NCT03652961

Rheumatoid Arthritis Memory B cells and Abatacept (RAMBA)

Single-Open Label Study to Assess Changes in the Immune Profile in Response to Treatment with Intravenous Abatacept Adults with Rheumatoid Arthritis who are Naive to Biologic Disease-Modifying Antirheumatic Drugs

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Study Product: Abatacept

Protocol Number: Insert Protocol Number Used by Sponsor

BMS Protocol Number: IM101-768

IND Number: BB-IND 9391

Initial version: 24 JUL 18
Amended: [date]
Amended: [date]

Table of Contents

List of Abbreviations

Term	Definition
ACPA	anti-citrullinated protein antibody
ACR	American College of Rheumatology
AE	adverse event
ALT	alanine aminotransferase
ANA	anti-nuclear antibody
ANC	absolute neutrophil count
anti-CCP	anti-cyclic citrullinated peptide
anti-CCP2	commercially available test for ACPA
AST	aspartate aminotransferase
BMS	Bristol-Myers Squibb
BP	blood pressure
C	Celsius
CBC	complete blood count
CRP	C-reactive protein
DIP	distal interphalangeal
DMARD	disease-modifying anti-rheumatic drug
dsDNA	double-stranded DNA
EDC	Electronic Data Capture
eg	exempli gratia (for example)
ET	early termination
F	Fahrenheit
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HR	heart rate
F	Fahrenheit
hsCRP	high-sensitivity C-reactive protein
INOVA	Inova Diagnostics
IP	investigational product
IRB	Institutional Review Board
kg	Kilogram
mg	Milligram
mL	Milliliter
MTX	Methotrexate
N	number of subjects or observations
N/A	not applicable
NIMP	non-investigational medicinal products
NSAID	nonsteroidal anti-inflammatory drug
NYU	New York University

Term	Definition
PBMC	Peripheral blood mononuclear cell
PGA	Physicians Global Assessment of Disease Activity
PO	per so (by mouth route of administration)
QD	qd quaque die, once daily
RA	rheumatoid arthritis
RBC	red blood cell
RF	Rheumatoid factor
SAE	serious adverse event
SC	Subcutaneous
SOP	Standard Operating Procedures
Subj	Subject
TB	Tuberculosis
TNF	tumor necrosis factor
WOCBP	women of childbearing potential

Study Summary

Title	Rheumatoid arthritis memory B cells and Abatacept
Short Title	RAMBA
Protocol Number	IM101-768
BMS Protocol Number	IM101-768
Phase	Phase 4
Methodology	Open label
Study Duration	12 months
Study Center(s)	Single-center
Objectives	We will test the hypothesis that ABATACEPT treatment influences the levels of circulating autoimmune anti-citrullinated protein antigen (ACPA) memory B cells are central drivers of pathogenesis.
Number of Subjects	25
Diagnosis and Main Inclusion Criteria	Adults with Seropositive (CCP or ACPA) Rheumatoid Arthritis who are Naive to Biologic Disease-Modifying Antirheumatic Drugs
Study Product, Dose, Route, Regimen	Abatacept Time 0, Week 2, Month 1, 2, 3, 4, & 5 IV administration on Abatacept (7 infusions)
Duration of administration	6 months with active therapy followed by holding Abatacept for 6 months or until flare occurs while concurrent MTX or csDMARDs are continued.
Reference therapy	
Statistical Methodology	We will assess whether ABATACEPT challenge that induces clinical benefits are paralleled by reductions (i.e.,normalization) in the in vivo representation of disease-associated anti-citrullinated protein antigen (ACPA) memory B cells, and circulating autoantibody levels after 6 months of treatment.

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

Rheumatoid arthritis (RA) is the most common chronic inflammatory arthritis, affecting approximately 1% of the population worldwide. [1] Women are 2 to 3 times more likely to develop the disease compared to men, with a peak incidence between the fourth and sixth decades of life. [2,3,4,5] The natural history of RA is characterized by joint destruction, impaired physical function, and poor health-related quality of life. [6] Joint erosions can be seen within 6 months of disease onset in the majority of patients, and occur more rapidly in the first year compared with later disease.

Activated T-cells are believed to play an important role in the pathogenesis of RA, especially early in the disease process, by participating in the autoimmune cascade that leads to joint inflammation and destruction. It is hypothesized that autoreactive T cells may be central to this process by producing pro-inflammatory cytokines and providing help to B cells leading to the production of autoantibodies, which in turn contribute to downstream inflammatory events, including the recruitment of neutrophils, elaboration of cytokines, such as tumor-necrosis factor (TNF)-alpha, synovitis and ultimately joint destruction. [7]

1.2 Investigational Agent

Abatacept is a selective costimulation modulator that blocks the interaction between CD80/CD86 on antigen presenting cells and CD28 on T cells.[8] This interaction provides a key signal necessary for full activation of T cells. By inhibiting CD28-mediated immune activation, Abatacept blocks antigen recognition and modulates the immune response to decrease T cell activation and antibody production. Therefore, Abatacept interferes with a step hypothesized to be early in the pathogenesis of RA.

Intravenously (IV) administered Abatacept was first approved in the United States (US) for the treatment of moderate to severe RA in adults in December 2005. Since then, IV Abatacept has received marketing approval for the treatment of adult RA in many other countries, including the European Union (EU), Japan, Latin America and other countries.[8] The subcutaneous (SC) formulation was first approved in the US for the treatment of moderate to severe RA in adults in July 2011. Abatacept SC has

subsequently received marketing approval or the treatment of adult RA in the EU and other regions of the world.[8]

1.3 Preclinical Data

Not applicable

1.4 Clinical Data to Date

Abatacept has been shown to be effective therapy in patients who have had inadequate responses to Methotrexate (MTX-IR) and TNF inhibitors.[9] In the AMPLE trial Abatacept showed equivalent efficacy and safety to the TNF-inhibitor, Adalimumab.

While it is clearly resolved that continued therapy with MTX alone induces remission in ~30% of patients, the addition of Abatacept increased that to 60% in the AVERT trial. Moreover, MTX +Abatacept induced drug-free remission in up to 10% of patients for up to 6 months later.[10]

In this challenging landscape of RA therapeutics it is unresolved whether Abatacept in addition to MTX in new onset RA can induce a remission that can be maintained with MTX alone. Drug-free remission appears unlikely with Abatacept + methotrexate, so the next step to a cure would naturally examine this question. A corollary to this question is whether this effect of Abatacept is transduced in concert with a decline in memory B cells.

The time has come to address this question for Abatacept because autoimmune memory B cells have been shown to persist at high levels during therapy with TNF-inhibitors in RA, typically given with MTX as concurrent therapy.[11] The rate of remission on methotrexate alone was even more powerful given the fact that patients enrolled in this latter trial had previously failed methotrexate. The premise being tested (that Abatacept decreases circulating arthritogenic B cells)—is a very real possibility, given the effect of Abatacept to reduce B cell infiltration in the synovium and circulating memory B cell levels. [12,13]

1.5 Dose Rationale and Risk/Benefits

Abatacept intravenous should be administered as a 30-minute intravenous infusion utilizing the weight range-based dosing specified below. Following the initial intravenous administration, an intravenous infusion should be given at 2 and 4 weeks after the first infusion and every 4 weeks thereafter for a total of 7 doses.

2 Study Objectives

As a step toward a cure, we will directly assess the impact of a treatment on the underlying autoimmune disease process. Because Abatacept has unique mechanisms of action we believe that ABATACEPT treatment ameliorates RA clinical disease activity through beneficial effects on the pathologic breaches in adaptive immunity that are causal for disease. We will therefore conduct a prospective open therapeutic trial with adult seropositive (i.e., ACPA-positive) RA patients and perform intensive quantitative surveys of pathologic autoantigen-specific B cell memory.

We will test whether the clinical benefit induced by ABATACEPT treatment are paralleled by reductions (i.e., normalization) in the in vivo representation of disease-associated anticitrullinated protein antigen (ACPA) memory B cells after 6 months of treatment. The corollary is to determine whether reductions of disease-associated memory B cells are the most meaningful marker of therapeutic response? ii) Hypothesis 2: The cessation of ABATACEPT treatment (i.e., dechallenge) with continued methotrexate therapy results in clinical flare, is then paralleled by reaccumulation in the bloodstream of disease-associated ACPA memory B cells.

Primary Objective

To assess the efficacy of Abatacept + csDMARD to induce low disease activity that can be maintained on csDMARD (primarily MTX) alone. A necessary co-primary objective is the relationship between clinical response and changes in B cell and antibody parameters that are unaffected by TNF-inhibition.

To directly determine whether ABATACEPT treatment normalizes immune (i.e., B cell and antibody) abnormalities associated with seropositive RA over time and assess for correlations with clinical response measures. The investigations will include: i). Direct quantitation of the frequency of circulating ACPA-bearing memory B cells (2); ii Flow cytometric determinations of effects on B-cell subsets, to determine whether ABATACEPT normalizes disease-associated increases in activated memory B cells, and the plasmablast expansions that are associated with active RA disease. iii) The effects of ABATACEPT on circulating IgM-, IgG- and IgG-ACPA antibody levels, in assays using a panel of matched citrulline- and arginine-containing peptides/self-proteins. iv) Serum will be collected for cytokine/chemokine profiling, which will be highly informative due to the challenge/dechallenge design.

Secondary Objective

We will correlate the relationships between co-primary endpoints over time and then confirm this relationship by dechallenge of Abatacept after induction of low disease activity at 24 weeks.

We will assess whether ABATACEPT therapy that induces clinical benefits, are paralleled by reductions (i.e., normalization) in the in vivo representation of disease-associated anti-citrullinated protein antigen (ACPA) memory B cells after 6 months of

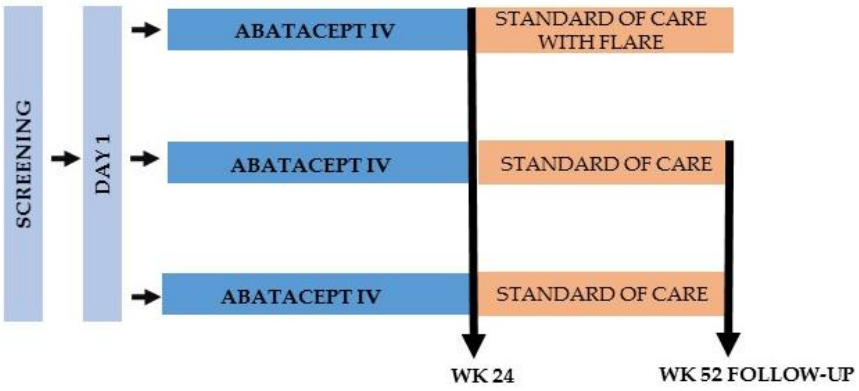
treatment. This can be confirmed by dechallenge experiments in the approximately 70-80% we expect to be in low-disease activity at this time point. While MTX therapy will be maintained, little or no effect of MTX on memory B cell formation is expected as seen in Juvenile Idiopathic Arthritis.[14]

3 Study Design

3.1 General Design

A phase IV open-label clinical trial in which each CCP/ACPA+ patient will be their own longitudinal control for the immunomodulatory activity of Abatacept. All patients will have blood collection, including for peripheral blood mononuclear cells (PBMC), PBMC RNA and plasma, at screening and at day 0 after which Abatacept will be initiated in concert with methotrexate or pre-existing csDMARD. Each patient will then be reevaluated at 3 months and 6 months. In all patients, Abatacept will be discontinued after 6 months. Patients who have flared or failed to achieve low disease activity at 6 months, will exit the trial except for one post study visit for lab work at 9 months.

In patients who have achieved low disease activity by DAS28-CRP (<3.2) or CDAI (<10), Abatacept will be held for 6 months or until a flare results. A flare is defined by an examination demonstrating a DAS28-CRP that is greater than an absolute value of 4.0) or a CDAI >15, both defining the mid-range of a moderate flare. Alternatively, a 30% increase in the absolute level of the DAS28-CRP or CDAI that result in measures of 3.2 and 10 respectively, will be considered evidence of a flare. If patients do not experience a flare after 6 months off Abatacept (by week 52) they will also exit the study after a final visit with an exit blood draw.



Overall, in this pilot study, patient screening will continue until 25 suitable patients are enrolled and started on therapy in the trial. We predict enrollment of 2-3 patients/month, and hence the study should be fully enrolled by month 14 with the expectation that 70-80% will achieve low disease activity at week 24 enabling 17-20

patients to be followed for flare following Abatacept dechallenge. This estimate is based on the observation that treat provides nearly 60% ACR 50 responses, despite the fact that patients were selected for evidence of erosive disease.[15]

NON-RESPONDERS TABLE OF EVENTS

Procedure	Screening Period	DAY 1	WEEK 2	MONTH 1, 2, 3,4,5	MONTH 6/ET	MONTH 9	FOLLOW-UP (WEEK 48-52)
Medication review	X	X	X			X	X
Review of side effects	X	X					
Physical examination	X	X			X		
Height (screening only) & weight	X	X	X	X	X		
Blood sample(s) (Approx.166-176 - ml, or - 12tablespoons per visit)	X	X	X	X	X	X	
Urine sample	X	X	X	X	X		
Pregnancy test for women who can become pregnant	X	X	X	X			
Vital signs (temperature, blood pressure, heart rate (pulse))	X	X	X	X	X		
Assessments of your tender and swollen joints	X	X	X	X	X	X	
Assessments of disease activity	X	X	X	X	X	X	
Your Assessment of pain	X	X	X	X	X	X	
Rapid 3 patient questionnaire	X	X	X	X	X		
Abatacept infusion		X	X	X			
Adverse events		X		X	X	X	X

REMISSION OR LOW DISEASE ACTIVITY TABLE OF EVENTS WITH FLARE

Procedure	Screening Period	DAY 1	WEEK 2	MONTH 1,2,3,4,5	MONTH 6/ET	FLARE	EVERY 4 WEEKS	FOLLOW-UP (WEEK 48-52)
Medication review	X	X	X	X		X	X	X
Review of side effects	X	X				X		
Physical examination	X	X			X	X		
Height (screening only) & weight	X	X		X	X	X	X	
Blood sample(s) (Approx.166-176 - ml, or – 12 tablespoons per visit)	X	X		X	X	X	X	
Urine sample	X	X		X	X	X	X	
Pregnancy test for women who can become pregnant	X	X		X	X	X	X	
Vital signs (temperature, blood pressure, heart rate (pulse))	X	X		X	X	X	X	
Assessments of your tender and swollen joints	X	X		X	X	X	X	
Assessments of disease activity	X	X		X	X	X	X	
Your Assessment of pain	X	X		X	X	X	X	
Rapid 3 patient questionnaire	X	X		X	X	X	X	
Abatacept infusion		X	X	X		X	X	
Adverse events		X		X	X	X	X	X

REMISSION OR LOW DISEASE ACTIVITY TABLE OF EVENTS

Procedure	Screening Period	DAY 1	WEEK 2	MONTH 1, 2, 3,4,5	MONTH 6/ET	MONTH 9	FOLLOW-UP (WEEK 48-52)
Medication review	X	X	X			X	X
Review of side effects	X	X					
Physical examination	X	X			X		
Height (screening only) & weight	X	X	X	X	X		
Blood sample(s) (Approx.166-176 - ml, or - 12tablespoons per visit)	X	X	X	X	X	X	
Urine sample	X	X	X	X	X		
Pregnancy test for women who can become pregnant	X	X	X	X			
Vital signs (temperature, blood pressure, heart rate (pulse))	X	X	X	X	X		
Assessments of your tender and swollen joints	X	X	X	X	X	X	
Assessments of disease activity	X	X	X	X	X	X	
Your Assessment of pain	X	X	X	X	X	X	
Rapid 3 patient questionnaire	X	X	X	X	X		
Abatacept infusion		X	X	X			
Adverse events		X		X	X	X	X

3.2 Primary Study Endpoints

To assess the efficacy of Abatacept + csDMARD to induce low disease activity [DAS28-CRP (<3.2) or CDAI (<10) that can be maintained on csDMARD alone. A necessary co-primary objective is the relationship between clinical response and changes in B cell and antibody parameters that are unaffected by TNF-inhibition.

3.3 Secondary Study Endpoints

We will correlate the relationships between co-primary endpoints over time and then confirm this relationship by dechallenge of Abatacept after induction of low disease activity at 24 weeks.

3.4 Primary Safety Endpoints

This is a Phase 4 study using an agent with demonstrated efficacy and safety in all stages of RA.[9] Most relevant to this study, the efficacy and safety of Abatacept in combination with MTX in early RA has already been demonstrated.[10]

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

1. Signed Written Informed Consent
    a) Subject is willing to participate in the study and has signed the informed consent.
2. Target Population
    a) Men or women (not nursing or pregnant) over 18 years old who have active RA, defined as symptoms of RA prior to screening and have satisfied the ACR/EULAR 2010 criteria for the classification of RA prior to signing the informed consent.
    b) Subjects must have a DAS28CRP or CDAI assessment at screening and have at least 3 tender and at least 3 swollen joints (excluding distal interphalangeal joints) at screening and at Day 1. Patients must have at least moderate disease activity {CDAI>16); DAS28CRP (≥4.0)].
    c) Subjects must be naive to biologic DMARDs
    d) Subjects must be naive to targeted synthetic DMARDs such as tofacitinib, baricitinib, and investigational therapies for RA.
    e) Subjects receiving oral corticosteroids must be on a stable dose and at the equivalent of 10 mg prednisone daily for at least 4 weeks. Subjects may not receive an IM, IV or IA administration of a corticosteroid within 4 weeks prior to screening visit or initiation of therapy
    f) Patients with prior (including discontinued) therapy with Methotrexate and/or Hydroxychloroquine are permitted as long as they meet other inclusionary criteria.
    g) Subjects must have a DAS28CRP or CDAI at screening and have at least 3 tender and at least 3 swollen joints (excluding distal interphalangeal joints) at screening and at Day 1.

Age and Reproductive Status

a) Men and women, age's ⊚ 18 years (or age of majority)
b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.
c) Women must not be breastfeeding and must agree not to breastfeed during the study and for 100 days thereafter
d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of study drug (70 days) plus 30 days (duration of ovulatory cycle) for a total of 100 days post-treatment completion.
e) Males who are sexually active with WOCBP must agree to follow instructions for

method(s) of contraception for the duration of treatment with study drug, plus 5 half-lives of the study drug (70 days) plus 90 days (duration of sperm turnover) for a total of 160 days post-treatment completion.
f) Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in this section. Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy.
Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.
At a minimum, subjects must agree to use one highly effective method of contraception as listed below.

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION
Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. WOCBP and female partners of male subjects, who are WOCBP, are expected to use one of the highly effective methods of contraception listed below. Male subjects must inform their female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner.
1) Progestogen only hormonal contraception associated with inhibition of ovulation.
2) Hormonal methods of contraception including oral contraceptive pills containing estrogen + progesterone, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena®.
3) Nonhormonal IUDs, such as ParaGard®
4) Bilateral Tubal occlusion
5) Vasectomized partner with documented azoospermia 90 days after procedure
Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.
6) Intrauterine hormone-releasing system (IUS)
7) Complete abstinence- Complete abstinence is defined as the complete avoidance of heterosexual intercourse

a) Complete abstinence is an acceptable form of contraception for all study drugs and must be used throughout the duration of the study treatment (plus 5 half-lives of the investigational drug plus 30 days).

b) It is not necessary to use any other method of contraception when complete abstinence is elected.

c) Subjects who choose complete abstinence must continue to have pregnancy tests

d) Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.
e) The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

UNACCEPTABLE METHODS OF CONTRACEPTION

1) Periodic abstinence (calendar, symptothermal, post-ovulation methods)
2) Withdrawal (coitus interruptus)
3) Spermicide only
4) Lactation amenorrhea method (LAM)

4.2 Exclusion Criteria

1. Target Disease Exceptions

a) Subjects with autoimmune disease other than RA [e.g., psoriasis, systemic lupus erythematosus (SLE), vasculitis, seronegative spondyloarthritis, Inflammatory Bowel Disease, Sjogren's syndrome] or currently active fibromyalgia.
b) Prior history of or current inflammatory joint disease other than RA (such as psoriatic arthritis, gout, reactive arthritis, Lyme disease).

2. Medical History and Concurrent Diseases

a) Subjects at risk for tuberculosis (TB) defined as follows:
Current clinical, radiographic or laboratory evidence of active TB. Chest x-rays (posterior anterior and lateral) obtained within the 3 months prior to obtaining written informed consent will be permitted but the images must be available and reviewed by the investigator. TB testing (IFN-gamma release assay or PPD) performed in the past month prior to Screening will be accepted; however, a copy of the report must be placed in the subject binder.
b) A history of active TB
c) Subjects with a positive TB screening test indicative of latent TB will not be eligible for the study unless they:

1) Have no evidence of current TB based on chest x-ray performed And they are actively being treated for TB or the site has documentation of successful prior treatment of latent TB. Treatment regimens should be dictated by local guidelines as long as the treatment dose and duration meet or exceed local health authority guidelines.

b) Subjects with recent acute infection defined as:

1) Any acute infection within 60 days prior to randomization that required hospitalization or treatment with parenteral antibiotics.

2) Any acute infection within 30 days prior to randomization that required oral antimicrobial or antiviral therapy.
c) Subjects with history of chronic or recurrent bacterial infection (such as chronic pyelonephritis, osteomyelitis, and bronchiectasis etc.).
d) Subjects with any history of infection of a joint prosthesis or artificial joint.
e) Subjects who have a history of systemic fungal infections (such as histoplasmosis, blastomycosis, or coccidiomycosis).
f) Subjects with history of recurrent herpes zoster (more than 1 episode) or disseminated (more than 1 dermatome) herpes zoster or disseminated herpes simplex, or ophthalmic zoster will be excluded. Symptoms of herpes zoster or herpes simplex must have resolved more than 60 days prior to screening.
g) Subjects with history of Human Immunodeficiency Virus (HIV) infection or who tested positive for HIV
h) Subjects with history of primary immunodeficiency
i) Subjects who have a present malignancy or previous malignancy within the last 5 years prior to screening (except documented history of cured non-metastatic squamous or basal cell skin carcinoma or cervical carcinoma in situ). Subjects who had a screening procedure that is suspicious for malignancy, and in whom the possibility of malignancy cannot be reasonably excluded following additional clinical, laboratory or other diagnostic evaluations.
j) Current clinical findings or a history of a demyelinating disorder
k) New York Heart Association (NYHA) Class III or IV heart failure
l) Any previous or current medical conditions that are warnings against the use of TNF inhibitor agents.
m) Current clinical findings of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, pulmonary, psychiatric, cardiac, endocrine, neurological, or cerebral disease including severe and uncontrolled infections, such as sepsis and opportunistic infections. Concomitant medical conditions that, in the opinion of the investigator, might place the subject at unacceptable risk for participation in this study.
n) Subjects who have received any live vaccines within 3 months of the study drug administration or are scheduled to receive live vaccines during the study. Study subjects should not be administered a live virus vaccine for a minimum of 3 months following the last dose of study medication. Subjects who are in close contact with others who have received a live vaccine may be enrolled at the investigator’s discretion.
o) Subjects who have undergone a major surgical procedure within the 60 days prior to randomization.

p) Subjects for whom 5 or more joints cannot be assessed for tenderness or swelling (i.e. due to surgery, fusion, amputation, etc.).

3. Subjects who are prisoners, or compulsory detained.

4.3 Subject Recruitment and Screening

Eligibility will be based on specified inclusion and exclusion criteria, medical history, disease activity and safety assessments. Day 1 must occur within 28 days of signing the informed consent. Subjects that experience an acute infection or initiate treatment for latent TB may extend the screening period to 42 days.

Eligible subjects will have had symptoms and diagnosis of RA prior to signing the informed consent. Symptoms of RA are defined as pain, stiffness or swelling in joints which are typically inflamed in RA. Subjects must also have fulfilled criteria for rheumatoid arthritis by ACR/EULAR 2010 classification prior to signing informed consent.

Subjects treated with MTX must remain on a stable dose of oral methotrexate for at least 4 weeks prior to Day 1. The stable dose of oral MTX should be the maximum tolerated dose (minimum of 15 mg and maximum of 25 mg per week). A dose of methotrexate 7.5-12.5mg/week is permitted if intolerance to 15 mg or higher doses has been recorded in the source documents and the dose of oral methotrexate is stable for 4 weeks prior to randomization.

To minimize potential methotrexate toxicity, all subjects must receive folic acid, folinic acid, or leucovorin according to the manufacturer recommendations, methotrexate label instructions, and the local medical standard of care guidelines.
Subjects receiving oral corticosteroids must be on a stable dose and at the equivalent of 10 mg prednisone daily for at least 4 weeks prior to randomization. Subjects may not have received an IM, IV or IA administration of a corticosteroid within 4 weeks prior to randomization.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

All subjects who have received at least one dose of study drug and exit the study early will complete an early termination (ET) visit at the time of study discontinuation. Subjects will continue standard of care appointments with their primary rheumatologist after ET visit.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject. Lost

to follow-up is defined by the inability to reach the subject after a minimum of 3 documented phone calls, faxes or emails (not performed on the same day), as well as a lack of response by the subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death and as much other information as can be obtained, including post-mortem reports. Data to be collected at subsequent visits will be considered missing.

4.2.1 **End of Study**

At the end of the study period, Bristol-Myers Squibb Company will not continue to supply study drug to subjects/investigators unless the Sponsor-Investigator chooses to extend their study. The investigator is responsible to ensure that the subject receives appropriate standard of care or other appropriate treatment in the independent medical judgement of the Investigator to treat the condition under study.

5 Study Drug

5.1 Description and Treatment Regimen

Abatacept for adult patients with RA, ABATACEPT will be administered as an intravenous infusion. Abatacept will be used concomitantly with DMARDs other than TNF antagonists or JAK inhibitors. Intravenous Dosing Regimen Abatacept lyophilized powder should be reconstituted and administered after dilution [see Dosage and Administration below] as a 30-minute intravenous infusion utilizing the weight range-based dosing specified. Following the initial intravenous administration, an intravenous infusion should be given at 2 and 4 weeks after the first infusion and every 4 weeks thereafter.

Dose of ABATACEPT for Intravenous Infusion in Adult RA Patients
Body Weight of Patient Dose Number of Vials

Each vial provides 250 mg of Abatacept for administration.

1. Less than 60 kg: 500 mg 2 vials
2. 60 to 100 kg: 750 mg 3 vials
3. More than 100 kg 1000 mg 4 vials

Dose Modifications in the Absence of Adverse Events
Subjects should complete their scheduled infusions as described above.
Dose Modifications Due to Adverse Events

If abnormal laboratory test results or clinical adverse events indicate toxicity that, in the judgment of the investigator, could place the subject at risk, study drug administration should be interrupted. Subjects may receive further study medication treatment only if full resolution of the adverse event or abnormal laboratory finding is documented. **Under no circumstances should the dose of study drug be altered due to an adverse event.**

5.2 Method for Assigning Subjects to Treatment Groups

N/A.

5.3 Preparation and Administration of Study Drug

Abatacept for reconstitution and dilution prior to intravenous administration. Following reconstitution of the lyophilized powder with 10 mL of Sterile Water for Injection, USP, the solution of Abatacept is clear, colorless to pale yellow, with a pH range of 7.2 to 7.8. Each single-use vial of Abatacept for Injection provides 250 mg Abatacept, maltose (500 mg), monobasic sodium phosphate (17.2 mg), and sodium chloride (14.6 mg) for administration.

Reconstitute using only the silicone-free disposable syringe provided with each vial and an 18- to21-guage needle. If the Abatacept powder is accidentally reconstituted using a siliconized syringe, the solution may develop a few translucent particles. Discard any solutions prepared using siliconized syringes. Administer the entire, fully diluted Abatacept solution over a period of 30 minutes with an infusion set and a sterile, nonpyrogenic, low-protein–binding filter (pore size of 0.2 μm to 1.2 μm).

The Dartmouth-Hitchcock Medical Center Investigational Pharmacy will ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity). If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed. Investigational product documentation will be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

5.4 Subject Compliance Monitoring

All subjects are expected to receive study therapy as outlined in the protocol. Subjects will use diary cards to document self-injection of study drug between clinic visits.

5.5 Prior and Concomitant Therapy

Patients with newly diagnosed or established seropositive active RA will be allowed to enter this clinical trial that meet the above inclusion and exclusion criteria. The

ideal candidate for this trial is newly diagnosed RA about to be initiated on weekly methotrexate therapy (20 mg/week or the maximally tolerated dose). Prior or concurrent therapy with methotrexate or hydroxychloroquine (≤ 400 mg/d). Established treatment (>4 weeks) with daily Prednisone (≤10 mg/d) is permitted.

5.6 Packaging

N/A

5.7 Blinding of Study Drug

N/A

5.8 Receiving, Storage, Dispensing and Return

5.8.1 Receipt of Drug Supplies

Upon receipt of the of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The investigator must notify study sponsor of any damaged or unusable study treatments that were supplied to the investigator's site.

5.8.2 Storage

The fully diluted Abatacept solution may be stored at room temperature or refrigerated at 36°F to 46°F (2°C to 8°C) before use. The infusion of the fully diluted Abatacept solution must be completed within 24 hours of reconstitution of the Abatacept vials. Discard the fully diluted solution if not administered within 24 hours.

The infusion of the fully diluted Abatacept solution must be completed within 24 hours of reconstitution of the Abatacept vials. Discard the fully diluted solution if not administered within 24 hours.

5.8.3 Dispensing of Study Drug

The investigator is responsible for ensuring adequate accountability of all used and unused study drugs. This includes acknowledgement of receipt of each shipment of study drugs (quantity and condition). All used and unused study drugs dispensed to subjects must be returned to the site.
Abatacept accountability records will be provided by Dartmouth-Hitchcock Investigational Pharmacy:

- Record the date received and quantity of study drugs

- Record the date, subject number, subject initials, the study drug number dispensed
- Record the date, quantity of used and unused study drugs returned, along with the initials of the person recording the information.
- Dispensing records will include the initials of the person dispensing the study drug

5.8.4 Supplies, Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site. Any unused study drugs can only be destroyed,

5.9 Vi sit 1

See above

5.10 Visit 2

5.11 etc.

6 Statistical Plan

6.1 Sample Size Determination

Not applicable, this is a pilot study

6.2 Statistical Methods

These studies are considered exploratory and will enable power analyses for subsequent larger studies. We anticipate that clinical responders will concurrently have more than 25% decreases in IgG anti-CCP3 levels (INOVA). The mean change in IgG anti-CCP levels in responders versus non-responders will be analyzed by t-test. A proportional decrease in the estimated level of IgG anti-CCP3 secreting recirculating memory B cells is predicted as well. Clinical non-responders are predicted to not have a significant change. No significant effects on total IgG, IgA or IgM are anticipated. In a recent report with cross-sectional analyses we documented highly significant correlations r=0.57 p=0.0033) between ACPA and memory B cell levels in studies of 24 RA patients (11). With longitudinal analyses we anticipate that relationships should require fewer subjects to document correlations between shifts in clinical activity and ACPA IgG and ACPA-memory B cell levels overtime. We will

assess non-parametric paired-sample comparisons by Spearman correlations, and longitudinal measurements using paired t test, with Prism v6.0e (GraphPad, La Jolla, CA). P<0.05 will be considered significant.

6.3 Subject Population(s) for Analysis

All treated subjects in study.

7 Safety and Adverse Events

7.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event
An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- 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 and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

Although pregnancy, overdose, potential drug-induced liver injury (DILI), and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

NONSERIOUS ADVERSE EVENT

- Non-serious Adverse Events (AE) are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [e.g., IND US trial] as part of an annual reporting requirement.
- Non-serious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

A ***non-serious adverse event*** is an AE not classified as serious.

Non-serious Adverse Event Collection and Reporting

The collection of non-serious AE information should begin at initiation of study drug. All non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 30 days following the last dose of study treatment.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if <u>any one of the following</u> conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

any laboratory test result that is clinically significant or meets the definition of an SAE

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported to BMS as such. It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

Potential Drug Induced Liver Injury (DILI)

Specific criteria for identifying potential DILI have not been identified for this protocol. Standard medical practice in identifying and monitoring hepatic issues should be followed.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.
- A visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for participant).

The investigator must immediately notify Worldwide.Safety@bms.com of this event via either the CIOMS, MedWatch or appropriate Pregnancy Surveillance Form in accordance with SAE reporting procedures.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the CIOMS, MedWatch, BMS Pregnancy Surveillance Form, **or** approved site SAE form. A BMS Pregnancy Surveillance Form may be provided upon request.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, X-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

7.1 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly

related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

7.2 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators and the protocol sponsor must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others
  (see definitions, section 8.1).

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

7.2.1 Investigator reporting: notifying the study sponsor

Any study-related unanticipated problem posing risk of harm to subjects or others, and any type of serious adverse event, must be reported to the study sponsor by telephone within 24 hours of the event. To report such events, a Serious Adverse Event (SAE) form must be completed by the investigator and faxed to the study sponsor within 24 hours. The investigator will keep a copy of this SAE form on file at the study site. Report serious adverse events by phone and facsimile to:

24-hr Emergency Telephone Number

(603) 650-5000

Within the following 48 hours, the investigator must provide further information on the serious adverse event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the study sponsor

Investigator Reporting to BMS

- All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 30 days of discontinuation of dosing must be reported to BMS Worldwide Safety, whether related or not related to study drug. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).
- Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these aforementioned time periods, which is believed to be related to study drug or protocol-specified procedure.
- An SAE report should be completed for any event where doubt exists regarding its seriousness;
- If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.
- If the BMS safety address is not included in the protocol document (eg, multicenter studies where events are reported centrally), the procedure for safety reporting must be reviewed/approved by the BMS Protocol Manager. Procedures for such reporting must be reviewed and approved by BMS prior to study activation.

An appropriate SAE form (e.g. ex-US = CIOMS form or USA = Medwatch form) should be used to report SAEs to BMS. If you prefer to use your own Institutional form, it must be reviewed by BMS prior to study initiation. Note: Please include the BMS Protocol number on the SAE form or on the cover sheet with the SAE form transmission.

  - The CIOMS form is available at: http://www.cioms.ch/index.php/cioms-form-i
  - The MedWatch form is available at: MedWatch 3500 Form

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- Worldwide.Safety@bms.comaepbusinessprocess@bms.com
- In accordance with local regulations, BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the IB). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of a SUSAR Report.
    - Other important findings which may be reported by BMS as an Expedited Safety Report (ESR) include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.
    - Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.
    - In addition to the Sponsor Investigator's responsibility to report events to their local HA, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours \ 1 Business Day of becoming aware of the event. SAEs must be recorded on either CIOMS, MedWatch, or approved site SAEform.

Pregnancies must be reported and submitted to BMS on any of the following form(s):

1. MedWatch or, CIOMS or
2. BMS Pregnancy Surveillance Form or,
3. Approved site SAE form

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: +1 609-818-3804

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours \ 1 Business Day to BMS using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

7.2.2 Investigator reporting: notifying the Dartmouth IRB

This section describes the requirements for safety reporting by investigators who are Dartmouth faculty, affiliated with a Dartmouth research site, or otherwise responsible for safety reporting to the Dartmouth IRB. The Dartmouth College IRB (CPHS) requires expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The Dartmouth IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined below. The Dartmouth IRB requires researchers to submit reports of the following problems within 10 working days from the time the investigator becomes aware of the event:

- Any adverse event (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is:

  Unexpected (An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

  AND

  Related to the research procedures (An event is "related to the research procedures" if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

Reporting Process
Unanticipated problems posing risks to subjects or others as noted above will be reported to the Dartmouth IRB using the form: "Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events" or as a written report of the event (including a description of the event with information regarding

its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

Reporting Deaths: more rapid reporting requirements
Concerning deaths that occur during the course of a research study, the following describes the more rapid reporting requirement of the Dartmouth IRB for specific situations:

- Report the event within 24 hours when the death is unforeseen (unexpected) and indicates participants or others are at increased risk of harm.
- Report the event within 72 hours, for all other deaths, regardless of whether the death is related to study participation.

For reportable deaths, the initial submission to the Dartmouth IRB may be made by contacting the IRB Director or Associate Director. The AE/Unanticipated Problem Form is required as a follow up to the initial submission.

Other Reportable events:
For clinical drug trials, the following events are also reportable to the Dartmouth IRB:

- Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
- Any adverse event that would cause the sponsor to modify the investigators brochure, protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
  - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
  - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.

- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

7.2.3 Investigator reporting: Notifying another IRB

Investigators who are not Dartmouth faculty or affiliated with a Dartmouth research site are responsible for safety reporting to their local IRB. Investigators are responsible for complying with their local IRB's reporting requirements, though must submit the required reports to their IRB no later than 10 working days. Copies of each report and documentation of IRB notification and receipt will be kept in the investigator's study file.

7.2.4 Sponsor reporting: Notifying participating investigators

It is the responsibility of the study sponsor to notify all participating investigators, in a written IND safety report, of any adverse event associated with the use of the drug that is both serious and unexpected, as well as any finding from tests in laboratory animals that suggest a significant risk for human subjects. Additionally, sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

7.3 Stopping Rules

7.4 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

7.4.1 Independent Data and Safety Monitoring Board

There is no DSMB.

8 Data Handling and Record Keeping

8.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

8.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

8.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

8.4 Records Retention

The clinical research records are the property of the clinical subcontractor awardee institution. These records include clinical research records, IRB records, and records related to investigations or proceedings of research misconduct.

Storage

Clinical research records are stored in a manner that ensures privacy, confidentiality, security, and accessibility when the clinical research is being conducted and after the research is completed. Records can be kept in hardcopy, electronic or other media form. It is permissible to transfer these documents from paper records to electronic formats and to archive this information on available media.

Record Keeping

The research team will maintain adequate documentation of all IRB/EC records and clinical research records. Records must be retained for at least three 2 years after the completion of research. Records must be accessible for inspection and copying by authorized representatives of the department or agency at reasonable times and in a reasonable manner

9 Study Monitoring, Auditing, and Inspecting

9.1 Study Monitoring Plan

N/A

9.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and Dartmouth compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable Dartmouth compliance and quality assurance offices.

10 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in

agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment 1 for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

11 Study Finances

11.1 Funding Source

From BMS

11.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All Dartmouth investigators will follow the Dartmouth conflict of interest policy.

11.3 Subject Stipends or Payments

N/A

12 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

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14 Attachments Insert what is needed

1. Informed consent
2. Patient Rapid 3 questionnaire