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

SYNOPSIS

Final Clinical Study Report for Study IM119015

TITLE OF STUDY: A Randomized, Parallel Group, Double-Blind, Placebo Controlled Study to Evaluate the Clinical Efficacy and Safety of BMS-582949 Given Orally to Subjects with Rheumatoid Arthritis Having an Inadequate Response to Methotrexate

INVESTIGATORS/STUDY CENTERS: 28 sites, including 8 sites in the United States (US), 5 sites in Mexico, 3 sites in Argentina, 3 sites in France, 3 sites in Spain, 3 sites in the Czech Republic, 2 sites in Taiwan, and 1 site in Korea

PUBLICATIONS: None.

STUDY PERIOD: Study Initiation Date: 26-Mar-2008 **CLINICAL PHASE:** 2a

Study Completion Date: 30-Sep-2009

INTRODUCTION: BMS-582949 is a selective and potent inhibitor of p38 mitogen-activity protein kinases and is expected to show activity in rheumatoid arthritis (RA) by inhibiting the production of inflammatory mediators of this disease, including tumor necrosis factor-α (TNF-α) and interleukin-1β.

OBJECTIVES:

Primary Objective: To assess the clinical efficacy of BMS-582949 at a dose of 300 mg q.d. compared to placebo at 12 weeks as measured by American College of Rheumatology 20% improvement criteria (ACR 20) in subjects with RA who are on background therapy with methotrexate (MTX).

Secondary Objectives:

- To assess the safety and tolerability of BMS-582949 in subjects with RA
- To assess the proportion of subjects who achieve ACR 50% improvement criteria (ACR 50) or ACR 70% improvement criteria (ACR 70) response in each treatment arm
- To assess the reduction in disease activity over time as measured by the Disease Activity Score (DAS) 28 and ACR-N over 16 weeks
- To assess the proportion of subjects achieving a 20 percent change in the assessment of pain, disease activity, and fatigue using the ACR Disease Activity Visual Assessment Scales (VAS)
- To assess the percent change in physical function as measured by the disability index of the Health Assessment Questionnaire-Disability Index (HAQ-DI) over 16 weeks of treatment in each treatment group.
- To determine the trough plasma concentrations of BMS-582949 (Cmin).

The exploratory, tertiary objectives are listed in the clinical study report.

METHODOLOGY: This multicenter, randomized, double-blind, placebo-controlled study consisted of a screening period, a 12-week double-blind treatment period, and a 4-week blinded, treatment-free follow-up period. Following discontinuation and washout of disallowed therapies, including those for the treatment of RA, subjects with active RA who had an inadequate response to MTX and who met the study eligibility criteria were randomly assigned in a 1:1 ratio to once daily (q.d.) double-blind treatment with placebo or BMS-582949 300 mg. All subjects who remained in the study at the end of the double-blind treatment period were followed, in a blinded manner for an additional 4 weeks to assess safety and worsening or rebound of RA disease activity following withdrawal of study treatment.

NUMBER OF SUBJECTS (Planned and Analyzed): Planned: ~ 120 subjects (~ 60 in each of the 2 treatment groups). Randomized, treated, and analyzed for efficacy (Intent-to-treat analysis population): 61 placebo, 60 BMS-582949 300 mg. Intent-to-treat analysis population was identical to the All Treated Subjects population in this study, which was used in the analysis of safety.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Subjects at least 18 years of age at entry, who met the criteria for the diagnosis of RA for at least 6 months according to American Rheumatology Association criteria, who had received treatment with MTX for at least 3 months at a stable weekly dose of 7.5 to 20 mg/week. Subjects were considered to have had an inadequate responder to MTX, with 6 or more swollen joints (66 joint count) and 8 or more tender joints (68 joint count) and a C-reactive protein (CRP) value above the upper limit of normal range (ULN) or an erythrocyte sedimentation rate (ESR; (Westergren method) > 28 mm/hr. Prior treatment with up to 2 TNFα inhibitors was permitted, provided washout requirement was met.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT: BMS-582949 300 mg (3 x 100-mg tablet) was administered orally once daily at the same approximate time each day for 12 weeks (double-blind treatment period). The batch numbers of BMS-582949 100-mg tablets were 8A37643 and 8D37832.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT: Three (3) placebo tablets matching BMS-582949 100-mg tablets, administered orally once daily at the same approximate time each day by the subject for 12 weeks. The batch number of the matching placebo tablets was 6L20474.

CRITERIA FOR EVALUATION:

Efficacy: Proportion of subjects in each treatment group with ACR 20 response at Day 85 (Week 12) (primary endpoint); proportions of subjects in each treatment group with ACR 20, ACR 50 or ACR 70 response at each scheduled assessment, percent improvement from baseline in each scheduled assessment in ACR scores (ACR-N), change from baseline in Disease Activity 28 (DAS 28 based on ESR) score at each scheduled assessment, percent improvement from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at each scheduled assessment, proportion of subjects achieving 20% change in physician-rated global assessment of disease activity, and subject-rated assessments of pain, disease activity, and fatigue at each scheduled assessment.

Safety: Adverse events (AEs), serious adverse events (SAEs) including deaths, discontinuations due to AEs, changes in vital signs (including orthostatic changes in blood pressure [BP] and heart rate), clinical laboratory test abnormalities, and QTcF interval changes reported during the study. Additionally, the AEs that may be associated with the use of immunomodulatory drugs, including p38 inhibitors, were assessed, including infections, rash-related events, and dizziness.

Pharmacokinetics (PK): Observed trough plasma BMS-582949 concentration (Cmin) versus time data.

Pharmacodynamics: Change from baseline in plasma levels of hsCRP, rheumatoid factor (RF), and anti-citrullinated peptide antibody (anti-CCP)

STATISTICAL CONSIDERATIONS:

Sample Size Determination: The planned total of 120 subjects allocated in a 1:1 ratio to the BMS-582949 300 mg q.d. group and the placebo group yielded 88% power to conclude at the 2-sided 5% significant level that the ACR 20 response rate at 12 weeks was higher in the BMS-582949 treatment group than in the placebo group. This power estimate assumed ACR 20 response rates of 30% and 60% at 12 weeks in the placebo and BMS-582949 treatment groups, respectively.

Efficacy Analyses: The frequency of subjects achieving an ACR 20 response at Day 85 (primary efficacy endpoint) was compared for the 2 groups using a Cochran Mantel-Haenszel test, controlling for previous exposure to TNF inhibitor. Treatment group differences in ACR 20 response rates were summarized using point estimates and 95% confidence intervals (CIs). A continuity corrected Chi-square test was also used to compare the ACR 20 response rates at Day 85 in the 2 treatment groups. Subjects who discontinued prior to Week 4 or who were withdrawn for lack of efficacy were considered ACR 20 non-responders at all subsequent timepoints; a last observation carried forward (LOCF) approach was used in analyzing ACR 20 responses for all subjects who discontinued prematurely after Week 4 for reasons other than lack of efficacy.

Similar analyses were conducted for the ACR 50 and ACR 70 responses at Day 85. Analyses of the other efficacy variables were based on as observed data. ACR 20, ACR 50 and ACR 70 response rates at each study visit were calculated for both treatment groups, and the differences in response rates between the treatment groups at each visit were summarized using 95% CIs. The difference in ACR-N between the 2 treatment groups was compared using point estimates and 95% CIs derived from an analysis of variance model that included treatment as the main factor.

For DAS 28 (ESR), summary statistics of the actual and change from baseline values were tabulated by treatment and visit, and treatment group comparisons of change from baseline and corresponding 95% CI at Day 85 were based on an analysis of covariance model with treatment as the main factor and the baseline DAS 28 (ESR) value as a covariate.

Summary statistics were tabulated by treatment and visit for the HAQ-DI scores, physician global assessment of disease activity, and subject assessments of pain, disease activity, and fatigue and the corresponding percent improvements from baseline. The frequency of subjects achieving a 20% improvement from baseline in the physician global assessment of disease activity and subject assessments of pain, disease activity, and fatigue were tabulated by treatment group and visit, and treatment group differences at Day 85 were compared using Cochran Mantel-Haenszel test, controlling for previous exposure to TNF inhibitor.

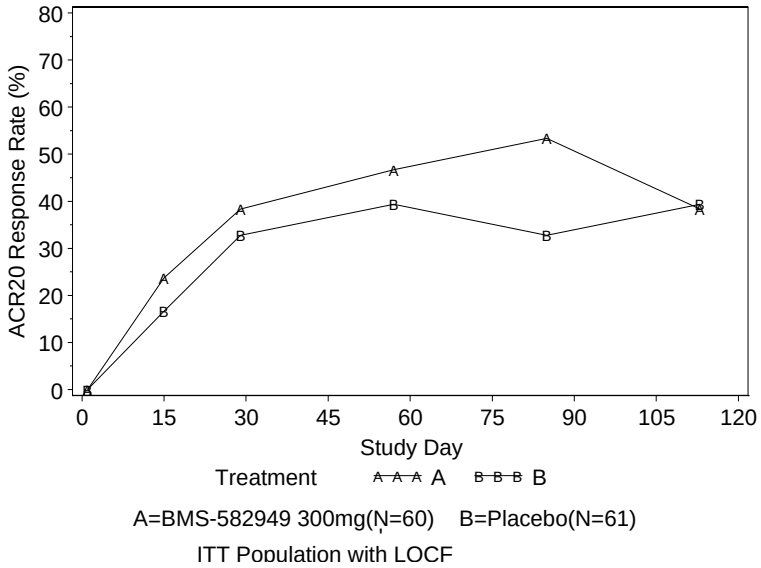
SUMMARY OF RESULTS:

Disposition, Demographics, and Other Pertinent Baseline Characteristics: The discontinuation rate for the double-blind treatment period was similar for the BMS-582949 300 mg (n =12, 20.0%) and placebo (n = 10, 16.4%) groups. The mean extent of exposure during the double-blind treatment period in the BMS-582949 300 mg and placebo groups was 80.9 and 83.8 days, respectively. Of the 69 subjects who entered the follow-up period, all but 1 subject in the placebo group completed this period.

	BMS-582949 300 mg (N = 60)	Placebo (N =61)	Total (N = 121)
Age, mean (SD) years	48.4 (11.85)	52.8 (12.04)	50.6 (12.10)
Gender, Female, n (%)	51 (85.0)	50 (82.0)	101 (83.5)
Race, Caucasian, n (%)	57 (95.0)	55 (90.2)	112 (92.6)
MTX dose (mg), mean (SD)	13.73 (5.09)	14.70 (6.43)	N/A
Prior anti-TNF exposure, n (%)	8 (13.3)	9 (14.8)	17 (14.0)

Efficacy Results: In subjects with active RA and receiving background MTX therapy, this study met its primary objective in demonstrating that the proportion of subjects who achieved an ACR 20 response was significantly higher at the Day 85 (Week 12) time point for the BMS-582949 300 mg group (53.3%) compared with the placebo group (32.8%) (p = 0.036). A plot of the ACR 20 responses over time is shown below.

ACR 20 Responses by Study Day (LOCF Analysis)



BMS-582949 300 mg was associated with a larger improvement in disease activity at Day 85 compared with placebo as reflected by a larger mean reduction from baseline in DAS 28 (ESR) (treatment group difference of -0.83 [95% CI: -1.29, -0.36]) and a larger mean ACR-N value (treatment group difference of 12.48 [95% CI: 3.77, 21.19]). Treatment with BMS-582949 300 mg for 12 weeks was associated with a larger mean percent improvement relative to baseline in physical function (HAQ-DI score) compared with placebo (25.86% and 14.98%, respectively). The proportion of subjects with at least a 20% improvement in the physician ratings of disease activity at Day 85 also favored BMS-582949 300 mg (87.5%) over placebo (64.8%), and this difference was statistically significant after controlling for prior exposure to anti-TNF therapy (p = 0.009). Other measures of efficacy, such as the ACR 50, ACR 70, and subject ratings of fatigue, pain, and disease activity failed to discriminate between the BMS-582949 and placebo groups.

Safety Results: BMS-582949, administered orally at a dose of 300 mg once daily for 12 weeks, was generally well tolerated in the treatment of adults with active RA receiving background MTX therapy.

	BMS-582949 300 mg (N = 60)	Placebo (N = 61)
Deaths, n (%)	0	0
SAEs, n (%)	0	1 (1.6%)
AEs, n (%)	41 (68.3)	43 (70.5)
Related AEs, n (%)	28 (46.7)	19 (31.1)
Discontinued due to AEs, n (%)	2 (3.3)	3 (4.9)
AEs of interest:		
Infections	15 (25.0)	13 (21.3)
Rash-related	1 (1.7)	1 (1.6)
Dizziness	4 (6.7)	2 (3.3)

AEs reported from Day 1 through 5 days (30 days for SAEs) after last dose of study drug during double-blind period or after last visit of follow-up period, which came later.

No clinically significant safety issues emerged from review of the clinical laboratory data. There was no signal for QTc interval prolongation or orthostatic changes in blood pressure or heart rate with BMS-582949 300 mg in this study.

PK Results: The BMS-582949 geometric mean of plasma Cmin ranged from 53.6 to 60.2 ng/mL between Days 15 and 85.

PD Results: Administration of BMS-582949 300 mg for 12 weeks was associated with a larger median decrease at Day 85 in hsCRP (-1.7 mg/L) compared with placebo (0.1 mg/L). Median changes from baseline at the Day 85 visit in anti-citrullinated peptide antibody and rheumatoid factor were minimal in both treatment groups.

CONCLUSIONS:

- In adult subjects with active RA who had an inadequate response to MTX, the ACR 20 response rate at the Day 85 (LOCF) visit (primary efficacy endpoint) was significantly higher in the BMS-582949 300 mg/day group compared with the placebo group.
- Once daily oral treatment with BMS-582949 300 mg for 12 weeks was associated with a larger improvement in disease activity at Day 85 compared with placebo as reflected by a larger mean reduction from baseline in DAS 28 (ESR) and a larger mean ACR-N value.
- A larger mean percent improvement in physical function, as measured using the HAQ-DI, was seen for the BMS-582949 300 mg group compared with the placebo group.
- Other measures of efficacy, such as the ACR 50, ACR 70, and subject ratings of fatigue, pain, and disease activity failed to discriminate between the BMS-582949 and placebo groups in this relatively short, 12 week study.
- Once daily oral administration of BMS-582949 300 mg for 12 weeks was well tolerated by subjects with RA receiving background MTX therapy.
- BMS-582949 exposure was consistent between Days 15 and 85.

DATE OF REPORT: 02-Jun-2010