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

Final Clinical Study Report for Study IM101179

TITLE OF STUDY: Multicenter, open-label study to assess early response to abatacept with background methotrexate using Power Doppler Ultrasonography (PDUS) in patients with active rheumatoid arthritis (RA) and inadequate response to methotrexate (MTX)

INVESTIGATORS/STUDY CENTERS: 23 sites in Europe in the ST period, including 7 sites in Italy, 5 sites in Spain, 5 sites in France, 2 sites in Norway, and 1 site each in Denmark, Hungary, Germany, and the United Kingdom

PUBLICATIONS: D'Agostino MA, Wakefield R, Berner-Hammer H, et al. Early response to abatacept plus MTX in MTX-IR RA patients using power Doppler ultrasonography: an open-label study. Presented at European League Against Rheumatism (EULAR) Annual European Congress of Rheumatology, 6-9 June 2012, Berlin, Germany.

STUDY PERIOD: Study Initiation Date: 08-Dec-2008 **CLINICAL PHASE** 3b

Final Subject Visit: 28-Oct-2011

INTRODUCTION: The management of RA has evolved to include more early aggressive therapy, according to the Treat to Target recommendations, to reach at least Low Disease Activity Score (LDAS) in the first 3 to 6 months and prevent long-term structural damage progression and disability. The imaging modality, PDUS, has shown superiority for visualizing synovial inflammation in RA that is not detected by clinical and conventional radiographic examinations. It can simultaneously image bone and soft tissue, detect effusion, distinguish between active and fibrotic synovial hypertrophy, and permit a dynamic evaluation of the affected joint(s). Study IM101179 is the first international multicentre clinical trial using a global validated ultrasound synovitis score in RA; no other study has previously assessed a composite scoring system consisting of Grayscale and Power Doppler. In addition to assessing the early impact of abatacept on synovitis, this study explored whether PDUS can predict clinical response at later time points.

OBJECTIVES:

Primary Objective: The primary objective was to assess the occurrence of early signs of response to abatacept with background MTX, as defined by improvement of synovitis measured by global Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) PDUS score of the affected metacarpophalangeal (MCP) joints (MCP 2-5 only) during the study in subjects with active RA and inadequate response to MTX.

Secondary Objective: The secondary objective was to estimate the predictability of the Global PDUS score or its components of the synovitis level of the MCP 2-5 joints to disease activity measured by Disease Activity Score 28 based on C-reactive protein (DAS28-CRP) or DAS28-CRP derived criteria at specified time points during the study.

Exploratory Objectives: Exploratory study objectives included:

- To explore the occurrence of early signs of response to abatacept with background MTX, as defined by improvement in synovitis measured by PDUS, on 22 joints evaluated bilaterally (i.e., MCP 1, wrist, 1-5th proximal interphalangeal joint (PIP), elbow, shoulder, knee, 1-5th metatarsophalangeal (MTP), tibiotalar, talonavicular, and calcaneocuboidal joints)
- To estimate the predictability of the Global 44-joints PDUS score measured by DAS28-CRP or DAS28-CRP derived criteria at specified time points during the study
- To identify a minimum set of joints that needs to be monitored to adequately assess disease activity through PDUS assessment

The remaining exploratory objectives are listed in the report body.

METHODOLOGY: This was a multi-national, multi-center, open-label study that consisted of a screening period (including washout for subjects on combination therapy including MTX or another disease-modifying antirheumatic drug[s] [DMARDs]) and a 6-month open-label treatment period. During the open-label treatment period, all subjects received intravenous (IV) infusions of abatacept at a weight-tiered dose of 10 mg/kg (based on screening body weight) on background therapy with MTX (stable dose of at least 15 mg/week) at approximately monthly intervals through Day 169 (8 infusions in total). Thirty days after the last infusion of abatacept, subjects were evaluated at a final follow-up visit, and this was considered the final visit of the study for the subject.

NUMBER OF SUBJECTS (Planned and Analyzed): Planned: 100 subjects. Enrolled and treated: 104 subjects.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Men and women with active RA according to the American Rheumatism Association (ARA) diagnostic criteria (1987) for at least 6 months, receiving treatment with MTX at a dose of ≥ 15 mg/week for at least 3 months, and on a stable dose for at least 28 days, prior to baseline. At screening and baseline, subjects must have had a Disease Activity Score 28 based on C-reactive protein (DAS28-CRP) of > 3.2 (or a tender joint count [TJC] ≥ 6 and CRP > upper limit of normal [ULN]) and a total synovitis PDUS score > 1 for at least 2 MCP joints (MCP 2-5) and a ≥ 1 for at least 1 other MCP joint. Subjects receiving oral corticosteroids were to be on a stable dose (≤ 10 mg predisone/day) for at least 25 of the 28 days prior to baseline, and could not have received any prior treatment with a biologic DMARD.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT: Abatacept was administered IV at a fixed dose approximating 10 mg/kg (500 mg for subjects weighing < 60 kg, 750 mg for subjects weighing 60 to 100 kg, and 1 gram for subjects weighing > 100 kg) on Days 1, 15, 29, 57, and then at monthly intervals through Day 169. Batch numbers of IV abatacept were 7M21179, 8A37103, 8B36751.8A, 8B36751.8G, 8B36751.8H, 8B36751.8P, 8H35745.8C, 8H35745.8D, 9A48666.9G, and 9A48666.9H.

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

CRITERIA FOR EVALUATION:

Efficacy: The primary efficacy assessments consisted of PDUS assessments of the MCP 2-5 joints. The Global PDUS (MCP 2-5) corresponded to the sum of the Total synovitis scores across the MCP 2-5 joints bilaterally (n = 8), with each synovitis component evaluated separately and scored on a scale of 0 to 3. Secondary efficacy endpoints included the predictability of the Global PDUS (MCP 2-5) score or its components (Synovial Hypertrophy, Power Doppler Signal, Joint Effusion) to the DAS28-CRP based clinical status criteria, the actual and change from baseline for the Global PDUS (MCP 2-5) component scores at each scheduled assessment, the proportion of subjects who improved their disease status, based on the DAS28-CRP score, to Remission (< 2.6), LDAS (≤ 3.2), or Clinically Meaningful Improvement (decrease from baseline of < 1.2), and the change from baseline in the DAS28-CRP. The exploratory endpoints provided at all assessment time points included baseline and change from baseline in Global

PDUS scores (MCP 2-5, component MCP 2-5 and 44 joint) and Global PDUS scores for the individual joints.

Safety: Safety was assessed by monitoring adverse events (AEs), serious adverse events (SAEs) including deaths, and discontinuations due to AEs, and by evaluating changes in vital signs and clinical laboratory test abnormalities during the 6-month treatment period. Additionally, AEs of special interest including infections, autoimmune disorders (pre-specified), malignancies, and infusional reactions (acute reactions occurring within 1 hour after the start of infusion, and peri-infusional reactions occurring within 24 hours after the start of infusion) were assessed.

STATISTICAL CONSIDERATIONS: Descriptive statistics of the change from baseline scores were provided by time point using a last observation carried forward (LOCF) approach, with calculation of the point estimate, standard error (SE), and 95% confidence interval (CI) of the mean change. The primary efficacy endpoint was the time point showing the earliest sign of improvement in the Global PDUS (MCP 2-5) score, defined as the first time point for which the 95% CI did not include '0'at that and all subsequent time points. Receiver Operator Characteristics (ROC) analysis methodology was used to examine whether imaging efficacy endpoints at early time points are predictive of disease activity as measured by DAS28-CRP at later time points. The ROC curve was considered acceptable for prediction if its area under the curve (AUC) was ≥ 0.7. Principal component analysis (PCA) based method was used to define a reduced set of joints that best represents Global PDUS (44 joints) score.

SUMMARY OF RESULTS:

Disposition, Demographics, and Other Pertinent Baseline Characteristics: Of the 104 treated subjects, 89 (85.6%) completed the 6-month open-label treatment period. The most common reason for discontinuation was AEs (n = 7, 6.7%). At study entry, subjects had a mean age of 56.4 years, had been diagnosed with RA for an average of 7.3 years, had a mean DAS28-CRP score of 5.3, and a Global PDUS (MCP 2-5) score of 12.6 (Table 1). All subjects were receiving background MTX therapy. Approximately one-half (52.9%) of treated subjects were receiving oral and/or injectable corticosteroids at baseline, with the mean oral corticosteroid dose of 6.41 mg.

Table 1: Demographic and Baseline Characteristics: All Treated Subjects

Parameter	Abatacept 10 mg/kg N = 104
Age (years), mean (SD)	56.4 (14.1)
Gender, Female, n (%)	87 (83.7)
Race, White, n (%)	101 (97.1)
Duration of RA (yr), mean (SD)	7.3 (9.1)
Tender joint count, mean (SD)	19.5 (12.5)
Swollen joint count, mean (SD)	13.0 (7.6)
High sensitivity CRP (mg/dL), mean (SD)	1.433 (1.919)
DAS28-CRP score, mean (SD)	5.288 (1.105)
Global PDUS (MCP 2-5) score, mean (SD)[a]	12.6 (4.1)

[a] Based on 96 subjects; excluded data from site 32 due to quality and compliance issues with PDUS.

Efficacy Results: The following is a brief summary of efficacy, as it relates to the primary and key secondary efficacy endpoints.

- The primary objective of this study was to assess the occurrence of early signs of response to abatacept as defined by improvement of synovitis measured by PDUS of the affected MCP 2-5 joints bilaterally. The time point at which early signs of Global PDUS improvement were observed was defined as the earliest time point for which '0' was not included in the 95% CIs for the mean changes from baseline in Global PDUS (MCP 2-5) score at that and all later time points.

  - A LOCF analysis showed that this criterion was met at Day 7, where a mean change from baseline in Global PDUS (MCP 2-5) score of -0.7 [95% CI: (-1.2, -0.1)] was observed, that further increased gradually over time up to and including Day 169, where the mean change from baseline in Global PDUS (MCP 2-5) score was -4.8 [95% CI: (-5.8, -3.9)].
  - These findings were fully confirmed using an as observed case analysis.
- Similar results showed an improvement as early as Day 7 with the Power Doppler Signal, one of the core components of the Global PDUS (MCP 2-5) score; the mean change from baseline at Day 7 for the Power Doppler Signal (MCP 2-5) score was -0.9 [95% CI: (-1.5, -0.3)]. For the 2 other core components of the Global PDUS (MCP 2-5) score, Synovial Hypertrophy and Joint Effusion, the earliest time point at which an improvement from baseline was observed was Day 15 and Day 29, respectively.
- The secondary objective of this study was to examine whether the imaging efficacy endpoint, Global PDUS (MCP 2-5) score at early time points was predictive of disease activity at Day 169 as measured by clinical efficacy endpoints with the following DAS28-CRP derived criteria: Remission, LDAS, or Clinically Meaningful Improvement (DAS28 $\geq$ 1.2). In the ROC curve analyses performed to address the secondary objective, an AUC of $\geq$ 0.7 was considered acceptable for prediction.
  - None of the early Global PDUS (MCP 2-5) or Global PDUS Component (MCP 2-5) scores (Days 7 to 113) were able to predict a clinical response of Remission, LDAS, or Clinically Meaningful Improvement (based on DAS28 CRP) at Day 169 (or at any other time point) with an AUC of at least 0.7.
- There was a significant decrease (i.e., improvement) in the DAS28-CRP score at Day 7, which gradually improved to -2.13 [95% CI: (-2.39, -1.86)] at Day 169. At Day 169, 40.8% of subjects experienced Remission (DAS28-CRP score $<$ 2.6), 57.1% of subjects fulfilled the criteria for Low Disease Activity (DAS28-CRP score $\leqslant$ 3.2), and 74.2% of subjects had a Clinically Meaningful Improvement (change from baseline in DAS28-CRP of $\geq$1.2). The 95% CIs for the mean change from baseline in the DAS28 CRP score did not include -1.2 (i.e., the threshold for clinically meaningful improvement) as of Day 57.
- For the exploratory objectives:
  - A reduced subset of joints that best represents the Global PDUS (44 joints) score over the 3 time points (baseline, Day 85, Day 169) was identified and comprised of the shoulder, elbow, wrist, MCP 1, MCP 4, PIP 2, knee, MTP 3, and MTP 5 joints.
  - Progressive improvements from baseline were seen in the Global PDUS (44 joint) score over the 6 month treatment period with abatacept. The mean change from baseline (95% CI) at Day 7 was -1.7 (-3.4, -0.1) and improved up to Day 169 to -15.7 (-19.0, -12.5). In general, the earliest signs of improvement in the Global PDUS scores (i.e., earliest time point at which 95% CI for mean change from baseline score consistently did not contain 0) were observed for the wrist, MCP 1, sum of PIP 1-5, sum of MTP 1-5, and MTP 2, MTP 3, MTP 4, and MTP 5 joints (Days 15 to 29).
  - None of the early Global PDUS (44 joint) scores were associated with a ROC AUC of at least 0.7 for predicting a clinical response (Remission, LDAS, Clinically Meaningful Improvement) at later time points. No optimal threshold time point combination could be identified that would permit classification of subjects as future DAS28-CRP responders or non-responders according to their Global PDUS (44 joint) score.
  - A single time point combination involving these scores showed acceptable predictability. Synovial Hypertrophy at Day 7 could predict LDAS at Day 169. Overall, 69.9% of subjects in this study were classified correctly as responders or non-responders based on both their Global PDUS (44 joint) Synovial Hypertrophy score at Day 7 and DAS28-CRP LDAS response at Day 169 (accuracy).

Safety Results: Abatacept, administered IV monthly at a fixed dose approximating 10 mg/kg for 6 months on a background of MTX in subjects with RA was consistent with previous studies of abatacept in this population (Table 2). No new safety signals were identified in this study.

Table 2: Overview of Safety - All Treated Subjects

Parameter	Abatacept 10 mg/kg N = 104
Deaths	0
SAEs	6 (5.8)
Related SAEs	2 (1.9)
Discontinuations due to SAEs	1 (1.0)
AEs	62 (59.6)
Related AEs	22 (21.1)
Discontinued due to AEs	6 (5.8)
AEs of interest:	
Infections	20 (19.2)
Malignancy	1 (1.0)
Autoimmune disorders (pre-specified)	2 (1.9)
Infusion reactions (pre-specified)	
Acute (≤ 1 hour after start of dosing)	4 (3.8)
Peri-infusional (≤ 24 hours after start of dosing)	10 (9.6)

AE = adverse event; SAE = serious adverse event.

- There were no deaths in this study.
- Six subjects (5.8%) experienced a SAE (pulmonary fistula, pleural effusion, hypertension, endometriosis, atrial fibrillation, dementia, infective bursitis), 2 of which were considered by the investigator to be at least possibly related to study treatment (infective bursitis, atrial fibrillation).
- Overall, AEs were reported during the open-label treatment period for 59.6% of subjects receiving abatacept, of which 21.2% were assessed as related to study drug. Cough (8.7%) and nasopharyngitis (6.7%) were the only AEs reported in 5% or more of subjects.
- Six subjects (5.8%) were discontinued from the study treatment due to AEs; for 1 subject, the AEs leading to discontinuation were serious (dementia). For 3 subjects, the AE leading to discontinuation occurred within 56 days after receiving the last dose of abatacept; for the other 3 subjects, the AE(s) leading to discontinuation occurred while the subject was still on treatment.
- The overall occurrence of AEs in the SOC, Infections and Infestations, was 19.2%, and the most frequently reported infection was nasopharyngitis (6.7%). All but 1 of the reported infection/infestation AEs were assessed as mild or moderate in intensity, and none led to discontinuation of study drug. One infection (infective bursitis) was severe in intensity and serious.
- One subject (1.0%) was reported to have a malignant neoplasm (skin cancer) during the open-label treatment period.
- Autoimmune disorders (prespecified) were reported for 2 subjects (1.9%), both of which were mild in intensity and not serious (dry eye and psoriasis).
- Acute infusional AEs (prespecified), occurring within 1 hour after the start of study drug infusion, were reported for 4 subjects (3.8%). For 1 subject, the acute infusional AEs (dizziness, tachycardia, erythema multiforme) led to discontinuation of treatment. None of the acute infusional AEs were severe in intensity or serious.

- Peri-infusional AEs (prespecified), occurring within 24 hours after the start of study drug infusion, were reported in 9.6% of subjects. None of these events were severe in intensity or serious.
- Evaluation of clinical laboratory and vital sign data revealed no clinically significant trends or safety concerns.

CONCLUSIONS:

- In patients with RA and an inadequate response to MTX, abatacept plus background MTX resulted in early signs of significant improvement in synovitis as assessed by changes in the Global PDUS score at Day 7.
- Early signs of improvement were seen at Days 7, 15 and 29 for Doppler signal, synovial hypertrophy and joint effusion, respectively.
- Increasing reductions in the Global PDUS score and its components were observed throughout the 6 months of the study.
- The Global PDUS (MCP 2-5) was not able to adequately predict later clinical response at Day 169 when using DAS28-CRP-derived criteria.
- This study identified a global PDUS reduced 9 paired joint score that best represents the global PDUS 44-joint score.
- Exploratory analysis suggested that abatacept + MTX resulted in early (Day 7, by global PDUS 44-joint score) and continuous reductions in synovitis to Day 169 (with global PDUS 44-joint score and reduced joint set).
- Post-hoc analysis suggested that early responders could be identified by numerically greater improvement of either global PDUS 44 joint score or reduced set of joints.
- Reductions in DAS28 (CRP) were observed from Day 7 onwards, and increasingly higher proportions of patients achieved remission, LDAS and clinically meaningful improvement over time, consistent with recent other abatacept trials in patients with an inadequate response to MTX
- Abatacept plus MTX treatment was well tolerated, and safety findings were consistent with those of previous reports in a similar patient population.

DATE OF REPORT: 11-Oct-2012