BRISTOL-MYERS SQUIBB COMPANY

BMS-936557

(MDX-1100)

Clinical Study Report for Study IM129004 (MDX1100-06)

A Phase 2, Multi-dose, Double-blind, Placebo-controlled, Randomized, Multicenter Study of MDX-1100 (Anti-CXCL10 Human Monoclonal Antibody) in Subjects with Active Ulcerative Colitis

Indication:	Ulcerative Colitis
Phase:	Phase 2
Study Initiation Date:	26-Mar-2008
Study Completion Date:	14-Sep-2009
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THIS STUDY WAS CONDUCTED IN ACCORDANCE WITH GOOD CLINICAL PRACTICE

Sponsor's Responsible Medical Officer:
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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

Clinical Study Report for Study IM129004 (MDX1100-06)

TITLE OF STUDY: A Phase 2, Multi-dose, Double-blind, Placebo-controlled, Randomized, Multicenter Study of MDX-1100 (anti-CXCL10 Human Monoclonal Antibody) in Subjects with Active Ulcerative Colitis

INVESTIGATORS/STUDY CENTERS: **Czech Republic:** [redacted] **Hungary:** [redacted] **Romania:** [redacted] **Ukraine:** [redacted] **USA:** [redacted] **Canada:** [redacted] **Russia:** [redacted]

PUBLICATIONS: None

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

Study Completion Date: 14-Sep- 2009

COMPOUND NAME: After the acquisition of Medarex, Inc. by BMS, the compound name of MDX-1100 was changed to BMS-936557 and will be referred to as such in this clinical study report (CSR).

OBJECTIVES:

Primary Objectives

- Determine the clinical response rate (defined as a decrease from baseline in the total Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or an absolute subscore for rectal bleeding of 0 or 1) at Day 57 in subjects with active ulcerative colitis (UC) administered BMS-936557; and
- Assess the tolerability and safety of this BMS-936557 regimen in subjects with active UC.

Secondary Objectives

- Determine the remission rate (defined as a total Mayo score of 2 points or lower with no individual subscore exceeding 1 point and no blood in stool) at Day 57 in subjects administered BMS-936557;
- Assess the Quality of Life (QoL) outcome using the Inflammatory Bowel Disease Questionnaire (IBDQ);
- Determine the mucosal healing score rate at Day 57 for subjects administered BMS-936557;
- Determine the peak and trough pharmacokinetic profile (concentrations) of BMS-936557; and
- Investigate the effects of BMS-936557 on CXCL-10 levels and CXCL-10 responsive markers.

METHODOLOGY:

This was a Phase 2, double-blind, placebo-controlled, randomized, multicenter, multidose study of BMS-936557 (anti-CXCL10 human monoclonal antibody) in subjects with active UC experiencing flare. A total of 106 eligible subjects were randomized to receive either placebo or BMS-936557 10 mg/kg by IV infusion every other week for a total of 4 doses. A blinded interim analysis (IA) of efficacy and safety was performed when 50% of all enrolled subjects were assessed for efficacy at Day 57. The independent Data Monitoring Committee (DMC) recommended for the study to be completed as originally designed. Subject participation was to be up to a maximum of 113 days in duration.

NUMBER OF SUBJECTS (Planned and Analyzed):

Planned: 106 subjects

Analyzed: 109 subjects (Intent-to-Treat Population)

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

All subjects ≥ 18 years of age were to have active disease while on stable doses of 5-aminosalicylates (5-ASA), corticosteroids, azathioprine (AZA), and/or 6-mercaptopurine (6-MP). Flare was defined as a Mayo score of 6 to 10 with moderate to severe active disease on endoscopy (Mayo endoscopic subscore of at least 2) within 2 weeks before study drug administration. Doses of permitted UC concomitant medications (corticosteroids, AZA, 6-MP, and 5-ASA-containing compounds) were to remain constant during the course of the study. Sigmoidoscopy was to be performed at screening and at Day 57 (or early withdrawal).

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS:

BMS-936557, 10 mg/kg by 60-minute IV infusion (every other week for a total of 4 doses), 8-week study, Batch numbers M53A-07-03FC, M53A-07-04FC, M53A-08-01FC, M53A-08-04FC.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT:

Placebo (saline), IVinfusion (every other week for a total of 4 doses), 8-week study.

CRITERIA FOR EVALUATION:

Efficacy:

Primary efficacy was measured as the clinical response rate at Day 57. Clinical response was defined as a decrease from baseline (Screening) in the total Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or an absolute subscore for rectal bleeding of 0 or 1. The secondary efficacy parameters were remission rate by the Mayo score at Day 57, mucosal healing score rate at Day 57, and change in QoL from baseline measured by IBDQ score.

Safety:

Assessment of safety was determined by vital sign measurements, clinical laboratory tests, physical examinations, immunogenicity assessments, electrocardiograms (ECGs), chest radiographs, and the incidence and severity of treatment-emergent adverse events. Anti-BMS-936557 antibodies were measured using a validated electrochemiluminescent bridging immunoassay in human serum. Plasma samples were obtained and tested on Days 1, 29, 57 and 85 (42 days post last dose).

Pharmacokinetics:

Serum samples for the evaluation of the pharmacokinetics of BMS-936557 were taken up to 60 minutes prior to each dose and 30 minutes after infusion on Days 1, 15, 29, and 43. A single serum sample was collected on Days 8, 57 and 85. BMS-936557 in human serum was assayed using a validated ELISA assay method. Except for serum trough concentrations (Cminss), no other individual PK parameters were derived in this study.

Immunogenicity: Anti- BMS-936557 antibodies were measured using a validated electrochemiluminescent (ECL) bridging immunoassay in human serum using the Meso-Scale Discovery (MSD) platform with a sensitivity of 107 ng/mL in the presence of 5 μg/mL BMS-936557. Plasma samples were obtained and tested on Days 1, 29, 57 and 85 (42 days post last dose).

STATISTICAL CONSIDERATIONS:

A sample size of 37 subjects per group was necessary to make a statistically significant decision, using a two-sided Fisher's exact test. This was based on the expected response rate of 65% in the treatment group and the response rate of 30% in the placebo group, with an alpha level of 5% and a power of 80%. A total of 106 subjects (53 subjects per group) were required in order to account for approximately a 30% dropout rate over 8 weeks (16 subjects).

Efficacy: The primary efficacy parameter of clinical response rate at Day 57 was defined as the proportion of subjects in each treatment group who had a clinical response.

The secondary efficacy parameters are clinical remission rate, mucosal healing rate, and QoL change from baseline measured by IBDQ scores. Post-hoc analyses were performed to evaluate the exposure-response relationship, as were subgroup analyses of clinical response, remisison, and mucosal healing rates by steady state trough serum concentrations (Cminss) of BMS-936557.

Safety: The safety analysis was conducted on the safety population, which included all subjects who received at least 1 full dose or any partial dose of BMS-936557 or placebo. All safety assessments, including vital sign measurements, clinical laboratory tests, physical examinations, immunogenicity assessments, chest radiography, ECGs, and the incidence and severity of adverse events (AEs), were listed and where appropriate, summarized with descriptive statistics. An AE was defined as a sign or symptom that emerges during treatment or within 70 days of the last dose of the treatment including those that were absent pretreatment or that had worsened relative to the pretreatment state. Any adverse event deemed related to treatment was also considered an AE regardless of elapsed time since last study drug.

All safety parameters were summarized using descriptive statistics. Descriptive statistics included: mean, standard deviation, median, and minimum and maximum values for continuous variables, frequencies, and percentages for categorical variables.

Pharmacokinetics: The PK analysis population included all subjects who received at least 1 dose of study drug and had at least 1 BMS-936557 Cmin value. Plasma concentrations of treatment were summarized by study day (Days 1, 8, 15, 29, 43, 57, and 85) and scheduled sample time using descriptive statistics by treatment group per SAP. The geometric mean concentrations were plotted by scheduled time.

Pharmacodynamics: The analyses of pharmacodynamic data will be provided in a separate report.

Post-hoc analyses: The pre-specified analyses per the SAP used the mean of 7 days of diary entries prior to assessment date for the stool frequency and rectal bleeding subscores and defined subjects as non-responders if <3 diary entries were present during the 7 days prior to assessment. Analyses were performed post-hoc using the more conventional method, where the mean of 3 days of diary entries prior to assessment date for the stool frequency and rectal bleeding subscores were used. For the post-hoc analyses, Day 1 for baseline was defined as the first dose date for treated subjects and the randomization date for non-treated subjects. Days 8, 15, 29, 43, and 57 were interpreted as the actual PGA assessment dates (provided they were within the relevant visit window). Post-hoc analysis for efficacy was based on ITT population. After unblinding, all ITT subjects who had steady state trough serum concentration (Cminss) on Day 57 were stratified into tertiles based on their Cminss: Low (26.4-78.6 μg/mL), mid (79.2-105 μg/mL), and top (108-235 μg/mL); and post-hoc graphical analyses on clinical response, clinical remission, and mucosal healing rate were conducted within each of the tertiles. Logistic regression was used to further explore the exposure-response relationships.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics:

Table 1: Subject Disposition (ITT Population)

	No. of Subjects, N (%)		
	Placebo	**BMS-936557**	**Total**
	N=54	**N=55**	**N=109**
ITT population	54 (100.0)	55 (100.0)	109 (100.0)
Completed Day 57	49 (90.7)	49 (89.1)	98 (89.9)
Primary reason for discontinuation before Day 57			
Adverse event	0	2 (3.6)	2 (1.8)
Protocol violation	1 (1.9)	2 (3.6)	3 (2.8)
Unsatisfactory therapeutic effect	1 (1.9)	0	1 (0.9)
Subject withdrew consent	2 (3.7)	0	2 (1.8)
Death	0	0	0
Lost to follow-up	0	0	0
Other	1 (1.9)	2 (3.6)	3 (2.8)
Completed Day 113 follow-up	48 (88.9)	48 (87.3)	96 (88.1)

Table 2: Demographics (ITT Population)

	No. of Subjects, N (%)		
	Placebo	**BMS-936557**	**Total**
	N=54	**N=55**	**N=109**
Age (years)			
N	54	55	109
Mean (SD)	41.8 (14.2)	44.7 (12.8)	43.2 (13.5)
Median	37.0	45.0	43.0
Range	18-75	25-73	18-75
Sex, n (%)			
N	54	55	109
Male	31 (57.4)	37 (67.3)	68 (62.4)
Female	23 (42.6)	18 (32.7)	41 (37.6)
Race, n (%)			
N	54	55	109
White	54 (100.0)	53 (96.4)	107 (98.2)
Black	0	2 (3.6)	2 (1.8)
Asian	0	0	0
Other	0	0	0
Weight (kg)			
N	54	55	109
Mean (SD)	74.5 (18.1)	81.9 (16.1)	78.2 (17.4)
Median	71.3	79.0	75.0
Range	50.0-139.1	52.0-124.1	50-139.1

Approximately 5% of subjects enrolled in the study have previous received anti-TNF therapy. The majority of subjects in the ITT population received at least 1 concomitant UC therapy during the study. The majority of subjects (90.7% placebo and 96.4% BMS-936557) were on concomitant 5-ASA. Approximately half of the subjects (50% placebo and 54.5% BMS-936557) were on concomitant coricosteroids, with a mean daily dose of 17.2 mg.

Efficacy Results:

Although a greater number of subjects in the BMS-936557-treated group (52.7%) achieved clinical response compared to that in the placebo group (35.2%), the difference was not statistically significant (Table 3). The clinical remission rate in BMS-936557-treated subjects (18.2%) was comparable to that observed for the placebo-treated subjects (16.7%). The mucosal healing rate in BMS-936557-treated subjects (41.8%) was slightly higher than that observed for the placebo-treated subjects (35.2%). The

change in QoL outcome was comparable between the BMS-936557 and placebo treatment groups (Table 3).

Table 3: Summary of Primary and Secondary Efficacy Results (ITT Population)

	No. of Subjects, %			
	Placebo N=54	BMS-936557 N=55	Difference (95% CI)	P-value
Clinical Response at Day 57	35.2	52.7	17.5 (-0.8, 35.9)	0.083
Remission Rate at Day 57	16.7	18.2	1.5 (-12.7, 15.8)	1.000
Mucosal Healing at Day 57	35.2	41.8	6.6 (-11.6, 24.9)	0.556

Analysis of the rectal bleeding, stool frequency, and PGA subscores showed decreases in rectal bleeding, in the frequency of stools, and in the Physician's Global Assemssment subscoures over the course of 57 days compared with baseline for both study drug and placebo treatment groups. The decrease in stool frequency and rectal bleeding were not markedly different between treatment groups

Safety Results:

BMS-936557 (10 mg/kg) administered as an IV infusion every other week for 8 weeks was well tolerated in subjects with UC in this study. No deaths were reported during this study. More SAEs were reported in the BMS-936557 than in the placebo group (7.3% vs. 1.9%, respectively). All of the SAEs were considered to be unlikely or unrelated to study drug. Discontinuations due to SAEs or AEs were uncommon; 1 subject in the BMS-936557 group discontinued due to SAEs of appenditis perforated and appendiceal abscess and another subject in the BMS-936557 group discontinued due to an AE of vasculitis. Peri-infusional events, all mild to moderate in severity, were reported for 6 subjects (10.9%) in the BMS-936557 group and 2 subjects (3.8%) in the placebo group. Infections were reported for 7 subjects (12.7%) in the BMS-936557 group and 3 subjects (5.8%) in the placebo group, with only one event in BMS-936557 group considered at least possibly related to treatment with study drug. There were no malignancies reported. An autoimmune disorder of moderately severe vasculitis was reported in 1 subject in the BMS-936557 group which was considered probably related to study drug. None were reported for the placebo group. Overall AEs were reported in 32.7% of the placebo group and 40% of the BMS-936557 group. 13.5% of the AEs reported in the placebo group were considered at least possibly related to study drug while 20% were considered at least possibly related to study drug in the BMS-936557 group.

Table 4: Summary of Adverse Eventsa (Safety Population)

	No. of Subjects, N (%)	
	Placebo	**BMS-936557**
	N=52	**N=55**
Death	0	0
SAEs[b]	1 (1.9)	4 (7.3)
Related SAEs[a]	0	0
Discontinued due to SAEs	0	1 (1.8)
AEs	17 (32.7)	22 (40.0)
Related AEs	7 (13.5)	11 (20.0)
Discontinued due to AEs	0	1 (1.8)

a AE is defined as a sign of symptom that emerges during treatment or within 70 days of the last dose of the treatment including having been absent pre-treatment or that has worsened relative to the pre-treatment state and any treatment-related AE regardless of timing.

b SAEs include all Grade 3 (severe) and above events (or events with missing severity) considered serious by the investigator up to 70 days post study drug.

a Possibly, probably, or definitely related to the study drug (missing relationships presumed as related)

Analysis of immunogenicity samples in the Safety population at Days 1, 29, 57, and 85 (42 days after last dose of study drug) were negative for human anti-human antibodies to BMS-936557.

Pharmacokinetic Results: After 4 doses of 10 mg/kg BMS-936557, the serum concentration at 30 min after infusion increased from 164 μg/mL to 310 μg/mL and the trough concentration increased from 42.2 μg/mL on Day 15 to 91.3 μg/mL at the primary efficacy timepoint on Day 57.

Post-hoc Analyses: After unblinding of the data, a post-hoc analysis of the primary efficacy response vs. serum trough concentration at Day 57 (Cminss) was performed. Exposure-response relationship was demonstrated where higher Cminss exposure was associated with an increase in clinical response, remission, and mucosal healing rates. Results of the analysis showed significantly higher clinical response rates for the 16 subjects in the highest Cminss tertile subgroup (108-235 μg/mL) compared with the placebo group, 87.5% vs. 37%, respectively (95% CI for the difference in treatment groups [29.8, 71.2], $p<0.001$). Considerably higher remission rate (43.8% vs. 18.5% in placebo, $p<0.051$) and mucosal healing rate (68.8% vs. 35.2% in placebo, $p<0.023$) were also observed in the highest Cminss tertile subgroup. Analysis of safety in the subgroup of subjects in the highest Cminss tertile did not demonstrate differential safety profile compared to the other subjects in the BMS-936557 group as well as placebo. Logistic regression of clinical response showed that an increase in Cminss led to an increase in clinical response with an odds ratio of 3.77 ($P=0.017$), ie. if the exposure increases by a factor of two, the odds of achieving clinical response increases by 3.77 times.

Immunogenicity: Analysis of immunogenicity samples in the Safety population at Days 1, 29, 57, and 85 (42 days after last dose of study drug) were negative for human anti-human antibodies to BMS-936557.

Pharmacodynamic Results: Samples for the evaluation of pharmacodynamic variables were collected. The results of the final analyses will be presented in a separate report.

CONCLUSIONS:

- The study provided proof of concept that BMS-936557 has the potential to be effective as an induction therapy for subjects with moderate to severely active UC
  - Efficacy as measured by clinical remission and mucosal healing rate was not robust at the test dose of 10 mg/kg
  - There appears to be a relationship between BMS-936557 trough levels and the response rate, with higher trough levels resulting in a higher rate of clinical response, clinical remission, and mucosal healing that are clinically meaningful
- Treatment with BMS-936557 was safe and well tolerated in subjects with active UC
  - There was a higher frequency of infection and mild to moderate infusion reactions in the BMS-936557 group compared to placebo
  - The safety profile observed in the subjects with higher trough levels was comparable to the overall BMS-936557 and placebo treatment groups
- There was no immunogenicity detected in any of the subjects in the study up to 42 days after the last dose

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