SYNOPSIS

Clinical Study Report IM101031 - Double-blind Period

TITLE OF STUDY: Protocol IM101031: A Phase III, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Clinical Use Study to Evaluate the Safety and Tolerability of BMS-188667 Administered Intravenously to Subjects with Active Rheumatoid Arthritis (RA) With or Without Medical Co-Morbidities Receiving Disease Modifying Anti-Rheumatic Drugs (DMARDs) and/or Biologics Approved for RA

INVESTIGATORS: 161 investigators treated subjects in this study.

STUDY CENTERS: A total of 161 study centers treated subjects in this study: 91 sites in the United States; 24 sites in Europe (Czech Republic, France, Hungary, Italy, Poland, Russia, Spain); 8 sites in Canada; 4 sites in Australia; 3 sites in Argentina; 10 sites in Brazil; 7 sites in Mexico; 3 sites in Peru; 2 sites in Thailand; 4 sites in Taiwan; and 5 sites in Turkey.

PUBLICATIONS: None.

STUDY PERIOD:
Date first subject enrolled: 17-Dec-2002
Date last subject completed the Day 365 visit: 21-Jun-2004

CLINICAL PHASE: 3

OBJECTIVES:
Primary Objectives: The primary objective was to summarize the incidence of adverse events (AEs), serious adverse events (SAEs), and discontinuations due to AEs during 1 year of combined treatment with abatacept and 1 or more of the DMARDs and/or biologics approved for RA in subjects with active RA with or without co-morbid medical conditions.

There were no secondary objectives. Key exploratory objectives were to assess selected efficacy parameters, including subject physical function using the disability index of the Health Assessment Questionnaire (HAQ); subject global assessment of disease activity using a Visual Analog Scale (VAS); subject global assessment of pain using a VAS; and physician global assessment of disease activity using a VAS.

METHODOLOGY: This was a multinational, multicenter, randomized, double-blind, 2-arm, parallel-dosing designed study. The treatment period was 12 months. Eligible subjects were randomized to 1 of 2 treatment groups: abatacept fixed dose approximating 10 mg/kg or placebo intravenous (IV) infusion. All subjects continued their background therapy(ies) for rheumatoid arthritis (RA) (non-biologic or biologic disease-modifying drugs [DMARDs], or combination) throughout the double-blind treatment period. Double-blind study medication (abatacept or placebo) was administered on Days 1, 15, 29, and
every 28 days thereafter, for a total of 14 doses. Dose modification of double-blind study medication was not permitted.

A 3:1 randomization of abatacept to placebo was planned, but a 2:1 randomization schedule was inadvertently prepared and used to assign subjects to double-blind treatment. This error was discovered after the double-blind period was completed, the database was locked, and treatment group assignment was unblinded. Despite this error, the number of subjects treated with abatacept was close to the intended number and the power of the study to detect an AE occurring at a rate of 0.2% was not substantially affected (87% power with planned sample size, 85% power with achieved sample size).

During the first 3 months of the double-blind period, adjustments in background RA therapy (non-biologic and/or biologic DMARDs, or corticosteroids) were not allowed except for decreases in dose due to toxicity. Adjustments to non-steroidal anti-inflammatory drugs (NSAIDs) were permitted, except for within 12 h preceding the subject global assessment of disease activity on Days 1, 85, 169, and 253. After the first 3 months (Days 86-365), adjustment in background RA therapy was permitted, including the addition of non-biologic and biologic DMARDs and corticosteroids.

All subjects who completed the 12-month double-blind period and provided consent were eligible to continue into the open-label period. Results of the ongoing open-label period are reported separately.

NUMBER OF SUBJECTS: A total of 1441 subjects were randomized and treated: 959 in the abatacept group and 482 in the placebo group.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Men and women, at least 18 years of age, meeting criteria of the American Rheumatism Association (1987) for the diagnosis of RA and the criteria of the American College of Rheumatology (ACR) (1991) for RA functional classes I, II, III, or IV; subject’s average global assessment of disease (VAS) at screening and Day 1 of ≥ 20 mm; and treated with 1 or more non-biologic and/or biologic drug approved for RA for at least 3 months and on a stable dose for 28 days prior to Day 1. Subjects with stable renal, endocrine, hepatic, hematologic, gastrointestinal, pulmonary, cardiac, neurologic, or cerebral disease(s) were eligible for participation.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: Abatacept for IV infusion was supplied as a whole or fragmented cake in vials containing 250 mg of abatacept. A fixed dose approximating 10 mg/kg was administered (500 mg for subjects < 60 kg, 750 mg for subjects 60 to 100 kg and 1 g for subjects > 100 kg). Infusion doses were based on body weight at screening visit and were administered in a fixed volume of 100 mL at a constant rate over 30 minutes. Batch numbers: 2J59315, 2J62801, 2J62804, 2J62805, 2J62806, 3A64967, 3A64965, 3D66861, 3E75222, and 3H65127.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: Placebo (dextrose 5% water [D5W] for injection U.S.P or normal saline [NS]) for IV infusion (fixed volume of 100 mL at a constant rate over 30 minutes). Investigational sites were responsible for providing D5W or NS.

CRITERIA FOR EVALUATION:

Efficacy: Exploratory efficacy outcome measures included median percent improvement from baseline to Day 365 (or the last post-baseline measurement prior to Day 365 in subjects prematurely withdrawn) in subject global assessment of pain, subject global assessment of disease activity, and physician global assessment of disease activity using VAS, and assessment of physical function using the Disability Index of the full HAQ.

Safety: All subjects who received at least one dose of study medication were evaluated for safety. AEs, SAEs, discontinuations due to AEs, deaths, clinically significant changes in vital signs, physical examinations, and clinical laboratory test abnormalities were examined.
Pharmacokinetics: Blood specimens for determination of trough abatacept serum concentrations were collected prior to dosing on Days 1, 29, 85, 169, and 281, and an end of infusion sample was obtained on Day 85. Serum concentrations obtained in the study will be combined with PK data from other studies and will be used to develop a statistical model of population pharmacokinetics. Results of this analysis are reported separately.

Pharmacodynamics: Not assessed in this study.

Immunogenicity: Blood samples for determination of anti-abatacept antibody titers in serum were collected throughout the study; these immunogenicity data are summarized in a separate report.

STATISTICAL METHODS: The primary objective of this study was to demonstrate and characterize the safety profile of abatacept in subjects representative of patients with RA in clinical practice. Safety analyses were based on a data set containing all available assessments from all treated subjects who received at least 1 infusion of study medication (Treated Subjects). No formal tests were planned to compare AE incidence rates between treatment groups. Exploratory efficacy analyses were performed on the 4 disease outcome measures. For each of these measures, descriptive statistics including median percent improvement from baseline, mean percent improvement from baseline, and mean change from baseline were provided for all timepoints.

STUDY POPULATION: A total of 1441 of the 1456 randomized subjects received at least 1 infusion of study medication, of whom 1231 completed the double-blind period. A greater proportion of subjects in the abatacept group (87%) completed double-blind therapy compared with the placebo (82%) group. More subjects in the placebo group (9%) discontinued for lack of efficacy compared with the abatacept group (3%). Adverse events led to discontinuation in 5% of abatacept-treated subjects and 4% of placebo-treated subjects.

The abatacept and placebo treatment groups were similar with respect to demographic characteristics and most baseline disease characteristics. The majority of subjects were women, white, with a mean age of 52 years, and a mean duration of RA of approximately 10 years. Medical history findings were consistent with active RA and were generally similar among treatment groups. In both treatment groups, the percentage of subjects with select comorbidities was 6 to 7% for type 1 or 2 diabetes, 6% for asthma, 4% for chronic pulmonary obstructive pulmonary disease, and 1 to 2% for congestive heart failure.

Baseline Demographic and Disease Characteristics (IM101031)

<table>
<thead>
<tr>
<th></th>
<th>Abatacept N = 959</th>
<th>Placebo N = 482</th>
<th>Total N = 1441</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age,(y), Mean (SD)</td>
<td>52.4 (11.7)</td>
<td>52.1 (12.0)</td>
<td>52.3 (11.8)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>170 (17.7)</td>
<td>84 (17.4)</td>
<td>254 (17.6)</td>
</tr>
<tr>
<td>Females</td>
<td>789 (82.3)</td>
<td>398 (82.6)</td>
<td>1187 (82.4)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>818 (85.3)</td>
<td>407 (84.4)</td>
<td>1225 (85.0)</td>
</tr>
<tr>
<td>Black</td>
<td>49 (5.1)</td>
<td>29 (6.0)</td>
<td>78 (5.4)</td>
</tr>
<tr>
<td>Other</td>
<td>92 (9.6)</td>
<td>46 (9.5)</td>
<td>138 (9.6)</td>
</tr>
<tr>
<td>Duration of RA (y), Mean (SD)</td>
<td>9.7 (8.7)</td>
<td>9.8 (9.2)</td>
<td>9.7 (8.9)</td>
</tr>
</tbody>
</table>

Population: All randomized and treated subjects.
Source: Tables 8.2A and 8.2B; Appendices 8.2A and 8.2B
Background anti-rheumatic medications use at the time of randomization (Day 1) was comparable in the abatacept and placebo groups, and the majority of subjects in either group did not have a change in their background RA therapy during the double-blind period. A total of 97% of subjects in both groups used at least 1 non-biologic DMARD, with methotrexate being the most common (75%–78%). Biologic RA therapy was used by 9% to 10% of subjects, and between 62% to 63% of subjects used an oral and/or injectable corticosteroid. Subjects receiving background biologic RA therapy during the double-blind period tended to be older (mean, 53–54 years), have a longer duration of RA (mean, 11–12 years), and be on 2 or more therapies for RA (56%–67%) compared with those who received non-biologic RA therapy only (52 years, 9-10 years, and 27%–32%).

**EFFICACY RESULTS:** In subjects with active RA (with or without medical co-morbidities) receiving other non-biologic and biologic DMARDs, abatacept improved physical function and physician- and subject-reported disease outcomes. Median percentage improvements from baseline in subject- and physician-reported disease outcomes (subject pain assessment, subject global assessment, physician global assessment) at Day 365 were higher for abatacept-treated subjects (47.5%, 47.1%, and 63.3%, respectively) compared with placebo-treated subjects (26.0%, 30.4%, and 43.0%, respectively). Median percentage improvements from baseline in physical function (HAQ disability index) (28.6% vs 14.3%) were greater for subjects treated with abatacept compared to placebo at Day 365.

**SAFETY RESULTS:** Overall, abatacept at a fixed dose approximating 10 mg/kg, administered IV monthly on a background of non-biologic and/or biologic DMARDs for 1 year to subjects with active RA, was generally well tolerated and associated with a favorable safety profile. The overall incidence rates of AEs and SAEs were comparable between the abatacept and placebo groups; the rate of discontinuation due to AEs was low in both treatment groups. Severe or very severe AEs were reported for 16% of abatacept subjects and 15% of placebo subjects.

**Overview of Safety During Double-blind Period (IM101031)**

<table>
<thead>
<tr>
<th>Number (%) Subjects</th>
<th>Abatacept</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 959</td>
<td>N = 482</td>
</tr>
<tr>
<td>Deaths</td>
<td>5 (0.5)</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>SAEs</td>
<td>123 (12.8)</td>
<td>59 (12.2)</td>
</tr>
<tr>
<td>Related SAE</td>
<td>23 (2.4)</td>
<td>13 (2.7)</td>
</tr>
<tr>
<td>Discontinuation due to SAE</td>
<td>23 (2.4)</td>
<td>7 (1.5)</td>
</tr>
<tr>
<td>AEs</td>
<td>866 (90.3)</td>
<td>417 (86.5)</td>
</tr>
<tr>
<td>Related AEs</td>
<td>534 (55.7)</td>
<td>239 (49.6)</td>
</tr>
<tr>
<td>Discontinuation due to AE</td>
<td>52 (5.4)</td>
<td>20 (4.1)</td>
</tr>
</tbody>
</table>

Population: All treated subjects. Source: Table 12.1 and Appendix 12.0 MedDRA version 7.0

SAEs include hospitalizations for elective surgical procedures.

Related AEs or SAEs defined as investigator assessment of certain, probable, possible, or missing.

The overall rates of AEs or related AEs among subjects receiving abatacept in combination with another biologic for RA (95% and 59%, respectively) were not appreciably different from rates seen for the placebo + Biologic RA Therapy subgroup (89% and 56%, respectively). The rates of discontinuation for AEs and
discontinuation for SAEs were higher in the abatacept + Biologic RA Therapy subgroup (9% and 5%, respectively) compared with the placebo + Biologic RA Therapy subgroup (3% each).

Five subjects (0.5%) in the abatacept group and 4 subjects (0.8%) in the placebo group died during the 1-year double-blind treatment period. Four of the deaths occurring in the abatacept group, and 3 of the deaths in the placebo group, were likely cardiac-related and a result of the subject's underlying co-morbidities. For the remaining abatacept subject, no autopsy was performed and the cause of death was unknown. The remaining death in the placebo group was the result of Pneumocystis carinii pneumonia.

Infections/infestations were the most common AEs reported in both treatment groups (abatacept: 56%; placebo: 54%). Upper respiratory tract infection and nasopharyngitis were the most frequent infections and occurred at similar rates in the abatacept and placebo groups. Fewer than 4% of subjects in either treatment group had a severe or very severe infection. Serious pre-specified infections were reported in 2% of subjects in the abatacept group and in 1% of subjects in the placebo group. For the majority of subjects, the serious pre-specified infections were treatable and did not result in discontinuation of treatment (abatacept: 12 of 17 subjects; placebo: 5 of 5 subjects). All of the serious pre-specified infections in the abatacept group were bacterial in origin. During the year-long study period, no infection attributed to an opportunistic microorganism was seen in subjects receiving abatacept, no cases of Mycobacterium tuberculosis (TB) were observed, and no fatalities due to infection occurred.

Pre-specified serious infections were reported for 4 (4%) subjects in the abatacept + Biologics RA Therapy subgroup, and these consisted of singular events of cellulitis, intestinal abscess, infective bursitis, and pyelonephritis. The rate of serious (pre-specified) infections were 2% in the placebo + Biologics RA Therapy subgroup.

The overall incidence rate of neoplasms (benign, malignant, unspecified) was 4% in both treatment groups. Neoplasms reported as SAEs occurred in 2% of abatacept-treated subjects and 1% of placebo subjects. Most of these were skin carcinomas (primarily basal cell or squamous cell carcinomas) that did not result in interruption or discontinuation of study treatment. Serious breast cancer was reported in 1 subject in the abatacept group and in 2 subjects in the placebo group; there were 3 reports of serious lung cancer (1 subject also had a cancerous renal mass) in the abatacept group compared to none in the placebo group. There were no reports of lymphoma.

Pre-specified autoimmune events were reported at a similar rate in the 2 treatment groups (3% for each). Reported events in both treatment groups included keratoconjunctivitis sicca and vasculitis which can be associated with RA. There were no reports of multiple sclerosis or other demyelinating disorders.

Pre-specified peri-infusional events represented a collection of AE terms selected from MedDRA codes for a possible association with an infusion reaction. Pre-specified acute infusional (within 1 hour of the start of infusion) and pre-specified peri-infusional (within 24 hours of infusion) events occurred more frequently in the abatacept group (acute: 10%; peri-infusional: 24%) compared with the placebo group (7% and 20%, respectively). The most frequent of these events were headache and dizziness, and few subjects in the abatacept group had a severe (pre-specified) acute (0.7%) or peri-infusional (2%) event. Two subjects in each treatment group experienced hypersensitivity reactions within 1 hour of infusion. Overall, pre-specified acute infusional or peri-infusional events resulted in discontinuation in only a small number of subjects (abatacept: 0.6%; placebo: 0.2%).

Clinical laboratory data were unremarkable and no safety issues were identified. Neutropenia (neutrophil count < 0.5 x 10^9) was observed in 1 subject in each treatment group. Treatment with abatacept was not associated with conversion to seropositivity for anti-sDNA or anti-ANA above the rate observed in the placebo group.
CONCLUSIONS:

The results of this multinational, multicenter, randomized, double-blind, placebo-controlled, Phase 3 study support the use of abatacept at a fixed dose approximating 10 mg/kg administered IV monthly when used in subjects with RA typical of patients seen in clinical practice. Conclusions from the study are:

- The overall rates of AEs (90% and 87%), severe or very severe AEs (16% and 15%), and SAEs (13% and 12%) were comparable between the abatacept and placebo treatment groups. Discontinuation for AEs was low in both treatment groups (abatacept: 5%; placebo: 4%).
- Infections (mainly upper respiratory tract infections and nasopharyngitis) occurred in similar proportions of subjects in the abatacept and placebo groups and were severe in only a small percentage of subjects (< 4%). None of the infections in the abatacept group were fatal. The incidence of serious (pre-specified) infections was higher with abatacept (2%) than with placebo (1%). All of the serious infections in the abatacept group were consistent with bacterial etiologies.
- No TB or opportunistic infection was reported with abatacept.
- There were increases in rates of discontinuation for AEs or SAEs and in serious (pre-specified) infections when abatacept was used in combination with another biologic for RA.
- The frequency of neoplasms was similar for abatacept and placebo.
- Infusions of abatacept were well-tolerated, although acute and peri-infusional AEs were somewhat more frequent with abatacept than with placebo. Headache and dizziness were most common (pre-specified) acute infusional and peri-infusional events. Few subjects in the abatacept group had a severe acute infusional (0.7%) or peri-infusional (2%) event, and no event was considered very severe. Pre-specified acute infusional and peri-infusional events resulted in discontinuation in less than 1% of subjects in either treatment group.
- Pre-specified autoimmune events were reported with a similar rate and no major autoimmune diseases (eg, multiple sclerosis or other demyelinating disorders) were reported during the study.
- Abatacept on a background of non-biologic and/or biologic RA therapies demonstrated improvements in subject assessments of pain, subject and physician global assessments of disease activity, and subject assessments of physical function (HAQ Disability Index).
- Abatacept was generally safe and well tolerated when given to subjects who had active RA, with or without co-morbidities, receiving other RA therapies.

DATE OF REPORT: 29-OCT-2004