SYNOPSIS

Final Clinical Study Report for Study IM126004

TITLE OF STUDY: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of BMS-817399 in Adults with Active, Moderate to Severe Rheumatoid Arthritis and Inadequate Response to Methotrexate

PURPOSE: The purpose of this study was to assess the clinical efficacy, safety, and pharmacokinetics (PK) of BMS-817399 up to 12 weeks of treatment in subjects with active rheumatoid arthritis (RA) and an inadequate response to treatment with methotrexate (MTX). BMS-817399 is a CC-chemokine receptor-1 (CCR1) antagonist, which has been shown to inhibit cell-based functions driven by CCR1. A synoptic format was chosen for this report because Bristol-Myers Squibb (BMS) has terminated research on the compound as the primary endpoint in this study was not met due to lack of efficacy. The decision was not driven by any safety concerns. As all subjects were treated with background MTX, the BMS-817399 200-mg plus MTX group will be referred to as the BMS 200-mg group, the 400-mg plus MTX group as the BMS 400-mg group, and the placebo plus MTX group as the placebo group.

NUMBER OF SUBJECTS: **Planned:** 120 subjects, with approximately 40 per group. **Actual:** 123 subjects, 41 per group.

DISPOSITION, DEMOGRAPHICS AND OTHER PERTINENT BASELINE CHARACTERISTICS:

Disposition: A total of 107 (87.0% of 123) of enrolled subjects completed the 12-week treatment period of the study (Table 1). Four subjects were discontinued from treatment due to lack of efficacy and 4 due to an adverse event (AE), 3 of which were treated with BMS-817399.

Table 1: End-of-Treatment Subject Status Summary, All Treated Subjects, IM126004

	BMS 200mg	BMS 400mg	Placebo	Total
SUBJECTS	41	41	41	123
SUBJECTS COMPLETING THE STUDY (%)	36 (87.8)	34 (82.9)	37 (90.2)	107 (87.0)
SUBJECTS NOT COMPLETING THE STUDY (%)	5 (12.2)	7 (17.1)	4 (9.8)	16 (13.0)
REASON FOR NOT COMPLETING THE STUDY (%)				
LACK OF EFFICACY	0	3 (7.3)	1 (2.4)	4 (3.3)
ADVERSE EVENT	1 (2.4)	2 (4.9)	1 (2.4)	4 (3.3)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	2 (4.9)	0	0	2 (1.6)
SUBJECT WITHDREW CONSENT	2 (4.9)	2 (4.9)	1 (2.4)	5 (4.1)
DEATH	0	0	0	0
LOST TO FOLLOW-UP	0	0	1 (2.4)	1 (0.8)
POOR/NON-COMPLIANCE	0	0	0	0
PREGNANCY	0	0	0	0
SUBJECT NO LONGER MEETS STUDY CRITERIA	0	0	0	0
ADMINISTRATIVE REASON BY SPONSOR	0	0	0	0
OTHER	0	0	0	0

Percentages based on subjects treated

Demographics: The mean age was 54 years (range: 23–79 years). Most subjects were white females (Table 2). The demographics were balanced across treatment groups.

Baseline Disease Characteristics: The median duration of disease was 5.2 years and the mean baseline score for Disease Activity Score-C-reactive protein (DAS28-CRP) was 5.9. Of the 123 randomized subjects, 69.9% met the criteria for American College of Rheumatology (ACR) Functional Class II and 24.4% for Class III. All subjects were treated with MTX at baseline. Most subjects had morning stiffness (92.7%), arthritis of ≥ 3 joints (95.9%), arthritis of hand joints (96.7%), symmetric arthritis (92.7%), and rheumatoid nodules (18.7%). Radiographic changes were apparent in 47.2% of the 123 subjects. Baseline characteristics were balanced across treatment groups.

Table 2: Demographics Characteristics Summary, All Treated Subjects, IM126004

	BMS 200mg N=41	BMS 400mg N=41	Placebo N=41	Total N=123
AGE (YEARS)				
N	41	41	41	123
MEAN	49.8	55.4	56.7	54.0
MIN , MAX	23.0 , 78.0	25.0 , 79.0	23.0 , 75.0	23.0 , 79.0
GENDER (%)				
MALE	7 (17.1)	9 (22.0)	6 (14.6)	22 (17.9)
FEMALE	34 (82.9)	32 (78.0)	35 (85.4)	101 (82.1)
RACE (%)				
WHITE	34 (82.9)	36 (87.8)	35 (85.4)	105 (85.4)
BLACK OR AFRICAN AMERICAN	0	0	0	0
ASIAN	2 (4.9)	1 (2.4)	4 (9.8)	7 (5.7)
OTHER	5 (12.2)	4 (9.8)	2 (4.9)	11 (8.9)

SUMMARY OF SAFETY RESULTS: Treatment with either 200 or 400 mg of BMS-817399 was generally safe and well tolerated in this study. There were no deaths in this study (Table 3). Serious adverse events (SAEs) were reported for 3 subjects treated with BMS-817399; one SAE (perforated duodenal ulcer) led to discontinuation. No SAEs were considered by the investigator to be related. Four subjects were discontinued due to AEs (3 treated with BMS-817399). Adverse events were reported in greater proportions of subjects in the BMS 400-mg group than in the BMS 200-mg or placebo groups.

Table 3: Overall Summary of Safety, All Treated Subjects, IM126004

	BMS 200 mg	BMS 400 mg	Placebo	All BMS	Total
	N=41	N=41	N=41	N=82	N=123
			n (%)		
Deaths	0	0	0	0	0
Serious AEs	1 (2.4)	2 (4.9)	0	3 (3.7)	3 (2.4)
AEs leading to DC	1 (2.4)	2 (4.9)	1 (2.4)	3 (3.7)	4 (3.3)
At least 1 AE	25 (61.0)	30 (73.2)	26 (63.4)	55 (67.1)	81 (65.9)

MedDRA version 15.1
AE = adverse event; DC = discontinuation

Marked laboratory abnormalities (MAs) were observed for liver function tests (LFTs):

> 1.25× upper limit of normal (ULN)

- alanine aminotransferase (ALT) 5/41 subjects (12.2%)
- aspartate aminotransferase (AST) 4/41 subjects (9.8%)
- alkaline phosphatase (ALP) 2/41 subjects (4.9%

> 1.15× ULN

- g-glutamyl transferase 4/41 subjects (9.8%)

> 1.1× ULN, collectively

- total bilirubin (TBILI) 1/41 subjects (2.4%)
- direct bilirubin 1/41 subjects (2.4%)

Elevations of ALT and AST were observed in all treatment groups.

SUMMARY OF EFFICACY: Compared to placebo, no statistically significant changes for primary (change in DAS28-CRP), secondary (ACR 20, ACR 50, and ACR 70 response or Disability Index of the Health Assessment Questionnaire [HAQ-DI]) endpoints, or the exploratory endpoint of structural damage were observed.

SUMMARY OF PHARMACOKINETICS: Steady-state trough concentrations of BMS-817399 were reached by Day 15, and remained elevated on Days 29 and 57. Mean trough concentrations of BMS-817399 were at least twice as high for the 400-mg group compared to the 200-mg group.

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