7.3, Rationale

Replace:

The primary outcomes of interest are the incidence of serious infections and the incidence of serious hypersensitivity reactions. The incidence of other serious adverse events (safety concerns) will also be examined. The data collected by this registry study will provide information to further characterize the long-term safety of AMGEVITA.

With:

The primary outcome of interest **is** the incidence of serious infections. The incidence of **serious hypersensitivity reactions and** other serious adverse events (safety concerns) will also be examined. The data collected by this registry study will provide information to further characterize the long-term safety of AMGEVITA.

Section: 8.1, Primary Objective

Delete:

The primary objective of this study is to estimate the incidence rates of the following safety concerns (identified risks of adalimumab) in patients with RA exposed to AMGEVITA:

- serious infections (ie, infectious events which require IV antibiotics, hospitalization, or meet other criteria for a serious adverse event) hospitalization, or meet other criteria for a serious adverse event)
- ~~serious hypersensitivity reactions~~

Section: 8.2, Secondary Objectives

Add:

The secondary objectives of this study are to:

- estimate the incidence rates of other serious adverse events (safety concerns) in patients with RA exposed to AMGEVITA, including:
  - **serious hypersensitivity reactions**
  - opportunistic infections (a subset of serious infections)
  - **TB**
  - **malignancy (overall)**
  - nonmelanoma skin cancer
  - melanoma
  - lymphoma
  - congestive heart failure
  - myocardial infarction
  - cerebrovascular accident
  - interstitial lung disease
  - cutaneous vasculitis
  - hematologic disorders
  - elevated alanine aminotransferase levels, liver failure, and other liver events
  - demyelination disorders
  - pregnancy exposure
- estimate the incidence rates of the above listed safety concerns from **both** the BSRBR-RA anti-TNF **and nbDMARD** comparison cohort**s**, which **are** defined in Section 9.7.2.

Section: 9.1, Study Design, Paragraph 1

Replace:

These reports will be used to monitor the incidence of several important identified risks (eg, serious infections, serious hypersensitivity reactions, and other serious adverse events [safety concerns]) as well as the incidence of serious hypersensitivity events for patients switching from adalimumab to AMGEVITA (as part of the stratified analysis of the biologic-experienced group, as defined in Section 9.3.3.1). Current estimated incidence rates will also be calculated from the BSRBR-RA anti-TNF comparison cohort. A study design schema is provided at the beginning of the protocol.

With:

These reports will be used to monitor the incidence of several important identified risks (eg, serious infections, serious hypersensitivity reactions, and other serious adverse events [safety concerns]) as well as the incidence of serious hypersensitivity events for patients **with no prior biologic use and patients with prior use of a different anti-TNF before initiating** AMGEVITA (as part of the stratified analysis of the biologic-experienced group, as defined in Section 9.3.3.1). Current estimated incidence rates will also be calculated from the BSRBR-RA anti-TNF **and nbDMARD** comparison cohort**s**. A study design schema is provided at the beginning of the protocol.

Section: 9.3.2.1, Primary Outcome Measures

Delete:

The primary outcome measures are:

- incidence of serious infections (ie, infectious events which require IV antibiotics, hospitalization, or meet other criteria for a serious adverse event) in patients with RA exposed to AMGEVITA
- ~~incidence of serious hypersensitivity reactions in patients with RA exposed to AMGEVITA~~

Section: 9.3.2.2, Secondary Outcome Measures, Bullet 1 and 2

Add:

The secondary outcome measures are:

- **Incidence of serious hypersensitivity reactions in patients with RA exposed to AMGEVITA**
- incidence of other serious adverse events (safety concerns) in patients with RA exposed to AMGEVITA, including:
  - opportunistic infections (a subset of serious infections)
  - **TB**
  - **malignancy (overall)**
  - nonmelanoma skin cancer
  - melanoma
  - lymphoma
  - congestive heart failure
  - myocardial infarction
  - cerebrovascular accident
  - interstitial lung disease
  - cutaneous vasculitis
  - hematologic disorders
  - elevated alanine aminotransferase levels, liver failure, and other liver events
  - demyelination disorders
  - pregnancy exposure

Section: 9.3.2.2, Secondary Outcome Measures
Bullet 3

Replace:

- incidence rates of above listed safety concerns from both the BSRBR-RA anti-TNF and nbDMARD comparison cohorts, which are defined in Section 9.7.2.

With:

- incidence rates of above listed safety concerns from **both** the BSRBR-RA anti-TNF **and nbDMARD** comparison cohort**s**, which **are** defined in Section 9.7.2.

Section: 9.3.3, Covariate Assessment

Replace:

Covariates will be analyzed in the primary analysis report and include the following demographic and clinical characteristics, which are part of the BSRBR-RA CRF:

- age (years)
- gender (male/female)
- disease duration (years)
- rheumatoid factor status (positive/negative)
- number of previous DMARDs
- concomitant methotrexate (yes/no)
- concomitant steroids (yes/no)
- prior biologic use
- switching from Humira or naïve patient (where possible) – see below
- switching from other biologic/anti-TNF drug to AMGEVITA
- baseline anti-cyclic citrullinated peptide (CCP) status (yes/no)
- baseline nonsteroidal anti-inflammatory drug (NSAID) use (yes/no)

With:

Covariates will be analyzed in the primary analysis report and include the following demographic and clinical characteristics, which are part of the BSRBR-RA CRF:

- age (years)
- gender (male/female)
- disease duration (years)
- rheumatoid factor status (positive/negative)
- number of previous DMARDs
- concomitant methotrexate (yes/no)
- concomitant steroids (yes/no)
- **prior use of adalimumab (reference product or biosimilar)**
- **prior use of other biologics/anti-TNF**
- baseline anti-cyclic citrullinated peptide (CCP) status (yes/no)
- baseline nonsteroidal anti-inflammatory drug (NSAID) use (yes/no)

Section: 9.3.3.1, Stratified Analyses

Replace:

Both the primary and secondary outcome measures will be stratified by prior biologic status. Patients will be defined as either:

- biologic-naïve: no prior biologic use before initiating AMGEVITA, or
- biologic-experienced: prior use of a different TNFα inhibitor before initiating AMGEVITA

With:

Both the primary and secondary outcome measures will be stratified by prior biologic status. Patients will be defined as either:

- biologic-naïve: no prior biologic use before initiating AMGEVITA, or
- biologic-experienced: prior use of a different **anti-TNF** before initiating AMGEVITA

Section: 9.7.2, Planned Method of Analysis, Paragraph 3

Add:

For the purposes of context, current incidence rates will also be calculated from **both of** the **following** BSRBR-RA **comparison cohorts:**

- anti-TNF comparison cohort, which is a cohort of patients receiving an established anti-TNF drug (adalimumab, etanercept, or infliximab) who were recruited within 6 months of first exposure. Recruitment of this cohort began in 2010 and over 2000 patients have been recruited; BSRBR-RA plans to recruit over 4000 patients over the coming years if prescribing patterns in the UK allow.
- **nbDMARD comparison cohort, which is a cohort of patients with similar disease activity receiving conventional systemic DMARDs who have never been exposed to biologic therapy. The cohort was recruited from selected sites across the UK between 2002 and 2008 and continues to be followed up. In total, 3774 patients were recruited to this cohort.**

Section: 9.7.2.4, Analysis of the Primary and Secondary Endpoints, Paragraph 3 and 4

Replace:

Initial analyses, carried out when sufficient numbers of AMGEVITA patients (so they cannot be identified due to small numbers) have reached 6 months of follow-up, will consist of evaluation of baseline characteristics of AMGEVITA-treated patients and of the BSRBR-RA anti-TNF comparison cohort, which is defined in Section 9.7.2. The primary/final analysis of endpoints at 5 years will describe rates of events overall and, as

sample size allows, within relevant subgroups as determined by patient characteristics such as treatment history.

At the conclusion of the study, incidence rates will be recalculated with complete data and will reflect the appropriate risk windows. Event rates per 1000 PY (95% CI) will be presented for each cohort separately as well as for men and women within each cohort separately. We do not expect any differences between the AMGEVITA cohort and the BSRBR-RA anti-TNF comparison cohort because AMGEVITA has been shown to be similar to the reference product, adalimumab.

With:

Initial analyses, carried out when sufficient numbers of AMGEVITA patients (so they cannot be identified due to small numbers) have reached 6 months of follow-up, will consist of evaluation of baseline characteristics of AMGEVITA-treated patients and of the BSRBR-RA anti-TNF **and nbDMARD** comparison cohort**s**, which **are** defined in Section 9.7.2. The primary/final analysis of endpoints at 5 years will describe rates of events overall and, as sample size allows, within relevant subgroups as determined by patient characteristics such as treatment history.

At the conclusion of the study, incidence rates will be recalculated with complete data and will reflect the appropriate risk windows. Event rates per 1000 PY (95% CI) will be presented for each cohort separately as well as for men and women within each cohort separately. We do not expect any differences between the AMGEVITA cohort and the BSRBR-RA anti-TNF comparison cohort because AMGEVITA has been shown to be similar to the reference product, adalimumab. **The nbDMARD cohort may be different than the other 2 cohorts for several reasons. This cohort was enrolled between 2002 and 2008, and therefore there may be differences related to data collection and reporting as well as changes in treatment paradigms. Additionally, the nbDMARD cohort may have differences in disease severity as RA patients tend to initiate therapy on nbDMARD and then only progress to anti-TNF if disease worsens. For these reasons, the anti-TNF cohort is considered the primary comparison cohort of interest.**

Section: 9.7.2.5, Sensitivity Analysis

Replace:

No sensitivity analyses are planned. If any differences are noted between the AMGEVITA cohort and the BSRBR-RA anti-TNF comparison cohort based on evaluation

of incidence rates, modifications to the analyses (eg, regression modelling) could be made and would be reflected in a protocol amendment.

With:

No sensitivity analyses are planned. If any differences are noted between the AMGEVITA cohort and the comparison cohort**s** based on evaluation of incidence rates, modifications to the analyses (eg, regression modelling) could be made and would be reflected in a protocol amendment.

Section: 9.7.2.5.2, Stratified Analysis

Replace:

Analyses of incidence rates will be stratified by patients who are biologic-experienced and biologic-naïve. Where possible, patients switching from adalimumab will be a subset of the biologic-experienced stratum and will be of specific interest for the hypersensitivity-reactions outcome.

With:

Analyses of incidence rates will be stratified by patients who are biologic-experienced and biologic-naïve. Where possible, patients **with prior use of** adalimumab **(reference product or biosimilar) and other biologics** will be a subset of the biologic-experienced stratum and will be of specific interest for the hypersensitivity-reactions outcome.

Section: 11, Collection, Recording, and Reporting of Safety Information and Product Complaints, Paragraph 1

Add:

The BSRBR-RA collects systematic data on serious adverse events. Serious adverse events are reported to the BSRBR-RA registry on the CRF and then reported to the sponsor via the Biologic Studies Group Harmonized Serious Adverse Event Report Form (Appendix C). Events can also be picked up by the BSRBR-RA team via patient diaries and by the Health and Social Care Information Center (in some cases the BSRBR-RA will go back to the clinician/nurse for further information when required). All serious adverse events **that occurred in patients receiving Amgevita** will be reported by BSRBR-RA to Amgen. This will be carried out in 2 ways:

- 24-hour **reports for** serious adverse event**s related to Amgevita**: the BSRBR-RA is required to report all medically confirmed serious adverse events **related to Amgevita** to Amgen within 24 hours of the BSRBR-RA becoming aware of such an event. The 24-hour reporting rule starts from the moment that the BSRBR-RA becomes aware of a medically confirmed serious adverse event. Serious adverse

events are classified as medically confirmed if they have been reported to the BSRBR-RA via the consultant/nurse. When available, key information regarding non-medically confirmed serious adverse events **related to Amgevita** will also be reported within 24 hours of being aware. All serious adverse events **related to Amgevita** reported by the patient during the first 3 years of follow-up are classified as non-medically confirmed serious adverse events and are reported to the BSRBR-RA on the 6-monthly patient diary. The clinical team are then contacted by the BSRBR-RA to see whether the patient reported event can be medically confirmed.

Section: 11.2, Safety Collection, Recording and Submission to Amgen Requirements, Paragraph 2

Add:

The BSRBR-RA is responsible for ensuring that all safety events they become aware of during study period are recorded in the patients' appropriate study documentation. Serious adverse events **in patients receiving Amgevita** must be submitted to Amgen Safety using the BSRBR-RA Harmonized Serious Adverse Event Reporting Form within 24 hours of the BSRBR-RA's awareness of the event; a sample of this form is provided in Appendix C. The BSRBR-RA will provide a list of adverse drug reactions every 6 months, however these events will not be used in the study analysis.