Global Epidemiology and Outcomes Research (GEOR) Protocol IM101151

Long-term Experience with Abatacept in Routine Clinical Practice

Revised Protocol Number: 06

Incorporates Amendments 1, 2, 5, 7, 9 and 11

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Replace all previous version(s) of the protocol with Revised Protocol Number 05 supplied with this revision. Please provide a copy of this revised protocol to all study personnel under your supervision.

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol n°6	02-Oct-2012	Incorporates Amendment 11
Amendment 11	02-Oct-2012	• Specify the abatacept route of administration due to the fact that a new abatacept formulation (subcutaneous) will be available soon. • Consider the change of route of administration from Orencia IV -to Orencia SC during the follow up period and describe the data collected in this case and the analysis performed • Describe the development of abatacept SC formulation, the approval date and indications in Switzerland and Europe • Update the end of enrollment period (additional 6 months) in the subgroup of patients treated with Orencia in MTX inadequate responders • Update administrative information (Local medical monitor representative in Greece, Ireland, Denmark and Switzerland, HEOR representative change, details of protocol manager and data manger / biostatistician, BMS confidentiality statement, section name)
Revised Protocol n°5	11-Jul-2011	Incorporates Amendment 9
Amendment 9	11-Jul-2011	• To open a new enrolment period for patients anti TNF-Inadequate Responders for a maximum of 24 months, up to December 2013 in Europe. • To extend the study to Switzerland
Revised Protocol n°4	09-Jul-2010	Incorporates Amendment 7
Amendment 7	09-Jul-2010	• To extend the study enrolment period for a maximum of 24 months, up to December 2012 in Europe. • To extend the study to France and Spain
Revised Protocol n°3	27-Jul-2009	Incorporates Amendment 5
Amendment 5	27-Jul-2009	• To extend the study to Ireland and Denmark
Revised Protocol n°2	05-Aug-2008	Incorporates Amendment 2
Amendment 2	05-Aug-2008	• To extend the study to Romania
Revised Protocol n°1	04-Dec-2007	Incorporates Amendment 1
Amendment 1	04-Dec-2007	• To extend the study in Europe (Austria, Belgium, Czech Republic, Greece, Hungary, Italy, The Nederlands), and Canada
Original Protocol	08-Oct-2007	Not applicable

SYNOPSIS

Observational Study Protocol IM101151

Protocol Title: Long-term experience with abatacept in routine clinical practice
Department: HEOR / GDMA
Research Question: Abatacept has recently become available in the treatment of rheumatoid arthritis. It is critical to understand the long term retention of patients treated with abatacept in routine clinical practice, and the treatment experience and outcomes after switching to a biologic or conventional DMARD with the discontinuation of abatacept therapy.
Primary Objective: To estimate the retention rate of RA patients treated with abatacept over 24 months in routine clinical practice in every participating country and their combinations whenever appropriate, depending on the treatment line (i.e, abatacept as second or further biologics DMARDs or abatacept as first line of biologics DMARDs).
Secondary Objectives: 1. To identify the major determinants (including prior RA treatment experience with biologics and clinical outcomes, such as DAS28, HAQ-DI, CDAI, SDAI and their derived criteria) of treatment discontinuation of RA patients treated with abatacept in this study. 2. To estimate the distribution of time-to-discontinuation of abatacept therapy for each major determinant of treatment discontinuation, overall and depending on the treatment line.. 3. To estimate the association of prior RA treatment experience and clinical outcomes during the treatment course with patient reported outcomes (Patient satisfaction, Pain, Patient's Global Assessment). To summarize the treatment experience and outcomes after switching to a biologic or conventional DMARD for patients who discontinue abatacept therapy.
Study Design: This is a non-interventional, multicenter, prospective, longitudinal study of RA patients treated with abatacept according to SmPC in Europe and Product Monograph in Canada. A 2825 patient sample over a period of maximum 18-24 months for each treatment line of abatacept and for each enrolment period will be enrolled prospectively according to participating country regulatory requirements either at initiation of abatacept intravenous (IV) treatment or patients will already have been treated with abatacept IV for maximum 3 months. Patients already on treatment with the study drug may be included only if baseline data are available and can be collected retrospectively. Each patient will be followed up for 2 years. Therefore, a data collection period of a maximum of 7 years is anticipated. Assessment schedules and outcomes will be performed according to routine local clinical practice. It is estimated that patients will be evaluated every 3 months. If available, data at additional visits will also be collected (e.g. at time of drug administration)

Study Population: A total of 2825 patients with a diagnosis of moderate to severe active RA (as per the American College of Rheumatology revised criteria, 1987) and are aged 18 years or older who at their physician's discretion are treated with abatacept IV according to the SmPC in Europe and the Product Monograph in Canada (initiating or already on treatment for maximum 3 months) and for whom baseline characteristics are available.

Assessments:

- At baseline (1st administration of abatacept IV): the baseline data can be collected at abatacept IV treatment initiation or retrospectively within maximum 3 months following the first administration:
  - Socio-demographics
  - Disease history & characteristics
  - Prior RA treatments (biologic and conventional DMARDs, other concomitant medication)
- Prospectively, inclusive of baseline visit
  - Clinical outcomes : DAS28 and its individual components (SJC, TJC, CRP/BSG); HAQ-DI, CDAI, SDAI, Physician's global assessment
  - Patient-reported outcomes: Patient Global Assessment, Patient satisfaction, pain
  - Abatacept dosage and frequency of administration (IV and subcutaneous (SC) formulation)
  - Reasons and subsequent RA treatment with conventional/biologic DMARDs if abatacept is discontinued
  - Reason for change in the route of administration of abatacept (from IV to SC)Other concomitant medication for RA (doses, frequency)
  - Adverse Drug Reactions
  - Derived clinical outcomes:DAS28 derived criteria : EULAR response, LDAS (DAS 28≤3.2), remission (DAS28<2.6)
  - DAS 28 (DAS28) based on CRP (DAS28-CRP) or ESR (DAS28-ESR)
  - HAQ-DI derived criteria: HAQ response (change HAQ-DI≥0.3)
  - Response/status at each time point, onset of action, durability

Statistical analyses

The analysis will be performed for each participating country. Data from different countries may be pooled if appropriate, depending on treatment line of abatacept.

Descriptive analyses:

- Sample size, mean, standard deviation, minimum, median, mode, maximum, 95% CI and the number of missing data for continuous variables
- Frequency and percentage by modality, 95% CI and number of missing data for discrete variables
- Distribution and median of time-to-event data will be analyzed using Kaplan-Meier product limit estimator

Primary Analysis:

The retention rate of RA patients treated with abatacept (regardless of route of administration) over 24 months in routine clinical practices will be estimated for each country separately and pooled (if appropriate), depending on treatment line of abatacept.

Secondary Analysis:

Information of Participating Centres:

- Descriptive analysis of the participating physicians and assessment of the representativeness with national statistics will be performed.

Determinants of Treatment Discontinuation:

- The major determinants of treatment discontinuation of RA patients treated with abatacept (regardless of route of administration) in this study will be identified and summarized.
- The retention rate will be estimated for each determinant with corresponding 95% CIs
- The distribution and median of time-to-discontinuation of abatacept therapy for each major determinant of treatment discontinuation will be estimated using Kaplan-Meier method with corresponding 95% CIs.

Patient Reported Outcomes:

- The patient reported outcomes, such as patient satisfaction, pain, patient's global assessment, etc. of RA patients treated with abatacept in this study will be summarized.

Treatment Experience/Outcomes after Switching:

- The treatment experience/outcomes after switching to a biologic or conventional DMARD for patients who discontinue abatacept therapy will be summarized.

Exploratory Analysis:

- Description of potential changes in patient characteristics and in treatment pattern over time in clinical practice in patients treated with abatacept as second or further biologics DMARDs, enrolled during the period 2008-2010 and in patients enrolled during the period 2011-2013 in Europe (Germany, Italy, Austria, The Netherlands, Greece)
- Relationship between abatacept discontinuation and the derived clinical outcomes and the prior RA experience will be investigated.
- Cox proportional hazard regression model will be used to identify factors which contribute to patient discontinuation. The analysis will be conducted at 6 and 12 months and results will be compared to analysis at 24 months.
- Description of treatment experience/ outcomes after switching from abatacept IV to abatacept SC formulation

Reporting of Interim analysis

- Subsequent interim analysis will be conducted during the follow-up period (after LPFV, after 6 months and 1 year following LPFV)
- Each interim statistical analysis will be performed depending on treatment line of abatacept.

Sample size calculation

The primary objective of this study is to estimate the retention rate of RA patients' treatment with abatacept over 24 months in routine clinical practices in each participating country with a sufficient level of precision;

Based on the extent of biologics' use in each participating country (BMS market research data) and feasibility considerations, it is estimated that each country will be able to enrol the total number of patients over the planned 2-year accrual period (for each line of abatacept and for each enrolment period): 670 patients for Germany, 95 patients for Austria, 110 patients for Belgium, 20 patients for Czech Republic, 272 patients for Greece, 435 patients for Italy, 84 patients for the Netherlands, 200 patients for Canada, 25 patients for Denmark, 30 patients for Ireland, 620 patients for France, and 240 patients for Spain..

Assuming that the sample size of each country will vary from 20 to 400 patients in patients who had an inadequate response to at least one tumour necrosis factor inhibitor, and from 10 to 220 in patients s who had an inadequate response to at least one DMARD including Methotrexate or TNFα inhibitor, the level of precision for the country-specific estimates will be proportionally decreased. The data from different countries may be pooled if appropriate.

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1. INTRODUCTION

Rheumatoid arthritis (RA) is the most common form of the chronic inflammatory rheumatic diseases. It is a chronic progressive disease, associated with systemic inflammation. Disease onset is insidious in most cases. The main symptoms are pain, stiffness and swelling of peripheral joints. This autoimmune disease of unknown etiology evolves by flares and leads to progressive joint damage, functional disability, impaired quality of life[1,2,3] and even shortened life expectancy.[4,5]

Disease Modifying Anti-Rheumatic Drugs (DMARDs), particularly methotrexate (MTX), have been the standard of care for aggressively treating RA. In the last decade, however, the treatment of RA had a paradigm change with the launch of the TNF-blocking agents (etanercept [Enbrel®], infliximab [Remicade®] and adalimumab [Humira®]); and the B-cell depleting agent rituximab [MabThera®]. Biologics and DMARD combinations have shown their ability to reduce the rate of disease progression.[6,7,8] Furthermore, biological therapies have demonstrated, in the context of clinical trials, rapid disease control in terms of disease activity as measured by Disease Activity Score (DAS) and relief in signs and symptoms according to the American College of Rheumatology (ACR) criteria, which are associated with functional improvement, as measured by the Health Assessment Questionnaire (HAQ), and prevention of joint destruction.[9]

In a chronic disease like RA, the long term efficacy and safety are of great importance. In clinical practice approximately 30% of RA patients discontinue the treatment with a TNF blocking agent during the first year due to lack of efficacy or adverse events[10] and only around 50% of patients continue with the same TNF-blocking agent after two years.[11] This rate is lower than those seen in randomized clinical trials. Dose adjustment over time due to acquired drug resistance may be necessary with the TNF-blocking agents.[12] After failure on a TNF blocking agent, a second or third TNF-blocking agent may be considered. However, the treatment retention rate is decreasing progressively after failure on the 1st, 2nd or 3rd TNF blocking agent.[13]

Abatacept, the first selective co-stimulation modulator for the treatment of RA, has a mechanism of action that is fundamentally different from that of the TNF-blocking agents. Sustained and durable long-term response with abatacept was demonstrated in the double-blind phase of clinical trials and in the open label extension of the AIM (MTX-inadequate responders) and the ATTAIN (TNF-blocking agent inadequate responders) studies, where durable and sustained ACR 20, 50, and 70 responses were observed through 24 months. The proportion of patients reaching a good status of the disease (as measured by DAS28-derived criteria such as LDAS and remission) was maintained through 24 months and the progression of structural damage in year two was significantly reduced compared to year one (AIM).[14,15] In addition, among the patients who achieved an ACR 20 (but not ACR 50/70) at 6 months, the proportion of abatacept treated patients who developed an ACR 50 at one year was approximately three-fold higher compared to patients on placebo and the proportion that developed an ACR 70 was approximately ten-fold higher. Of the patients who achieved LDAS (but not remission) at 6 months, 36% on abatacept vs. 0% on placebo went on to achieve DAS28-defined remission at one year.[16]

Data available from the two year open label extension of these clinical trials show a good retention rate with abatacept. Specifically, the retention rate was around 80% in AIM trial and around 70% in ATTAIN trial.[14,15] A subgroup analysis of ATTAIN suggested that the efficacy of abatacept was similar regardless of previous failure with one or two TNF-blocking agents or after primary or secondary failure for efficacy with TNF-blocking agents.[17] However, the size of the analyzed subgroups was small and definitive conclusions could not be drawn. In addition, in routine clinical practice, patients treated with a new biologic agent like abatacept may be willing to stay longer on treatment than biologic-naïve patients,[9] since they already failed other biologics. These characteristics of abatacept are also acknowledged by the scientific community, in the latest consensus statement on RA therapies.[18]

Whether these dynamics of abatacept effect, which seem different from those of TNF-blocking agents is linked to its mechanism of action through the selective inhibition of co-stimulatory pathway in T-cell activation is still a matter of debate. Nevertheless, a validation of the favorable long-term retention rates with abatacept in routine clinical practice is proposed in an observational setting in Europe and Canada, in a number of countries where abatacept (Orencia) is available on the market and reimbursed (i.e. Germany, Austria, Belgium, Czech Republic, Greece, Italy, the Netherlands, Ireland, Denmark, France, Spain, Switzerland and Canada). Participating countries will need to fulfill both conditions (marketing authorization and reimbursement), in order to ensure that eligible patients have access to the drug and thus the study sample is representative of the abatacept-treated RA patients in that specific country.

In this protocol, we propose a design to validate the long term results of abatacept therapy found in clinical trials. Specifically, we plan to study the treatment effect of abatacept in routine clinical practice to investigate the patient retention and the determinants which affect retention. We will also study patients' experience after they switch from abatacept to other treatment regimens and after they switch from abatacept IV to abatacept SC. In addition, we will explore the possible relationship of patient discontinuation with disease activity, satisfaction with treatment outcomes, and other experiences related to their RA therapies. The study will be conducted through a representative sample of rheumatologists in participating countries for a planned duration of 7 years maximum. The data will be analyzed periodically and reported to the scientific community.

The proposed study will provide relevant information that will help understanding treatment patterns in RA, crucial for establishing the place of abatacept in the treatment pathway. These patterns may vary among countries due to differences in market access and other specificities of the respective health care systems. In addition, such differences are also determined by the heterogeneity of recommendations and clinical guidelines from local professional associations. The recommendations are not only based on evidence-based medicine but also on "expert opinion". The data provided by the proposed study will also be informative to these guidelines and recommendations in Europe and Canada.

In Canada, abatacept was approved since 29 June 2006 in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs and/or to Tumor Necrosis Factor antagonists.

In Switzerland, abatacept was approved since August 2007 for reducing signs and symptoms, improving physical function and reducing the rate of progression of structural damage in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to a Disease-Modifying Anti-Rheumatic Drugs, such as methotrexate or tumor necrosis factor (TNF) blocking agents.

In Europe, a recent change in abatacept SmPC occurred on 1st July 2010. Orencia is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who responded inadequately to previous therapy with one or more Disease-Modifying Anti-Rheumatic Drugs including methotrexate or TNF-alpha inhibitor.

In order to improve the precision of analyses performed in the subgroup of patients treated with Orencia in MTX inadequate responders, the study enrolment period will be extended for a maximum of 24 months, up to June 2013 in Europe. This will provide relevant information on patients in different lines of RA treatment.

In addition, to describe the potential changes in treatment pattern over time, the enrolment period will be extended for a maximum of 24 months, up to December 2013 in subgroup of patients treated with Orencia in TNF Inadequate Responders, in Europe.

As part of life-cycle management, BMS has developed a new abatacept formulation with the same active pharmaceutical ingredient which is enables to be administrated via the subcutaneous (SC) route. The non-inferiority phase IIIb study, ACQUIRE, demonstrated that abatacept SC provides efficacy and safety comparable with IV abatacept, with low immunogenicity and high retention rate, consistent with the established IV abatacept profile. Rate of injection site reactions were low[19].

The SC route of administration will allow for self-administration by patients, thereby providing greater prescribing flexibility and patient acceptance. This formulation was approved on 27 February 2012 in Switzerland and on 5 October 2012 in Europe.

1.1. Research Question

Abatacept has recently become available in the treatment of rheumatoid arthritis. It is critical to understand the long term retention of patients treated with abatacept (regardless of route of administration) in routine clinical practice, and the treatment experience and outcomes after switching to a biologic or conventional DMARD with the discontinuation of abatacept therapy.

1.2. Product Development Rationale

1.2.1. Name and Description of Investigational Product

Abatacept is a recombinant fusion protein consisting of the extracellular domain of human CTLA4 and a fragment (hinge - CH2 - CH3 domains) of the Fc domain of human IgG1 that has been modified to prevent complement fixation and antibody-dependent cellular cytotoxicity.

1.2.2. Pharmacologic Class of New Drug and Mechanism of Action

Abatacept is the first drug in a new class of agents termed "selective costimulation modulators". Activation of naive T cells during an immune response requires two stimuli from antigen presenting cells (APC). The first signal is antigen specific and is mediated through the T cell receptor. The second, or costimulatory signal is not antigen specific and is delivered following the engagement of a costimulatory ligand on the APC with a cognate receptor on the T cell. A key costimulatory receptor on T cells is CD28. CD28 is constitutively expressed on resting T cells and binds to both B7-1 (CD80) and B7-2 (CD86) on the APC.[20,21,22,23] A costimulatory signal is required for the full activation of naive T cells and may be required for the survival of auto-immune effector T cells.[24,25] Abatacept binds specifically to B7-1 and B7-2 and hence modulates the CD28-mediated costimulation of T cells by these molecules.

1.2.3. Therapeutic Indication

In Europe, abatacept, in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have had an insufficient response or intolerance to other disease-modifying anti-rheumatic drugs including at least one tumour necrosis factor inhibitor.

From 1st July 2010, in Europe, abatacept, in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who responded inadequately to previous therapy with one or more Disease-Modifying Anti-Rheumatic Drugs including methotrexate or TNF-alpha inhibitor.

In Canada, abatacept is indicated for reducing signs and symptoms, including clinical responses, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs and/or to Tumor Necrosis Factor antagonists. Abatacept may be used as monotherapy or in combination with DMARD therapy. Abatacept received marketing authorization in the EU on 22-May-2007, in Canada on 29-June-2006

In Switzerland, abatacept is indicated for the treatment of erosive rheumatoid arthritis in combination with methotrexate in methotrexate-naive patients. It is indicated for reducing signs and symptoms of RA, improving physical function and reducing the rate of progression of structural damage in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate (MTX) or a tumour necrosis factor (TNF)-inhibitor. In combination with a DMARD therapy, primarily with methotrexate.

In Europe, abatacept in combinaison with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who responded inadequately to previous therapy with one or more Disease- Modifying Anti-Rheumatic Drugs including methotrexate or TNF-alpha inhibitor.

In addition, abatacept SC received marketing authorization on 27 February 2012 in Switzerland and on 5 October 2012 in Europe.

1.3. Rationale

Abatacept has demonstrated a good retention rate (70% at two years in ATTAIN and 90% at two years in AIM) as well as sustained and durable long-term response in the double-blind and open-label phases of the clinical trials. In the two-year LTE of these trials, the ACR response rate was maintained over time and an improvement in disease status such as LDAS and remission was also noticed.

The studies performed with abatacept in different patient populations (i.e. MTX-incomplete responders or TNF-alpha inhibitor incomplete responders, early or established disease) suggest that absolute magnitude of response, the retention rates on long term and safety/tolerance look better when abatacept is used earlier in the treatment paradigm.

There is a need to confirm such findings in routine clinical practice. In addition, there are no data from routine clinical practice on treatment experience when patients switch to other biologic agents after failure with abatacept. These data are crucial to establish abatacept as an important alternative in the therapy of RA.

To further understand patient retention, it is important to identify the major determinants of patient retention and their association with outcomes (at baseline and during the study period) and prior treatment experience (e.g. past failure with 1, 2, or 3 TNF -blocking agents due to inefficacy or safety, etc.). The association of these factors with patient satisfaction are also valuable to explore.

In general, the efficacy and safety of abatacept have been shown in randomized clinical trials[26,27,28] but there is limited evidence of the effectiveness of abatacept in contemporary clinical practice[29]. Data from the German registry "Biologics in RA therapy" (RABBIT) show that patients from clinical trials meaningfully differ from patients seen in routine clinical practice. Zink et al. found that randomized clinical trials reflect only a minor proportion of patients treated with biologic agents in routine care.[30]

Moreover, in today's cost-conscious health-care environment, drug prescribers and regulators have increasing expectation that pharmaceutical manufacturers who had secured product marketing authorization investigate the performance of their drugs in routine clinical practice as well. Knowledge about efficacy and safety gained in controlled experimental environment should be supplemented with an understanding of the effectiveness, i.e. drug performance under routine clinical conditions.[31] One avenue to achieve these objectives is through observational or non-interventional trials.

In some countries (e.g. the Netherlands, France) abatacept's reimbursement status at the approved price is conditional upon the demonstration of its value within 3 or 5 years after its launch, when a full review with evaluation of its cost-effectiveness is performed, based on. abatacept data in local, routine clinical setting.

For all the above reasons, a prospective, observational study is proposed for a number of European countries (Austria, Belgium, Czech Republic, Greece, Italy, Ireland, the Netherlands, Denmark, France, Spain, Switzerland), and Canada.

In addition, at present there are no data on treatment experience when patients switch to other biologic agents after failure with abatacept. Obtaining such data from routine clinical practice is key to establish abatacept as an important alternative in the therapy of RA.

With news biologics approved in RA in the last 2 years and the recently published EULAR recommendations for treatment in RA[32], a change in treatment pattern may occur in routine clinical setting.

The enrolment of patients treated with abatacept as second or further biologics DMARDs will restart over a period of a maximum duration of enrolment of 24 months (and at the latest up to December 2013). This will allow to:

- Describe the potential changes in treatment pattern over time in clinical practice by comparing the patients enrolled in the study during the period 2008-2010 to patients enrolled in the study during the period 2011-2013 in Europe (Germany, Italy, Austria, The Netherlands, Greece)

- To provide relevant information on patients in different lines of RA treatment including all participating countries (i.e. France, Spain and Switzerland)

Baseline assessments for all patients entering the survey are mandatory in order to achieve the objectives. Therefore, in countries where patients can only participate in an observational study once they are already on treatment with the study drug, patients should be included only if baseline data are available and can be collected retrospectively.

Therefore, this study is proposed to collect and analyze data from a sample of prospectively recruited patients to explore the answers and achieve the objectives outlined in this section.

2. STUDY OBJECTIVES

2.1. Primary Objective

To estimate the retention rate of RA patients treated with abatacept (regardless of route of administration) over 24 months in routine clinical practice in every participating country and their combinations whenever appropriate, depending on the treatment line (i.e, abatacept as second or further biologics DMARDs or abatacept as first line of biologics DMARDs).

2.2. Secondary Objectives

1. To identify the major determinants (including prior RA treatment experience with biologics and clinical outcomes, such as DAS28, HAQ-DI, CDAI, SDAI, and their derived criteria) of treatment discontinuation of RA patients treated with abatacept in this study.
2. To estimate the distribution of time-to-discontinuation of abatacept therapy for each major determinant of treatment discontinuation, overall, depending on the treatment line

3. To estimate the association of prior RA treatment experience and clinical outcomes during the treatment course with patient reported outcomes (Patient satisfaction, Pain, Patient's Global Assessment).
4. To summarize the treatment experience and outcomes after switching to a biologic or conventional DMARD for patients who discontinue abatacept therapy.

2.3. Exploratory objective

To describe the potential changes in treatment pattern over time in clinical practice by comparing the patients treated with abatacept as second or further biologics DMARDs, enrolled in the study during the period 2008-2010 to patients enrolled in the study during the period 2011-2013 in Europe (Germany, Italy, Austria, The Netherlands, Greece)

To describe the treatment experience and outcomes after switching from abatacept IV to abatacept SC formulation.

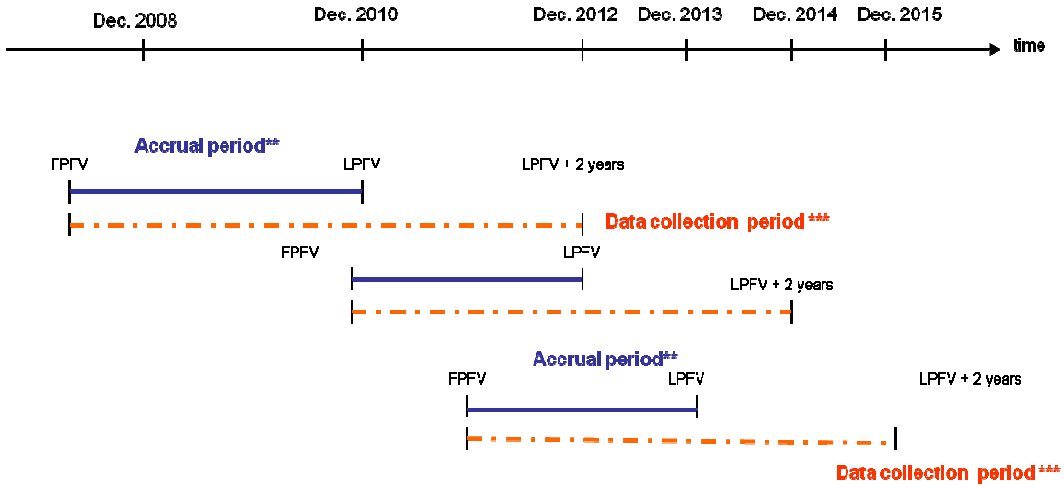
3. STUDY DESIGN AND EVALUATION

3.1. Study Design

This is a non-interventional, multicenter, prospective, longitudinal survey of RA patients treated with abatacept according to the SmPC in Europe, and the Product Monograph in Canada,.

A total of 2825 patients is expected to be enrolled in the study. The patients will be enrolled prospectively according to participating country regulatory requirements either at initiation of abatacept IV treatment or will have been treated with abatacept IV for maximum 3 months, over a period of a maximum duration of enrolment of 18-24 months for each treatment line of abatacept and for each enrolment period; and at the latest in December 2013. The diagram below (see Figure 1) describes the different study periods:

Figure 1 Study periods description



* Except in Canada where the Product Monography includes the indication in first line of biologics DMARDs

** In each country the enrolment period duration will be no more than 2 years

*** The data collection period includes the enrolment period and the follow-up period (max 2 years by patient)

In countries where patients can only participate in an observational study once they are already on treatment with the study drug, patients should be included only if baseline data are available and can be collected retrospectively.

Each patient will be followed up for 2 years with a frequency according to routine local clinical practice. Data will be collected retrospectively at baseline (socio-demographics, disease history and characteristics, prior RA treatments such as biologic or conventional DMARDs, and other concomitant medication) and prospectively (clinical and patient-reported outcomes) at baseline and during visits to the treating physicians. Assessment schedules and outcomes will be performed according to routine local clinical practice. It is estimated that patients will be evaluated every 3 months. If available, data at additional visits will also be collected (e.g. at time of drug administration). Patients who discontinue abatacept treatment regardless of the reasons and time of discontinuation will be followed up for 6 months after discontinuation if feasible. Patients who changed abatacept route of administration from IV to SC during the follow up period will be followed up to 2 years. This change is not considered as a discontinuation of treatment, but as a treatment modification. Patient recruitment will be both from outpatient visits and one-day hospitalizations if applicable.

3.2. Study Population

3.2.1. Sampling Plan

The study will be proposed to rheumatologists at either hospital or private practice. Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis.

A two-stage recruitment strategy will be implemented, with patient recruitment following a center selection procedure.

Selection and recruitment of a national sample of centers:

A general list of rheumatologists (centers) will be compiled (BMS data on file) in each country:

- Approximately 700-1400 in Germany
- Approximately 200 in Austria
- Approximately 242 in Belgium
- Approximately 52 in Czech Republic
- Approximately 300 in Greece
- Approximately 880 in Italy
- Approximately 230 in the Netherlands
- Approximately 55 in Ireland
- Approximately 120 in Denmark
- Approximately 231 in Canada
- Approximately 700 in France
- Approximately 800 in Spain
- Approximately 70 in Switzerland

A letter will be sent to centers with an overall description of the study and an enquiry on potential interest to participate. Rheumatologists will be invited to participate in the study by a letter signed and mailed by Bristol-Myers Squibb. It is assumed that a minimum response rate of 10-20% will be obtained (as not all centers on the general list of centers are treating patients with biologics). To estimate the actual response rate, a small number of invitation letters will be sent to a subset of rheumatologists first. The number of additional letters to be sent out in order to recruit the required number of rheumatologists will be determined accordingly. Rheumatologists will be stratified by country. Obtained responses, either positive or negative, will be tracked and recorded. If the targeted number of rheumatologists is not reached after mailing, non-responding rheumatologists will be contacted by phone, within each stratum, until the targeted number is reached.

Rheumatologists will be requested to provide a brief description to characterize their center: by treatment setting (private rheumatologists or hospital, or institutions), geography (large city or town, ≥100,000 inhabitants, vs. small town), type of institution (academic vs. non academic), number of physicians providing care to RA patients, and volume of patients. Site eligibility will be determined based on site willingness to participate.

Selection of patient cohort:

Site initiation will take place for each rheumatologist agreeing to participate. When the site is initiated, the participating rheumatologist will have to collect data and include each subsequent RA patient, who at the rheumatologist's discretion is to be treated with abatacept IV, up to a maximum of 10 patients (for each treatment line of abatacept) over an accrual period of no more

than 2 years for each treatment line of abatacept and for each enrolment period, up to December 2013. Actual recruitment will depend on the volume of patients managed at each center.

To ensure that the patient sample is representative for the RA population, the targeted population of physicians should be representative for the rheumatologists involved in the treatment of RA patients.

The data of the rheumatologist sample will be closely examined by comparing the sample to the local rheumatologist population (BMS data on file) with respect to the characteristics detailed above (see Selection and recruitment of a national sample of centers) to determine the degree to which generalizabiliy of study samples (both rheumatologists and patients) may be established. The findings as well as the assessment of the potential sources/direction of biases introduced by non-random samples will be reported. The demographics of study respondents vs. non respondents will be also assessed.

National registry:

Participation of Rheumatologists in the study as defined before is based on a voluntary basis. If a national registry is already implemented or planned in the participating country, one can anticipate that a large part of the invited rheumatologists will refuse to participate to the study to avoid collecting the same data twice. In that case this sampling process should not be applied. This situation was identified in Czech Republic and in Belgium. Therefore in these countries data will be extracted from the registries to be integrated in the statistical analysis of the IM101-151 study.

The major part of rheumatologists prescribing biologics are participating to the national registry and we assume that they are representative for the rheumatologists treating RA patients. A sample of Rheumatologists involved in the registry and who accepted to participate in IM101-151 study will collect specific data of the first subsequent patients fulfilling the inclusion and exclusion criteria of this study (see sections 3.3. 3.4) .

3.3. Inclusion Criteria

- Male or female subjects of more than 18 years old
- Patients with a diagnosis of established moderate to severe active RA (as per the American College of Rheumatology revised criteria, 1987)[33], who at their physician's discretion are treated with abatacept IV according to the SmPC in Europe and the Product Monograph in Canada (initiating or already on treatment for maximum 3 months) and for whom baseline characteristics are available

3.4. Exclusion Criteria

- Patients who are currently included in any interventional clinical trial in RA.

3.5. Criteria for Evaluation

Assessments:

- Baseline (at 1st administration of abatacept IV).- the baseline data can be collected at abatacept IV treatment initiation or retrospectively within maximum 3 months following the first administration:
    - Socio-demographics (age, sex, employment status)
    - Disease history & characteristics
    - Prior RA treatments (biologic and conventional DMARDs, other concomitant medication)
- Prospectively, inclusive of baseline (as defined before):
    - Clinical outcomes: DAS28 and its individual components (SJC, TJC, CRP/ESR), CDAI, SDAI[34], HAQ-DI, Physician's global assessment
    - Patient-reported outcomes: Patient Global Assessment, Patient satisfaction, Pain (see Appendix)
    - Abatacept dosage and frequency of administration (IV or SC formulation)
    - Reasons and subsequent RA treatment with conventional/biologic DMARDs if abatacept treatment was discontinued
    - Reason for change in the route of administration of abatacept (from IV to SC)
    - Other concomitant medication for RA (doses, frequency)
    - Adverse Drug Reaction

3.6. Discussion of Biases and Study Limitations

3.6.1. Rheumatologist Selection Bias

Two potential rheumatologist selection biases can be anticipated: (1) participation in the study is on a voluntary basis, (2) rheumatologists "interested" in the study could be preferentially those having in their practice a more significant number of patients corresponding to the target population.

A minimum 10% participation rate is expected (as not all centers on the general list of centers are treating patients with biologics and the list of centers that prescribe biologics cannot be identified from the general list of centers before mailing). However, as detailed above (see section 3.2.1 Sampling Plan), the data of the rheumatologist sample will be compared to the local rheumatologist population to determine the degree to which generalizabiliy of study samples (both rheumatologists and patients) may be established. The findings as well as the assessment of the potential sources/direction of biases introduced by non-random samples will be reported. The demographics of study respondents vs. non-respondents will be also assessed.

3.6.2. Patient Selection Bias

To prevent rheumatologists from selecting "particular" patients, they will be asked to select the first series of consecutive patients (up to 10 for each treatment line of abatacept) fulfilling inclusion criteria and visiting over an accrual period of no more than 2 years. Some rheumatologists are likely not to adhere strictly to this requirement. However, if the reason is lack of time or oversight, or any reason independent of the evaluation criteria, it will not involve a selection bias.

4. DATABASE METHODOLOGY

4.1. Variable Definitions

4.1.1. Description of derived variables – derived clinical outcomes

Detailed definitions of the following derived efficacy criteria are provided in Appendix 1 (see Appendix 1):

- Disease Activity Score 28 (DAS28) based on CRP (DAS28-CRP) or ESR (DAS28-ESR)
- EULAR criteria based on DAS28 (non/moderate responders versus good responders, or non-responders versus moderate/good responders)[35]
- EULAR criteria based on DAS28:
    - Low Disease Activity State (LDAS) (DAS28 $\leq$ 3.2)
    - Remission State (DAS28 < 2.6)
- Health Assessment Questionnaire-Disability Index

The derived clinical outcomes will be used as calculated in Appendix 1 (see Appendix 1) but also according to the following definitions (see Appendix 2[36]). The Statistical Analysis Plan (to be developed separately later) will give more detail.

1. **Response:** expressed as % of patients achieving EULAR response criteria at each time point;
2. **Status**: expressed as % of patients achieving LDAS, remission at each time point;

4.2. Statistical Analysis plan

All the questionnaire parameters and evaluation criteria (see section 3.5) will be summarized using descriptive statistics in addition to statistical modelling if needed. Specifically, (1) the sample size, mean, standard deviation, minimum, median, mode, maximum, 95% CI and the number of missing data will be provided for continuous variables; (2) the frequency and percentage by modality, 95% CI and number of missing data will be provided for discrete variables; and (3) the distribution and median of time-to-event data will be analyzed using Kaplan-Meier product limit estimator. The 95 % CIs of the estimates will also be presented. A detailed statistical plan will be developed and approved before database lock.

Data from different countries may be pooled if appropriate, including data from registries.

The analysis will be performed for each participating country. Data from different countries may be pooled if appropriate.

The analysis will be performed separately depending on treatment line of abatacept.

More specifically, the following analysis will be performed:

Primary Analysis:

- The retention rate of RA patients treated with abatacept over 24 months in routine clinical practices will be estimated for each country separately and pooled (if appropriate), depending on treatment line of abatacept
- A change of abatacept route of administration from IV to SC during the follow up period will be not considered as a discontinuation of treatment, but as a treatment modification.

Secondary Analysis:

Information of Participating Centers:

- Descriptive analysis of the participating physicians and assessment of the representativeness with national statistics will be performed. Physicians from the different datasets (respondents accepting participation, respondents refusing participation, non respondents – active and inactive physicians) will be compared to assess the generalizability of the results.

Determinants of Treatment Discontinuation:

- The major determinants of treatment discontinuation of RA patients treated with abatacept in this study will be identified and summarized.
- The retention rate will be estimated for each determinant. The corresponding 95% CI will also be provided.
- The distribution and median of time-to-discontinuation of abatacept therapy for each major determinant of treatment discontinuation will be estimated using Kaplan-Meier method. The corresponding 95% CI will also be provided. In case of missing data at 24 months, the last data point available will be used for this analysis.

Patient Reported Outcomes:

- The patient reported outcomes, such as patient satisfaction, pain, patient's global assessment, etc., of RA patients treated with abatacept in this study will be summarized.
- Relationship between patient reported outcomes, and the derived clinical outcomes as well as the prior RA experience will be estimated.

Treatment Experience/Outcomes after Switching:

- The treatment experience/outcomes (choice of therapy, dose, duration) after switching to a biologic or conventional DMARD for patients who discontinue abatacept therapy will be summarized.

Exploratory Analysis:

Description of potential changes in patient characteristics and in treatment pattern over time in clinical practice in patients treated with abatacept as second or further biologics DMARDs, enrolled during the period 2008-2010 and in patients enrolled during the period 2011-2013 in Europe (Germany, Italy, Austria, The Netherlands, Greece)

- Relationship between abatacept discontinuation and the derived clinical outcomes and the prior RA experience will be investigated.
- Cox proportional hazard regression model will be used to identify factors which contribute to patient discontinuation. The analysis will be conducted at 6 and 12 months and results will be compared to analysis results at 24 months.
    - The distribution of time-to-discontinuation estimated in subgroups of patients based on derived clinical outcomes and prior RA treatment experiences (e.g., patients with incomplete response to 1 or 2 or 3 previous TNF blocking agents) will be compared using a log-rank test at a 95% significance level.
    - Decision-tree method will be utilized to explore the combinations of criteria that can possibly explain the retention at two years.

Description of switch from abatacept IV to abatacept SC including reasons for changing route of administration.

Description of treatment experience/outcomes after switching from abatacept IV to abatacept SC.

Reporting of Interim Analysis

- Interim analysis may be conducted during the follow-up period (e.g. after LPFV for the description of patient population and 6 months and 1 year following LPFV for the preliminary analysis of primary criteria).
- Each interim statistical analysis will be performed depending on treatment line of abatacept.

4.3. Sample Size

4.3.1. Patient sample requirement

The primary objective of this study is to estimate the retention rate of RA patients' treatment with abatacept over 24 months in routine clinical practices in each participating country with a sufficient level of precision.

Based on the extent of biologics' use in each participating country (BMS market research data) and feasibility considerations, it is estimated that each country will be able to enrol the following number of patients over the planned 2-year accrual period (for each treatment line of abatacept and for each enrolment period). The figures vary between 26% and 45% of the estimated total number of patients to be treated with abatacept in the respective countries (see Table 1) in second or further line:

Table 1 Patients number expected by country and by study period

Countries	Number of patients in second or further treatment line of abatacept*after failure of one or more TNF *(Accrual period 2008- 2010)*		Number of patients expected in first treatment line of abatacept**after failure to DMARD including MTX *(Accrual period up to June. 2013)*	Number of patients expected in second or further treatment line of abatacept* *(Accrual period up to Dec 2013)*
	Expected	Real (cut off Dec 2010)		
Germany	370	*398*	150	150
Italy	200	*235*	100	100
Greece	120	*152*	60	60
The Netherlands	100	*34*	25	25
Belgium	60	*15*	50	NA
Austria	50	*51*	20	25
Ireland	30	*0*	NA	NA
Denmark	25	*7*	NA	NA
Canada	200***	*233*	NA	NA
France	NA	*NA*	220	400
Spain	NA	*NA*	120	120
Czech Republic	20	*26*	NA	NA
Switzerland	NA	*NA*	10	40
TOTAL	**1175**	**1151**	**755**	**920**

* In Europe, abatacept in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have had an insufficient response or intolerance to other disease-modifying anti-rheumatic drugs including at least one tumour necrosis factor inhibitor.

** In Europe, abatacept, in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who responded inadequately to previous therapy with one or more Disease-Modifying Anti-Rheumatic Drugs including methotrexate or TNF-alpha inhibitor.

*** In Canada, abatacept is indicated for reducing signs and symptoms, including clinical responses, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs and/or to Tumor Necrosis Factor antagonists. Abatacept may be used as monotherapy or in combination with DMARD therapy.

Above initial assumptions were estimated based on existing data. These assumptions would be updated according to the real extent of biologics' use in each participating country and to evolution of feasibility of the study during the enrolment period. In some countries this estimated number of enrolled patient could be either increased or decreased.

The overall number of patients in this study from the countries listed above will be around 2825 patients.

The estimated 2-year retention rate was between 60% and 70% based on the ATTAIN study[26] in patients who had an inadequate response to at least one tumour necrosis factor inhibitor corresponding to an abatacept discontinuation rate between 30% and 40 %. Since the retention rate in clinical practice is usually lower than that in randomized controlled trials[11], we hypothesize the retention rate in this study will be about 60%. With a sample size of 370 patients in Germany, one can expect the observed retention rate to be within 60% ± 5%.

Assuming that the sample size of each country will vary from 20 to 400 patients who had an inadequate response to at least one tumour necrosis factor inhibitor, the level of precision for the country-specific estimates will be proportionally decreased. The data from different countries may be pooled if appropriate.

The estimated 2-year retention rate was around 80% based on the AIM study[37] in abatacept-treated patients who had an inadequate response to Methotrexate corresponding to an abatacept discontinuation rate of around 20% Since the retention rate in clinical practice is usually lower than that in randomized controlled trials[11], we hypothesize the retention rate in this study will be about 65% to 75%. Assuming that the sample size of each country will vary from 10 to 220 patients who had an inadequate response to at least one DMARD including Methotrexate or TNFα inhibitor, the level of precision for the country-specific estimates will be low. Therefore the data from countries may be pooled to increase the precision up to 3.0 to 3.5%.

4.3.2. Rheumatologist sample requirement

Internal data (BMS data on file) show that hospital based rheumatologists declare an average of 20 RA patients cared for per month and private practice rheumatologists declare an average of 12 RA patients cared for per month. It also appears that a majority of these RA patients are treated with a DMARD. The average number of patients that participating rheumatologists will be able to include during the accrual period was estimated at 6 patients for patients who had an inadequate response to at least one tumour necrosis factor inhibitor. . To take into account differences in recruitment capacity of the rheumatologists, the duration of the accrual period was set to 2 years and the maximum patient accrual will be set to 10 for each treatment line of abatacept.

To estimate the number of sites to be invited to participate in the study, we assume a minimum of 10% participation rate and among the participating sites, a minimum of 20% of inactive sites. However, as detailed in section 3.2.1 Sampling Plan, the actual number of invited sites per country will depend on the response rate obtained after contacting an initial small set of centers. A total of 2825 patients will be enrolled over a maximum 18-24 months period (for each

treatment line of abatacept and for each enrolment period) to follow-up over 2 years; and at the latest in December 2013.

4.4. Collected data

4.4.1. Participating rheumatologists

- Rheumatologist identification (center number, name, surname, sex, address, e-mail address)
- Description of the center:
    - Treatment setting (community vs. hospital)
    - Geography (region, large city or town (> 100,000 inhabitants) vs. small towns)
    - Type of institution (academic vs. non-academic)
    - Number of rheumatologists providing care to RA patients
    - Volume of patients

4.4.2. Patients

- Patient identification (N° center, N° patient)
- Data collected retrospectively at baseline (first administration of abatacept IV)
    - Socio-demographics
    - Disease history and characteristics
    - Prior RA treatments (biologic and conventional DMARDs, other concomitant medication)
- Data collected prospectively from baseline:
    - Clinical outcomes: DAS28 and its individual components (SJC, TJC, CRP/ESR), HAQ-DI, Physician's global assessment,
    - Patient-reported outcomes: Patient Global Assessment, Patient satisfaction, Pain (see Appendix)
    - Abatacept dosage and frequency of administration (IV and SC formulation)
    - Reasons and subsequent RA treatment with conventional/biologic DMARDs if abatacept treatment was discontinued for 6 months after discontinuation
    - Reason for change in the route of administration of abatacept (from IV to SC)
    - Other concomitant medication for RA
    - Adverse Drug Reactions

4.5. Data Set Description

4.5.1. Patient data sets

The data set will consist of all patients recruited, excluding those with missing data related to the patient's sex and age**.**

4.5.2. Rheumatologist data sets

Due to the sampling technique, the sampling database will be split into 3 different rheumatologist data sets:

Responding rheumatologists agreeing to participate in the study

Responding rheumatologists refusing to participate in the study

Non-responding rheumatologists

Rheumatologists agreeing to participate will be further split into 2 different populations:

Active rheumatologists, who included at least one evaluable patient

Non-active rheumatologists.

5. STUDY CONDUCT

5.1. Ethics

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and will be consistent with International Conference on Harmonization Good Clinical Practice (ICH GCP), Good Epidemiological Practices (GEP) and applicable regulatory requirements taking into account that this is an observational, non-interventional trial.

The study will be conducted in compliance with the protocol.

The rights, safety and well-being of the study patients are the most important considerations and should prevail over interests of science and society.

Study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s).

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

Systems with procedures that assure the quality of every aspect of the study will be implemented.

The study will be conducted according to the local regulations and ethicals considerations applicable.

The data collection method will comply with the privacy and confidentiality requirements applicable in local participating countries. There will be agreement between BMS and the investigators regarding the confidentiality of the data. Qualified representatives on behalf of BMS may monitor the patient medical records in order to determine the accuracy of the data, and these persons will treat the information as confidential. The patient identity (name, address and other identifiers) will not be collected and will remain confidential. In the database of the CRO in charge, patients will only be referred to by a code number. Only the investigators will be able to link the code number to the name of the patients.

5.2. Responsibilities within the Study

5.2.1. Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by BMS. The protocol authors should not implement any deviation or change to the protocol without prior review.

5.2.2. Monitoring for protocol compliance

Data reported on the CRF must be consistent with the source documents and plausible.

The confidentiality of records that could identify patients must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

Representatives of BMS may be allowed to visit sites to assess the data quality and study integrity. On site, they will indirectly review study records, via the participating physician, compare them with source documents, discuss the conduct of the study with the physician, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed indirect access to CRFs, source documents and other study files.

5.2.3. Records and reports

A correction must be made by striking through the incorrect entry with a single line and entering the correct information adjacent to the incorrect entry. The correction must be dated, initialled and explained (if necessary) by the person making the correction and must not obscure the original entry.

The completed CRF must be promptly reviewed, signed, and dated by the participating physician.

5.2.4. Study Organization

The following roles and responsibilities are detailed below (see Table 2):

Table 2 Study organization

BMS Staff	GEOR Department GMA Local medical departments	Design of the protocol and the data collection sheets, involvement in the data analysis in the presentation of the results and in their publication. Implementation and conduct of the study. Perform the analysis, report writing, responsible for publication writing, communication of the results.

5.3. Reports and Publications

The results obtained within the framework of the study are the exclusive property of BMS. They will be presented and discussed with the Scientific Committee, and after validation, diffused with the investigators of the study in the form of a bulletin of synthesis. They will also be the object of abstracts sent to scientific congresses and articles sent to scientific reviews.

5.4. Data Retention and Archiving

The participating physician will retain copies of CRFs, and the original source documents for the maximum period required by applicable regulations and guidelines, or Institution procedures, or for the period specified by the Sponsor, whichever is longer. The participating physician must contact BMS prior to destroying any records associated with the study.

BMS will notify the participating physician when the trial records are no longer needed.

If the participating physician withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another participating physician). Notice of such transfer will be given in writing to BMS. Location of final database and supporting documentation will be outlined in final report.

5.5. Adverse Event Reporting

Adverse event ascertained during BMS- sponsored observational studies should be reported (see appendix 3) in accordance with the recommendations of the CIOMS V working group, the guideline for Good Pharmacology Practices, and locally applicable regulations:

Adverse Event related to BMS drugs ascertained in observational studies should be submitted as individual serious event reports to local health authorities in accordance with local requirements. Where local regulations are silent concerning safety reporting in observational studies, serious, unexpected adverse events related to BMS drugs will be submitted to the health authorities in an expedited manner.

The physician will fill an adverse event data collection form (in the study kit) and will send it as soon as possible and no later than 24 hours of being aware of the event to local BMS Pharmacovigilance Department.

The participating physician shall also report individual adverse events ascertained in the study to the local health authority according to local requirements.

Adverse event reports will be sent to (see Table 3):

Table 3 Pharmacovigilance contacts details

Country	Contact Person	Email	Tel	Fax
Austria	Christina Ekholm	safety_Austria@bms.com christina.ekholm@bms.com	0043 1 60 143 0	0043 1 60143.229
Belgium	Patricia Vandamme	safety_belgium@bms.com patricia.vandamme@bms.com	0032.2.352.7278	0032.2.352.7566
Netherlands	Gert Jan van Beuge	safety_netherlands@bms.com gertjan.vanbeuge@bms.com	0031 348 574 274	0031 348 574 357

Table 3 Pharmacovigilance contacts details

Country	Contact Person	Email	Tel	Fax
		medischeafdeling@b-ms.nl		

(See Appendix 3)

6. GLOSSARY OF TERMS AND LIST OF ABBREVIATIONS

6.1. Glossary of Terms

No glossary of terms

6.2. List of Abbreviations

Term	Definition
ACR	American College of Rheumatology
BMS	Bristol-Myers Squibb
CI	Confidence Interval
CRO	Clinical Research Organisation
CRF	Case Report Form
CDAI	Clinical Disease Activity Index
DAS	Disease Activity Score
DAS-28	Simplified Disease Activity Score (based on 28 joints)
DMARD	Disease Modifying Anti-Rheumatismal Drug
EULAR	European League Against Rheumatism
GP	General Practitioner
IV	Intravenous
MTX	Methotrexate
RA	Rheumatoid Arthritis
SC	Subcutaneous
SDAI	Simple Disease Activity Index

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APPENDIX 1 DERIVED EFFICACY CRITERIA AND CLINICAL OUTCOMES

ACR Criteria

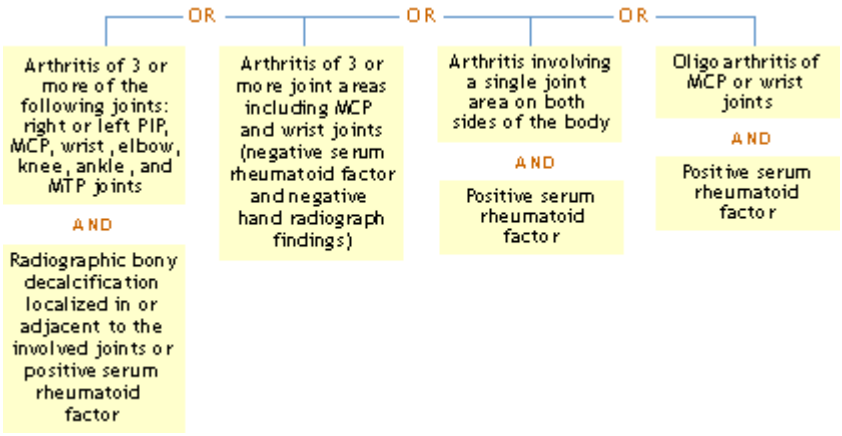
Using history, physical examination, laboratory and radiographic findings (Arnett, Edworthy et al. 1988): [33]

Traditional format:

4 OF THE FOLLOWING MUST BE PRESENT
WITH 1 THROUGH 4 PRESENT A MINIMUM OF 6 WEEKS

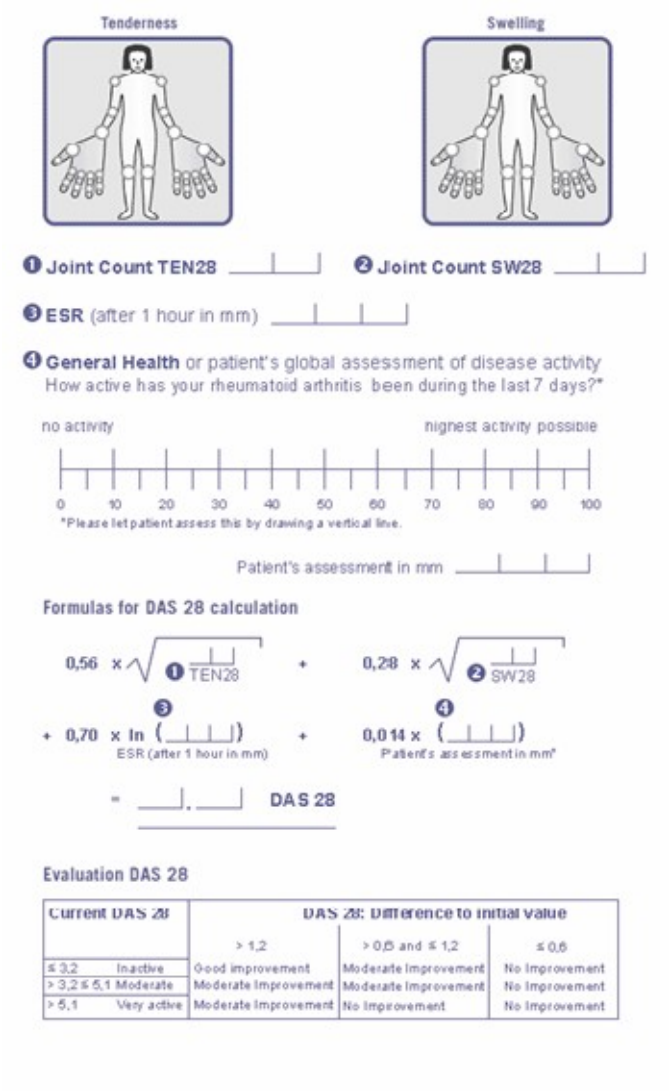
- Morning stiffness ≥ 1 hour
- Arthritis of 3 or more of the following joints: right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints
- Arthritis of wrist, MCP, or PIP joint
- Symmetric involvement of joints
- Rheumatoid nodules over bony prominences, or extensor surfaces, or in juxtaarticular regions
- Positive serum rheumatoid factor
- Radiographic changes including erosions or bony decalcification localized in or adjacent to the involved joints

Classification tree:



DAS-28

The Disease Activity Score (DAS/DAS28) is based upon treatment decisions of rheumatologists in daily clinical practice. DAS/DAS28 values are continuous and normally distributed. The DAS has been validated in clinical trials (van der Heijde, van 't Hof et al. 1993).



The DAS 28 is a continuous measure which is a composite of 4 variables: 28 tender joint count, the 28 swollen joint count, ESR and subject assessment of disease activity measure on a VAS of 100 mm. Scores for disease activity are defined as high (> 5.1); low (≤ 3.2); remission (< 2.6) An alternative calculation formula based on CRP will be used:

DAS28-CRP = 0.56*sqrt(tender28) + 0.28*sqrt(swollen28) + 0.36*ln(CRP +1) + 0.014*VAS + 0.96

Response criteria (EULAR criteria based on DAS28-CRP): Non and moderate responders versus good responders, or non responders versus moderate and good responders

EULAR criteria for Response to treatment (Fransen et al. Clin Exp Rheumatol 2005; 23 (suppl. 39): S93-S99): [36]

	Improvement in DAS28 at evaluation time compared to baseline measurement (absolute difference)		
DAS28 at evaluation time point	1.2 < difference	0.6 < difference ≤ 1.2	difference ≤ 0.6
score ≤ 3.2	**good responder**	moderate responder	non-responder
3.2 < score ≤ 5.1	moderate responder	moderate responder	non-responder
5.1 < score	moderate responder	non-responder	non-responder

- **Status :** Low Disease Activity State (LDAS) (DAS28-CRP ≤ 3.2); Remission State (DAS28-CRP < 2.6)

- Joint Assessments

All joint counts will be performed by a trained clinical assessor with at least one year of experience in performing examinations in clinical trials. Every effort should be made to ensure the same clinical assessor complete the swollen and tender joint counts for each subject. Visits requiring joint assessment should be scheduled with the availability of the clinical assessor taken into account. If the same clinical assessor is unable to complete the joint assessments, then a qualified individual (trained by the original clinical assessor), with overlapping experience may perform the evaluation. Documentation of training and who performed the joint assessments is to be recorded in the source notes. The joint assessor will also be recorded on the appropriate page of the CRF.

- Subject Global Assessment of Disease Activity

Subject global assessment of disease activity (as part of the DAS28-CRP evaluation) is required at each visits until the end of the study. Subject global assessment of disease activity is to be completed using the visual analog scale represented in Appendix 1. The appropriate page of the CRF should be used as the source document for these measurements and must be completed by the subject. Subjects should complete each assessment without reference to the previous assessment(s). The same ten-centimeter ruler should be used for each assessment.

- Physician Global Assessment of Disease Activity

Physician global assessment of disease activity is required at each visit until the end of the study). Physician Global Assessment pages may only be completed by a MD. Physician global assessment of disease activity is to be completed using the visual analog scale represented in Appendix 1. The appropriate page of the CRF should be used as the source document for these measurements and must be completed by the physician, without reference to the previous assessment(s). The same ten-centimeter ruler should be used for each assessment.

- Evaluation of HAQ Disability Index

The scoring conventions for this study are based on the Standard Disability Index of HAQ using the 20 response items. The Standard Disability Index (HAQ-DI) takes into account the patient's use of aids or devices or assistance in the scoring algorithm for a disability category. For each of the eight disability categories there is an AIDS OR DEVICES companion variable(s) that is used to record the type of assistance, if any, a patient uses for his/her usual activities. If either aids/devices and/or assistance from another person are checked for a disability category, the score for this category is set to 2 (much difficulty), if the original score is 0 (no difficulty) or 1 (some difficulty). The HAQ-DI is then calculated by summing the adjusted categories scores and dividing by the number of categories answered

SDAI, CDAI:
Aletaha D, Smolen JS.
The Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) to monitor patients in standard clinical care.
Best Pract Res Clin Rheumatol. 2007 Aug;21(4):663-75)[35]

Table 1. Disease activity indices: calculation and cutpoints of disease activity categories.

Index	Formula	Cutpoints
DAS-28	$0.56 \times \sqrt{(TJC28)} + 0.28 \times \sqrt{(SJC28)} + 0.70 \times \text{lognat}(ESR) + 0.014 \times GH$	$<2.6/<3.2/<5.1$*
SDAI	$SJC28 + TJC28 + PGA + EGA + CRP$	$\leq 3.3/\leq 11/\leq 26$
CDAI	$SJC28 + TJC28 + PGA + EGA$	$\leq 2.8/\leq 10/\leq 22$

Abbreviations: DAS: Disease Activity Score;DAS-28: DAS based on a 28 joint count; CRP, C-reactive protein; EGA, evaluator global assessment of disease activity; ESR, erythrocyte sedimentation rate; GH, global health; PGA, patient global assessment of disease activity; SJC, swollen joint count; TJC, tender joint count.
* Remission vs. Low disease activity/low vs. moderate disease activity/moderate vs. high disease activity GH in mm VAS; SDAI: CRP in mg/dl; SDAI, CDAI: PGA, EGA in cm on a Visual Analogue Scale (VAS).

APPENDIX 2 REPORTING TECHNIQUES[37]

Reporting techniques: Dougados M , Schmidely N, Le Bars M, Lafosse C, Schiff M, Smolen JS, Aletaha D, van Riel P, Wells G. (2009). Evaluation of different methods used to assess disease activity in rheumatoid arthritis: analyses of abatacept clinical trial data. Ann Rheum Dis 68(4):484-9.

ABSTRACT (250/250)

Objectives: To evaluate different methods of reporting response to treatment or disease status for their ability to discriminate between active therapy and placebo, or to reflect structural progression or patient satisfaction with treatment using an exploratory analysis of the AIM (Abatacept in Inadequate responders to Methotrexate) trial.

Methods: A total of 424 active- (abatacept ~10 mg/kg) and 214 placebo-treated patients with RA were evaluated. Methods of reporting included: 1) response (American College of Rheumatology [ACR] criteria) versus state (Disease Activity Score 28 (DAS28) criteria); 2) stringency (ACR20 vs 50 vs 70; Moderate Disease Activity State [MDAS; DAS<5.1] vs Low Disease Activity State [LDAS; DAS28≤3.2] vs DAS28-defined remission [DAS28<2.6]); 3) time to onset (time to first ACR50/LDAS); and 4) sustainability of ACR50/LDAS for consecutive visits). Methods were assessed according to: 1) discriminatory capacity (number of patients needed to study [NNS]); 2) structural progression (Genant-modified Sharp score); and 3) patient satisfaction with treatment. Positive likelihood ratios (LR+) evaluated the ability of the above methods to reflect structural damage and patient satisfaction.

Results: MDAS and ACR20 had the highest discriminatory capacity (NNS=49 and 69). Sustained LDAS best reflected no radiographic progression (LR+ ≥2). More stringent criteria (at least ACR50/LDAS), faster onset (≤3 months) and sustainability (>3 visits) of ACR50/LDAS best reflected patient satisfaction (LR+ >10).

Conclusions: The optimal method for reporting a measure of disease activity may differ depending on the outcome of interest. Time to onset and sustainability can be important factors when evaluating treatment response and disease status in patients with RA.

Key words: rheumatoid arthritis; disease activity; measure.

APPENDIX 3 ADVERSE EVENT NOTIFICATION

1. REPORTING OF ADVERSE DRUG REACTIONS

Timely and complete reporting of safety information assists BMS in identifying any untoward medical occurrence, thereby allowing: (1) protection of safety of patients; (2) a greater understanding of the overall safety profile of the product; (3) recognition of dose-related product toxicity; and (4) adherence to wordwide regulatory requirements.

2. COLLECTION OF SAFETY INFORMATION

In prospective non-interventional / observational studies, Adverse Drug Reactions to a BMS-product are reported to BMS (or designee).
Adverse Drug Reaction (ADR) is defined as a response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function (art 1 (11) of Directive 2001/83/EC).

Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out (ICH E2A Guideline). A reaction, in contrast to an event, is characterized by the fact that a causal relationship between the drug and the occurence is suspected (ICH E2D Guideline).

Adverse Reaction also includes adverse clinical consequences associated with use of the product outside the terms of Summary of Product Characteristics or other conditions laid down for the marketing and use of the product (including prescribed doses higher that those recommended, overdoses or abuse) (Volume 9A of the Rules governing Medicinal Products in the EU).

Following the initiation of BMS-product in the patient all ADRs should be collected. Following study completion, any serious ADR should also be reported to the Sponsor.

All identified ADRs must be recorded and described on the appropriate Non-serious or Serious ADR page of the CRF. The documentation and reporting of SADRs is described in section 5. If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms.

3. OVERDOSE

An Overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important. For reporting proposes, BMS considers an overdose, regardless of adverse outcome, as an important medical event (see Serious Adverse Drug Reactions).

4. PREGNANCY

Please refer to Summary of Product Characteristics regarding the use of BMS-product in pregnancy. For reporting purposes, BMS considers pregnancy during exposure to a BMS-product, regardless of adverse outcome, as an important medical event (see Serious Adverse Drug Reactions).

5. HANDLING OF SERIOUS ADVERSE DRUG REACTIONS (SADRS)

A serious ADR is one that at any dose:

- Results in death,
- Is life-threatening (defined as an event in which hypothetically might have cause death if it were more severe),
- Requires impatient hospitalization or prolongation of existing hospitalization, (refer to note for exceptions),
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/ birth defect,
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical judgement, may jeopardize the patient/subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above.)

NOTE

- Pregnancy: Incidence of pregnancy is not considered a serious adverse event; pregnancy must
- however, be reported immediately by the same way as an SADR and documented on the BMS Pregnancy Surveillance Form, which will be supplied upon reporting.

An SADR report should be completed for any ADR where doubt exists regarding its status of seriousness.

Adverse Drug Reactions classified as “serious” must be reported on SERIOUS ADR (SADR) page of the CRF and require expeditious handling and reporting to BMS to comply with regulatory requirements.

All SADRs to BMS-product must be reported within 24hours to BMS (or designee) by facsimile. If only limited information is initially available, follow-up reports are required.

Collection of complete information concerning SADRs is extremely important. Thus, follow-up information which becomes available as the SADR evolves, as well as supporting documentation (e.g., hospital discharge summaries and autopsy reports), should be collected subsequently, if not available at the time of the initial report, and immediately sent using the same procedure as the initial report, and immediately sent using the same procedure as the initial SADR report.

SADR TELEPHONE CONTACT: see section 5.5