BRISTOL-MYERS SQUIBB COMPANY

Abatacept

Final Clinical Study Report for Study IM101173

A Phase 3, Multicenter, Stratified, Open Label Study to Evaluate the Immunogenicity, Steady State Trough Level, and Safety of Subcutaneous Abatacept in Subjects with Rheumatoid Arthritis Administered with or Without Background Methotrexate

Indication: Rheumatoid Arthritis
Phase: 3
Study Initiation Date: 14-Dec-2007
Study Completion Date: 19-Dec-2008 for Short-term Period
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THIS STUDY WAS CONDUCTED IN ACCORDANCE WITH GOOD CLINICAL PRACTICE

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SYNOPSIS

Clinical Study Report for Study IM101173

TITLE OF STUDY: A Phase 3, Multicenter, Stratified, Open Label Study to Evaluate the Immunogenicity, Steady State Trough Level, and Safety of Subcutaneous Abatacept in Subjects with Rheumatoid Arthritis Administered With or Without Background Methotrexate

INVESTIGATORS/STUDY CENTERS: 22 sites worldwide: 15 sites in the United States of America, 3 sites in Australia, 2 sites in South Africa, and 2 sites in Mexico.

PUBLICATIONS: None.

STUDY PERIOD: Study Initiation Date: 14-Dec-2007
Study Completion Date (Short-term Period): 19-Dec-2008

INTRODUCTION: Concerns unique to subcutaneous (SC) administration of abatacept are local tolerance and the potential for increased immunogenicity.

OBJECTIVES:

Primary Objective: To evaluate the immunogenicity of abatacept when used with or without methotrexate (MTX) in the absence of an intravenous (IV) loading dose of abatacept.

Secondary Objectives:
- To determine the safety and tolerability of SC abatacept when administered concomitantly with or without MTX.
- To evaluate the trough serum concentration levels of subjects receiving SC abatacept when introduced concomitantly with or without MTX.
- To assess the disease activity between the 2 groups as measured by Disease Activity Score (DAS) 28 (C-reactive protein [CRP]) throughout 4 months.

Observed serum concentration data for abatacept will be presented in a separate report.

METHODOLOGY: This multicenter study was designed to evaluate the immunogenic potential of SC abatacept with or without background MTX and in the absence of an initial intravenous (IV) loading dose of abatacept. It consisted of a screening period, short-term treatment period of 4 month’s duration, and a long-term extension period. Adults with active rheumatoid arthritis (RA) who met the inclusion and exclusion criteria were stratified 1:1 into 2 cohorts based on their current use of MTX. Subjects in the SC abatacept monotherapy cohort (referred to as “SC Aba Only” in data displays) were not receiving MTX at screening (ie, MTX naive, or discontinued MTX due to lack of efficacy or tolerability at least 4 weeks prior to first injection of SC abatacept). Subjects in the SC abatacept + MTX cohort (referred to as “SC Aba +
MTX” in data displays) were receiving a stable MTX dose of ≥ 10 mg once weekly for at least 4 weeks prior to first injection of SC abatacept. During the short-term treatment period, all subjects received abatacept 125 mg SC, once weekly; subjects in the SC abatacept + MTX cohort remained on a stable dose of MTX. Subjects who completed the short-term treatment period were eligible for entry into the long-term extension period. Results of the long-term extension period are reported separately.

NUMBER OF SUBJECTS (Planned and Analyzed): Planned: ~ 100 subjects (~ 50 in SC abatacept monotherapy cohort and ~ 50 in the SC abatacept + MTX cohort). Treated and analyzed for safety and efficacy (all treated analysis population): 49 in SC abatacept monotherapy cohort, 51 in SC abatacept + MTX cohort. Treated and analyzed for immunogenicity (immunogenicity analysis population): 49 SC abatacept monotherapy cohort, 51 SC abatacept + MTX cohort.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Subjects at least 18 years of age at entry, satisfying diagnostic criteria for definite RA (1987 American Rheumatism Association criteria) with no other rheumatic disease, having a Subject Global Assessment of Disease Activity visual analogue scale (VAS) score of > 20 mm, and requiring a new therapeutic intervention for RA. Subjects in the SC abatacept monotherapy cohort must have been MTX naive and considered a non-responder to at least one non-biological disease-modifying antirheumatic drug, or discontinued MTX therapy due to lack or efficacy or tolerability at least 4 weeks prior to the first dose of SC abatacept. Subjects in the SC abatacept + MTX cohort must have currently been receiving MTX at a stable dose of ≥ 10 mg once weekly for at least 4 weeks prior to first injection of SC abatacept.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT: Abatacept was administered SC by the subject or caregiver on Day 1 and weekly thereafter through Day 113 (Month 4). Batch numbers of abatacept were 7F25817 and 7L34304.

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

CRITERIA FOR EVALUATION:

Efficacy: Mean change from baseline in DAS 28 (CRP) and HAQ-DI score at Day 113 (Month 4), and proportion of subjects with ≥ 1.2-unit reduction from baseline in DAS 28 (CRP) at Day 113.

Safety: Adverse events (AEs), serious adverse events (SAEs) including deaths, discontinuations due to AEs, changes in vital signs, and clinical laboratory test abnormalities reported during the study. Additionally, the AEs that may be associated with the use of immunomodulatory drugs were assessed. These AEs of special interest included infections, autoimmune disorders, malignancies, and injection reaction AEs (systemic AEs occurring within 24 hours of SC injection and local injection site reactions).

Pharmacodynamics: The primary immunogenicity endpoint was the proportion of subjects with positive antibody (anti-abatacept and anti-CTLA4-T) response at Day 113 (Month 4) based on enzyme-linked immunosorbent assay (ELISA).

STATISTICAL CONSIDERATIONS: A continuity-corrected Chi-square test was used to compare the immunogenicity rate of the 2 cohorts at Day 113 at the 2-sided 5% significance level; a 2-sided 95% confidence intervals (CI) of the difference in the proportion of subjects in each cohort with a positive antibody response was also calculated. Analyses of safety and efficacy were descriptive in nature and summaries were done by cohort and visit day. Efficacy analyses were conducted on as-observed data.

SUMMARY OF RESULTS:

Disposition, Demographics, and Other Pertinent Baseline Characteristics: Most subjects in the SC abatacept monotherapy (93.8%) and SC abatacept + MTX (98.0%) cohorts completed the 4-month short-term treatment period. There were slight imbalances between the 2 cohorts with respect to race and gender that were not unexpected given the lack of randomization and small cohort sizes, and were not considered clinically meaningful.
### Efficacy Results

Similar improvements were observed in the efficacy measures for the 2 cohorts over the short-term treatment period. At Day 113, the mean change from baseline (95% CI) in the DAS 28 (CRP) score was -1.67 (-2.06, -1.28) in the SC abatacept + MTX cohort and -1.94 (-2.46, -1.42) in the SC abatacept monotherapy cohort. The proportion of subjects in these 2 cohorts with a Clinically Significant Improvement, defined by a reduction from baseline in the DAS 28 (CRP) score of ≥ 1.2, was 62.5% and 66.7%, respectively.

### Safety Results

Abatacept, administered SC for 4 months, was generally well tolerated in subjects with RA when given as monotherapy or on a background of MTX. During the short-term treatment period, the frequency and type of safety events were generally comparable between the 2 cohorts. Evaluation of laboratory data revealed no clinically significant trends or safety concerns. All local injection site reactions were mild and none resulted in treatment discontinuation.

### Immunogenicity Results

At the end of the short-term treatment period (Day 113), none of the 95 subjects with immunogenicity data (50 in SC abatacept + MTX cohort; 45 in SC abatacept monotherapy cohort) were seropositive for anti-abatacept or anti-CTLA4-T antibodies (ELISA assay). Positive antibody responses (based on ELISA) were observed infrequently at earlier time points during the short-term treatment period or during the follow-up for subjects who did not enter the long-term period. These positive antibody responses were transient, generally occurred before Day 85, and were associated with low titers. During the short-term treatment period, the overall immunogenicity rate at any time in the SC abatacept monotherapy and SC abatacept + MTX cohorts was 4.1% (2/49) and 3.9% (2/51), respectively, based on the ELISA assay. Only 1 seropositive response was observed following treatment discontinuation.
subject in the SC abatacept monotherapy cohort was seropositive for anti-CTLA4-T antibodies at post-treatment Day 85 and did not develop neutralizing antibodies; this subject was withdrawn for lack of efficacy after receiving 12 SC injections. There did not appear to be any correlation of the development of antibodies with clinical safety or efficacy findings.

CONCLUSIONS:

- No positive immunogenicity response (based on ELISA assay) was seen at 4 months of treatment with abatacept, injected SC at a weekly dose of 125 mg, either as monotherapy or on a background of MTX and in the absence of an initial IV loading dose, in subjects with RA.

- Although the incidence of positive antibody responses at any time during the short-term treatment period was low, no clinically significant safety and efficacy issues were observed for those few subjects who exhibited a positive antibody response to abatacept. Only 1 seropositive response (anti-CTLA4-T antibody based on ELISA assay; negative for neutralizing antibodies) was observed following treatment discontinuation.

- Abatacept, administered SC at a weekly dose of 125 mg, for 4 months was generally well tolerated in subjects with RA.

- The limited open-label data are supportive of a clinical effect for abatacept, administered SC at a weekly dose of 125 mg, in improving the signs and symptoms of RA and physical function of subjects with RA.

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