Name of Sponsor/Company: Bristol-Myers Squibb	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Orencia		
Name of Active Ingredient: Abatacept		

SYNOPSIS

Influenza Vaccine Substudy for Protocol IM101174

TITLE OF STUDY: Influenza Vaccine Substudy for Protocol IM101174

Protocol IM101174: A Phase IIIB Multicenter, Randomized, Double-Blind, Double-Dummy Study to Compare the Efficacy and Safety of Abatacept Administered Subcutaneously and Intravenously in Subjects with Rheumatoid Arthritis, Receiving Background Methotrexate, and Experiencing an Inadequate Response to Methotrexate

INVESTIGATORS/STUDY CENTERS: 28 sites in the United States of America (US) and Mexico.

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 17-Oct-2011 **CLINICAL PHASE:** 3b

Study Completion Date: 12-Mar-2012

INTRODUCTION: This is an influenza vaccine substudy of IM101174; the results of the main study are reported separately. Patients with rheumatoid arthritis (RA) have an increased risk for infections, especially respiratory infections due to chronic inflammatory state and use of immunosuppressive agents and corticosteroids. Therefore, patients with RA are potential candidates for influenza vaccine. Given abatacept's mechanism of action, there is a possibility of reduced response to influenza vaccination in patients receiving abatacept therapy. Additionally, a study in healthy volunteers suggested that abatacept may blunt immune responses to vaccination, but the ability to mount a clinically meaningful response is not impaired. Therefore, the purpose of this influenza vaccine substudy to protocol IM101174 was to assess antibody response to the seasonal influenza trivalent virus vaccine in subjects with RA who were on a stable dose of subcutaneous (SC) abatacept and background disease modifying anti-rheumatic drug (DMARD) therapy.

OBJECTIVES:
Primary Objective: The primary objective of the substudy was to evaluate antibody response to the seasonal influenza trivalent virus vaccine in adult subjects with RA receiving a stable dose of SC abatacept and a background of DMARD therapy, and without protective antibody levels to the influenza antigens at baseline.

Secondary Objective: Not applicable

Exploratory Objective: The exploratory objective of this influenza substudy was to assess the antibody response to seasonal influenza vaccine in the Influenza Vaccination Population (i.e. all treated subjects with both prevaccine and postvaccine measures).

METHODOLOGY: This multi-centered, open labeled influenza vaccine substudy consisted of an initial visit for prevaccination blood sample collection and influenza vaccine administration, a 28 ± 3 day treatment period, and a final visit for postvaccination blood sample collection. The target population for this substudy was adult subjects with RA who are on a stable dose of SC abatacept and background DMARD, and did not demonstrate protective antibody levels to the influenza antigens at baseline. Subjects enrolled at specific sites in study IM101174 were enrolled in this substudy at any point during their abatacept SC treatment cycle after completion of at least 3 months of SC abatacept treatment.

NUMBER OF SUBJECTS (Planned and Analyzed): A total of 191 subjects enrolled in the Influenza Vaccine Substudy and received the influenza vaccination. Of the 191 subjects treated, 186 had pre- and postvaccination samples available and comprised the Influenza Vaccination Population. Of these, 121 subjects did not have protective antibody levels at baseline and were categorized into the Influenza Vaccination Population - Non protective at Substudy Baseline.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Subjects who completed the short term (ST) periods of study IM101174 were eligible to participate in the influenza vaccine substudy. In addition, subjects participating in this substudy were adults who were on a stable dose of SC abatacept defined by having received at least 3 months of SC abatacept.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT: All enrolled subjects received weekly abatacept by SC injection, 125 mg/syringe (125 mg/mL). Subjects received commercially available standard trivalent subvirion seasonal influenza virus vaccine (0.5mL) administered intramuscularly (IM) according to manufacturer's instructions. Batch numbers of the commercially available influenza vaccine were: 05249211, 05249211A, 1101801, 1102001, 111002, AB576651, AFLLA680BA, AFLLA681AA, N57507, UH453AA, UH453AC, UH454AB, UH463AA, UH471AA, UH476AA, UH477AB, UH47OAD, XFLUA610AA, XFLUA639, XFLUA639AA.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT: None.

CRITERIA FOR EVALUATION:

Efficacy: Efficacy assessments were based on antibody response to the seasonal influenza trivalent virus vaccine in adult subjects with RA receiving stable dose of SC abatacept and background of DMARD therapy. Antibody titers were evaluated for the following 3 antigens: H1N1, H3N2, and Brisbane from blood samples collected prior to the influenza vaccine at Day 1 and 28 days post vaccination. The primary efficacy endpoint was the proportion of subjects achieving a ≥ 4-fold increase in postvaccination titers to ≥ 2 of 3 influenza antigens in the vaccine at Day 28 in the Influenza Vaccination Population - Non protective at Substudy Baseline. Subjects were defined to have a protective antibody level to these antigens if their antibody titer was ≥ 1:40 for ≥ 2 of 3 antigens at baseline.

Safety: Safety assessments related to abatacept were collected as part of the main study. Adverse events (AEs), serious adverse events (SAEs) including deaths, discontinuations due to AEs, and AEs specific to the influenza vaccine occurring during the influenza vaccine were extracted from the main study; these included data up to the postvaccination sample date, or the discontinuation date for subjects who discontinued from the main study without postvaccination date or vaccination date plus 28 to 31 days for subjects who continue in the main study with no post vaccination date. The AEs of special interest included infections, autoimmune disorders, and injection reaction AEs (local injection site reactions and systemic injection reactions occurring within 24 hours of SC injection). The complete safety profile for abatacept treatment is presented in a separate report.

STATISTICAL CONSIDERATIONS:

Efficacy Analyses: Descriptive statistics (point estimate and 95% confidence interval [CI]) were provided for the primary and exploratory efficacy analyses and the geometric mean influenza antibody titers by antigen at pre-vaccination and postvaccination. Geometric mean ratios (postvaccination/prevaccination) were presented for the summaries of mean change from baseline in influenza antibody titers by antigen. A logistic regression model (Odds ration and 95%CI) was performed to evaluate the relationship of baseline factors with influenza vaccine response.

Safety Analyses: The evaluation of drug safety was based on clinical adverse AEs in the As Treated Subject Population. Frequency distribution and individual listings of AEs were generated.

SUMMARY OF RESULTS:

Disposition, Demographics, and Other Pertinent Baseline Characteristics: A total of 191 subjects enrolled in the Influenza Vaccine Substudy and received the influenza vaccination. Of the 191 subjects who received the influenza vaccination, 185 subjects completed the 4 week substudy. The definition of completing the substudy was having both pre- and postvaccination samples collected. One subject discontinued from the main study due to "lack of efficacy" of abatacept however, this subject was considered to be a completer in the substudy as a postvaccination sample was available.

The majority of subjects treated in the substudy period were white (98.4%) and female (90.1%) with a mean (± SD) age of 44.9 years (± 12.6). Subjects mean (± SD) weight was 68.4 kg (± 17.3). Methotrexate (MTX) was used concomitantly by 97.4% of subjects. Baseline information was collected during the screening period of the main IM101174 study**.**

Key Demographic and Baseline Disease Characteristics (All-Treated Subjects)

Parameter	Total (N=191)
Age, Mean (SD) years	44.9 (12.6)
Gender, Female, n (%)	172 (90.1)
Race, White, n (%)	188 (98.4)
Weight, Mean (SD) kg	68.4 (17.3)
Tender Joints, Mean (SD)	30.7 (14.4)
Swollen Joints, Mean (SD),	20.3 (8.0)
Subjects assessment of pain , Mean (SD)	65.5(22.2)
HAQ Disability Index, Mean (SD)	1.7 (0.6)
Subjects global assessment of disease activity, Mean (SD)	64.7 (21.5)
Physicians global assessment of disease activity, Mean (SD)	60.3 (17.9)
DAS28-CRP Score, Mean (SD)	6.3 (0.8)
CRP (mg/dL), Mean (SD)	2.4 (2.7)
Duration of exposure to abatacept from start of main study to vaccination date (months), Mean (SD)	37.6 (2.9)
Concomitant Methotrexate Usage, % (Mean dose mg/week)	97.4%, (6.0)

Efficacy Results: In the primary analysis population (Influenza Vaccination Population - Non protective at Substudy Baseline), 61.3% of subjects demonstrated a response to the influenza vaccine achieving a ≥ 4-fold increase in postvaccination titers to ≥ 2 of 3 influenza antigens assessed. In the overall Influenza Vaccination Population, 49.5% of subjects demonstrated a response to the influenza vaccine by achieving a ≥ 4-fold increase in postvaccination titers to ≥ 2 of 3 influenza antigens assessed. Analyses of baseline factors with influenza vaccine response showed protective antibody titers at baseline to be a confounding factor having a negative impact on influenza vaccine response with an odds ratio (95% CI) of 0.2 (0.1, 0.5). In addition, age <55 years showed a positive impact on vaccine response with an odds ratio (95% CI) of 2.3 (1.1, 4.7). The proportion of subjects in the Influenza Vaccination Population that achieved a ≥ 4-fold increase in antibody titer to each of the 3 antigens assessed compared to baseline ranged from 35.3% to 54.9% across the 3 antigens. In the Influenza Vaccination Population, 4 weeks postvaccination, 82.1% of subjects demonstrated protective antibody levels postvaccination (antibody titer ≥ 1:40) to ≥ 2 of 3 influenza antigens assessed.

Safety Results: The safety profile of abatacept SC (125 mg weekly) is consistent with that previously characterized with no new safety signal identified. Influenza vaccination during abatacept SC administration was well tolerated. There were no deaths and no discontinuations due to AEs reported during the substudy period. One subject experienced a serious AE of severe chest pain that began on Day 18 of the substudy, resolved within 3 days, and in the opinion of the investigator was not related to study drug administration. There were no injection site reactions specific to the influenza vaccine during the substudy and no local injection site reactions or prespecified autoimmune disorders. Overall AEs were reported in a total of 27 (14.1%) subjects in the substudy period. Most common AEs were in the system organ class (SOC) of Infections and Infestations in 9 (4.7%) subjects.

Summary of Adverse Events (All-Treated Subjects in Influenza Vaccine Substudy)

Subjects With	Cumulative Treatment Period (N=191)
Deaths, n (%)	0
SAEs, n (%)	1 (0.5%)
AEs, n (%)	27 (14.1%)
Related AEs	3 (1.6%)
Discontinued due to AEs	0
AEs specific to the influenza vaccine, n (%)	0
AEs of interest, n (%)	
Infections	9 (4.7%)
Autoimmune disorders (prespecified)	0
Injection site reactions (prespecified)	
Local	0
Systemic (≤ 24 hrs after dosing)	2 (1.0%)

AEs = Adverse events; SAEs = Serious adverse events.

CONCLUSIONS:

Following vaccination with the standard trivalent influenza virus vaccine during long-term abatacept therapy, a majority of subjects were able to mount an immune response to the vaccine. Influenza vaccination was well tolerated when administered during long-term abatacept therapy.

DATE OF REPORT: 03-Dec-2012