BRISTOL-MYERS SQUIBB COMPANY

CLAZAKIZUMAB

Final Clinical Study Report for Study IM133005

ABBREVIATED REPORT

A Phase IIb, Double-Blind, Randomized, Placebo-Controlled, Double-Dummy, Dose-Ranging Study to Evaluate the Clinical Efficacy and Safety of Induction and Maintenance Therapy with BMS-945429 in Subjects with Moderate to Severe Crohn's Disease

Indication:	Crohn's Disease
Phase:	2B
Study Initiation Date:	11-Jun-2012
Study Completion Date:	04-Jun-2013 (study termination date)
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THIS STUDY WAS CONDUCTED IN ACCORDANCE WITH GOOD CLINICAL PRACTICE

Sponsor's Responsible Medical Officer:
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Bristol-Myers Squibb
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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: clazakizumab		

SYNOPSIS

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TITLE OF STUDY: A Phase IIb, Double-Blind, Randomized, Placebo-Controlled, Double-Dummy, Dose-Ranging Study to Evaluate the Clinical Efficacy and Safety of Induction and Maintenance Therapy with BMS-945429 in Subjects with Moderate to Severe Crohn's Disease

INVESTIGATORS/STUDY CENTERS: 44 sites

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 11-Jun-2012 **CLINICAL PHASE:** 2B

Study Completion Date: 04-Jun-2013 (study termination date)

INTRODUCTION: Previously BMS-945429 (clazakizumab) had been studied in improving the signs and symptoms of joint disease in rheumatoid arthritis (RA). This is the first study in patients with Crohn's disease (CD). There is evidence to suggest the activity of interleukin 6 (IL-6) to play a role in the pathology in CD. An antagonist of IL-6 may be effective in reducing the signs and symptoms of CD. The current study was a phase IIb dose ranging study with a 12-week Induction Period (IP) and 48-Week Maintenance Period (MP) to evaluate the clinical efficacy and safety of clazakizumab (claza) in subjects with moderate to severe CD.

This study was voluntarily terminated by Bristol-Myers Squibb (BMS) on June 4, 2013 primarily due to safety concerns resulting from 2 confirmed cases of gastrointestinal (GI) perforation of which a single death occurred. In addition, the high clazakizumab doses that were used in this study could not be supported further given the new data from the Phase 2b study in RA (IM133-001) that had emerged suggesting that lower clazakizumab doses could be utilized effectively with a lower risk of adverse events (AEs). Given the 2 GI perforation events in combination with the need to adjust doses for any future studies, the decision was made to terminate the study and an abbreviated CSR format is used herein to provide the complete safety results from the study. Due to premature termination of the study, a limited amount of information on the efficacy results are presented and no definite statistical conclusions can be drawn from these results. In addition, only data for the IP are described in this CSR owing to only a few subjects entering the MP.

OBJECTIVES:

Primary Objective

- To compare the efficacy of clazakizumab versus placebo for induction of clinical remission (defined by an absolute CDAI score <150) at Week 8 (IP-57).

Secondary Objective

- To compare the efficacy of clazakizumab versus placebo for induction of clinical response (defined by a reduction in CDAI ≥ 100 or an absolute CDAI score < 150) at Week 8 (IP-57).
- To assess health-related quality of life outcomes (Inflammatory Bowel Disease Questionnaire [IBDQ]) with clazakizumab in the IP.

- To assess the safety, tolerability and immunogenicity of clazakizumab in the IP.
- To characterize the pharmacokinetics of clazakizumab during the IP.

METHODOLOGY: This study consisted of five (5) periods: Screening (SP), Induction (IP), Maintenance (MP), Open Label (OL), and a Post Dose Follow-up Period. After a brief SP, eligible subjects entered a 12-week, double-blind, placebo-controlled, double-dummy, IP. Subjects were randomized in a 2:2:1:1:2 ratio to 1 of 5 treatment arms for the 12 week IP (placebo, clazakizumab 600 mg IV/200 mg SC, 300 mg IV/100 mg SC, 150 mg IV/100 mg SC, or 400 mg SC/200 mg SC). Randomization was stratified according to prior inadequate response and/or intolerance to anti-TNF agents and a maximum of approximately 50% of subjects with inadequate response and/or intolerance to anti-TNF agents were to be enrolled.

All subjects who were responders at IP-Day 85 were to enter a double-blind and placebo-controlled MP for 48 weeks. Due to the early termination of the study during the IP, detailed methodologies for the remainder of the study are not provided in the body of the CSR but are provided in the study protocol in Appendix 1.1.

NUMBER OF SUBJECTS (Planned and Analyzed): A total of 288 subjects were planned to be randomized in the IP in a 2:2:1:1:2 fashion to receive placebo or 1 of 4 dose regimens of clazakizumab (see below for regimens). At the time of study termination, 72 subjects had been randomized of which 18 subjects were randomized to placebo, 18 subjects to 600 mg IV, 9 subjects to 300 mg IV, 9 subjects to 150 mg IV, and 18 subjects to 400 mg SC. Few subjects had entered the MP (total across treatment arms, n= 14) before study termination.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Adults with confirmed CD for at least 3 months, moderate to severely active CD as defined by a CD activity index (CDAI) score ≥220 to ≤450, insufficient response or intolerance to one of the conventional therapies (immunosuppressants, corticosteroids and/or anti-TNF), and have one of the following: hsCRP ≥5 mg/L, fecal calprotectin ≥250 μg/g, or confirmed active disease by magnetic resonance enterography (MRE).

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT: Clazakizumab was supplied as 100 mg/ml in 1.2 mL single use vials (normal saline was used as placebo and was not provided by BMS). Prior to any IV administration, the proper volume of clazakizumab was diluted in 250 mL 5% dextrose IV infusion bag (D5W).

During the 12-week IP, all subjects received in a blinded fashion 1 of 4 regimens of SC injections or IV infusions:

1) Clazakizumab 150 mg IV at Week 0, 100 mg SC at Week 8
2) Clazakizumab 300 mg IV at Week 0, 100 mg SC at Week 8
3) Clazakizumab 400 mg SC at Week 0 and Week 4, 200 mg SC at Week 8
4) Clazakizumab 600 mg IV at Week 0, 200 mg SC at Week 8

As part of the double-dummy study design, subjects that received IV infusions of clazakizumab also received SC injections of placebo and conversely, subjects that received SC injections of clazakizumab also received IV infusions of placebo. The number of IV infusions and/or SC injections for each subject, regardless of treatment assignment, was as follows:

a) IP-1: One IV infusion + four SC injections
b) IP-29: Four SC injections
c) IP-57: Two SC injections

During the MP, subjects received in a blinded fashion 1 of 3 regimens of SC injections:

1) Placebo on Day 1 of the MP and every 4 weeks thereafter
2) 100 mg clazakizumab on Day MP1 and every 4 weeks thereafter
3) 200 mg clazakizumab on Day MP1 and every 4 weeks thereafter

For the OL, subjects were able to enter this period in 1 of the following 3 ways:

1) Non-responders at the end of the IP
2) Due to disease relapse between MP-29 (Week 4) to MP-337 (Week 48)
3) Upon completion of MP-337 (Week 48)

During the OL, subjects received 200 mg of clazakizumab SC every 4 weeks.

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

Not applicable

CRITERIA FOR EVALUATION:

Efficacy: Given that the study was terminated at an early stage, only the CDAI change from baseline, CDAI remission, clinical response, IBDQ and Magnetic Resonance Index of Activity (MaRIA) were summarized for the IP by treatment and total clazakizumab group for this abbreviated study report.

Safety: Adverse events (AEs) starting from the day of first dose of study medication up to 150 days beyond the last dose of study medication or until the start of a new study period, whichever was earlier, was included in the tabular summaries. Frequency distribution and individual listings of all AEs was generated for the IP. For the MP and OL period, only individual listings of all AEs were provided. Laboratory marked abnormality using pre-defined abnormality criteria were also descriptively summarized. There was no statistical testing of group difference with respect to frequencies of AEs or laboratory marked abnormalities. Adverse events were coded and grouped into Preferred Terms (PT) by System Organ Class (SOC), using the latest approved version of the Medical Dictionary for Regulatory Activities (MedDRA, Version 16.1)

Other: Pharmacokinetic analysis: summary statistics for C_{min} were tabulated by treatment and scheduled sampling time for the IP only. Imaging Efficacy Analysis: MRE was performed at baseline and at end of IP and a MaRIA index score was listed at each time point and change from baseline summarized by treatment group and total clazakizumab group. Imaging Safety Analysis: MRE was performed at baseline, end of the IP, and at study termination; subjects received either a MRE or a Computerized Tomography (CT) Scan for multiple safety endpoints (i.e., diverticulitis, abdominal abscess, perianal abscess, peritonitis, and perforation). Fecal Calprotectin and hsCRP: descriptive summary was presented for fecal calprotectin and hsCRP for the IP only. Immunogenicity: immunogenicity was listed for clazakizumab treatment groups and placebo during the IP only.

STATISTICAL CONSIDERATIONS: Due to early termination of the study, only a small number of subjects were randomized (72) of the total planned sample size (288). Analyses are descriptive in nature. Formal statistical comparisons between treatment groups and formal statistical hypothesis testing were not conducted due to the small number of subjects. Moreover, efficacy and safety tables were not generated for the MP due to very few subjects in each re-randomized treatment arms - the listings present all data.

Categorical variables were summarized by counts and percentages, if not stated otherwise. Continuous variables were summarized with univariate statistics (e.g., n, mean, median, minimum, maximum, quartiles, standard deviation [SD]). Changes from baseline in continuous variables were summarized with univariate statistics (e.g., n, mean, standard error [SE], median interquartile range [IQR]).

Subjects had to have a baseline measurement (i.e., the last measured value before the first administration of study therapy) and at least 1 on-study measurement (i.e., after the first dose of study therapy) to have been evaluable for change from baseline analyses.

SUMMARY OF RESULTS:

Subject Disposition: Induction Period (IP): A total of 138 subjects were enrolled and of these, 72 (52.2%) subjects were randomized and treated. A total of 66/72 (91.7%) subjects had reached the primary end point at Week 8 and as shown in Table -1, 34/72 (47.2%) subjects had completed the 12-week IP. Maintenance Period (MP): There were 14/72 (19.4%) subjects that entered the MP and of these 14 subjects, 1 (7.1%) completed the period and 13 (92.9%) did not complete the MP. Open-Label Period (OL): There were 15/72 (20.8%) subjects that entered the OL and none of the subjects completed the OL due to early study termination.

Baseline/Demographic Characteristics: Subject demographics and baseline disease characteristics were comparable across treatment groups (except for minor differences in mean hsCRP levels) and were typical of subjects with moderate to severe CD in clinical trials Table -2.

Table -1: Subject Disposition - Induction Period

	PBO (IP)	150 IV/100 SC	300 IV/100 SC	600 IV/200 SC	400 SC/200 SC	Total
No. of Subjects Enrolled						138
No. of Subjects Treated	18	9	9	18	18	72 (52.2)
No. of Subjects Completing the IP	11 (61.1)	4 (44.4)	4 (44.4)	9 (50.0)	6 (33.3)	34 (47.2)
No. of Subjects Discontinued (%)	7 (38.9)	5 (55.6)	5 (55.6)	9	12	38 (52.8)
Lack of Efficacy	0	0	0	2	3	5 (6.9)
Adverse Event	1	1	2	0	2	6 (8.3)
Subject request to discontinue	1	0	0	0	0	1 (1.4)
Withdrew consent	1	0	0	1	2	4 (5.6)
No longer meets study criteria	0	2	0	1	0	3 (4.2)
Administrative reason by sponsor	4	2	3	5	5	19 (26.4)

Table -2: Baseline Demographic and Disease Characteristics - Induction Period

	PBO (IP) N=18	150 IV/100 SC N=9	300 IV/100 SC N=9	600 IV/200 SC N=18	400 SC/200 SC N=18	Total N=72
Age, mean	41.1	36.3	36.2	40.9	36.3	38.6
Gender, %						
Male	22.2	44.2	22.2	50.0	44.4	37.5
Race, N (%)						
White	15 (83.3)	8 (88.9)	8 (88.9)	16 (88.9)	18 (100.0)	65 (90.3)
Black/African American	1 (5.6)	0	0	0	0	1 (1.4)
Asian	1 (5.6)	1 (11.1)	1 (11.1)	2 (11.1)	0	5 (6.9)
American Indian/Alaska Native	1 (5.6)	0	0	0	0	1 (1.4)
CDAI Score, Mean (N)	307.2 (17)	296.0 (8)	312.3 (9)	301.3 (18)	341.1 (18)	313.8 (70)
MRE Score, Mean (N)	76.8 (10)	87.99 (4)	81.6 (5)	67.2 (14)	70.2 (14)	73.4 (47)
Duration of Disease, months, mean	122.9	111.2	94.6	143.4	110.7	120.0
Randomization Strata (IP) Inadequate Response and/or Intolerance to Anti-TNF						
Yes, N (%)	14 (77.8)	7 (77.8)	7 (77.8)	14 (77.8)	14 (77.8)	56 (77.8)

Safety Results:

- One subject ([redacted]) in the clazakizumab 300 mg IV/100 mg SC group died in the study. The death was due to septic shock due to septic peritonitis following GI perforation and the investigator considered it to be related to study drug.
- SAEs were reported in 16/72 (22.2%) total treated subjects and the proportion of subjects across treatment groups were slightly higher in the combined clazakizumab-treated groups compared to PBO (25.9% vs. 11.1%). A higher proportion of subjects in the 400 mg SC/200 mg SC reported an SAE (33.3%) compared to other treatment groups (22.2% reported in the other clazakizumab treatment groups and 11.1% reported in the PBO group). The most common SAEs included Crohn's disease (exacerbation), anal fistula, intestinal perforation, and peritonitis.
- Discontinuations due to AEs were reported for a total of 5 subjects: 1 subject each in the PBO, 150 mg IV/100 mg SC and 300 mg IV/100 mg SC groups, and 2 subjects in the 400 mg SC/200 mg SC group. There were no meaningful differences in discontinuations due to AEs between placebo and clazakizumab-treated dose groups.
- The proportion of subjects with AEs was lowest in the PBO group (44.4%) and was comparable across the clazakizumab treatment groups (72.2 - 83.3%). The most common AEs across treatment groups included nausea, vomiting, Crohn's disease, and nasopharyngitis.
- Related AEs were reported in 16/72 (22.2%) total treated subjects and the lowest proportion was in the PBO group (5.6%) and the highest proportion was in the 400 mg SC/200 mg SC group (44.4%). The most common AE related to treatment in the clazakizumab groups was injection site erythema.
- There were a total of 3 GI perforations reported (Subject [redacted]: 150 mg IV/100 mg SC, Subject [redacted]: 300 mg IV/100 SC, and Subject [redacted]: 600 mg IV/200 mg SC groups); two of which were considered by the investigator to be related to study drug (150 mg IV/100 mg SC and 300 mg IV/100 SC). One of the 3 reported GI perforations (Subject [redacted]) was not confirmed by MRE.
- The rate of infections was higher in the clazakizumab-treated subjects (38.8%) compared to the PBO group (22.2%). The most common infections among all subjects were nasopharyngitis (9.7%) and urinary tract infections (5.6%). The overall rate of serious infections across all subjects was 8.3%. There were no subjects that reported an opportunistic infection.
- A higher proportion of subjects in the 400 mg SC/200 mg SC group (27.8%) experienced an injection site event (ISE) compared to the other clazakizumab groups treated with IV (11.1%) and the placebo group (5.6%). One subject in the placebo group and no patients in the clazakizumab groups had experienced a peri-infusional event.
- The few ALT elevations that were observed occurred mostly in the post-treatment period, were asymptomatic and transient, and resolved spontaneously. None of the elevated liver enzymes were reported as an AE (or SAE). There were no cases that met Hy's Law.
- There were no significant abnormalities reported on ECGs.
- There were no clinically meaningful changes in vital signs (systolic or diastolic blood pressure, pulse, temperature) among the various treatment groups.
- No subjects developed anti-clazakizumab antibodies in the PBO, 150 mg IV/100 mg SC, 300 mg IV/100 mg SC, and 400 mg SC/200 mg SC treatment groups over the course of the study or post treatment. One subject [redacted]) in the 600 mg IV/200 mg SC treatment group developed anti-clazakizumab antibodies at IP-29 which persisted to the end of the study (IP-85) and post treatment with a titer of 1 throughout.

Table -3: Summary of Subjects with Adverse Events - Induction Period

	PBO (IP) N=18	150 IV/100 SC N=9	300 IV/100 SC N=9	600 IV/200 SC N=18	400 SC/200 SC N=18	Total N=72
Deaths	0	0	1 (11.1)	0	0	1 (1.4)
SAEs	2 (11.1)	2 (22.2)	2 (22.2)	4 (22.2)	6 (33.3)	16 (22.2)
Related SAEs	0	2 (22.2)	2 (22.2)	0	0	4 (5.6)
Discontinued due to SAEs	1 (5.6)	1 (11.1)	1 (11.1)	0	2 (11.1)	5 (6.9)
AEs	8 (44.4)	7 (77.8)	7 (77.8)	13 (72.2)	15 (83.3)	50 (69.4)
Related AEs	1 (5.6)	2 (22.2)	3 (33.3)	2 (11.1)	8 (44.4)	16 (22.2)
Discontinued due to AEs	1 (5.6)	1 (11.1)	1 (11.1)	0	2 (11.1)	5 (6.9)

Other Results: Efficacy: The results from all of the treatment groups, except for clazakizumab 400 mg SC/200 mg SC arm, reflect only a single (IV) dose administered on Day 1. Due to limited information (small number of subjects in each dose group reaching the predefined endpoints) and premature termination of the study, no definite statistical conclusions can be drawn. The rates of clinical remission (CDAI <150) and clinical response (≥100 point decrease in CDAI or an absolute CDAI <150) were comparable across all clazakizumab-treated groups when compared with placebo-treated subjects at Week 8 (primary endpoint) (Table -4). Pharmacokinetics: Clazakizumab Cmin increased with increasing IV dose. The geometric mean Cmin (%CV) at IP-85 for the clazakizumab 150 mg IV/100 mg SC, 300 mg IV/100 mg SC, 400 mg SC/200 mg SC, and 600 mg IV/200 mg SC treatment groups were 8.35 ug/mL (52.9%), 10.65 ug/mL (53.7%), 22.01 ug/mL (44.1%), and 15.56 ug/mL (33.4%), respectively. HrQoL: Improvements in IBDQ scores were comparable between the clazakizumab and placebo groups. MRE and MaRIA: There was no treatment benefit observed in the clazakizumab-treated groups when compared to the placebo group when considering disease severity on MRE based on the change from baseline in MaRIA scores at Day 85 (Table -5).

Table -4: Efficacy at Week 8 (Day 57) During Double-Blind Induction Period

	Placebo N=18	Claza 150 mg IV/100 mg SC N=9	Claza 300 mg IV/100 mg SC N=9	Claza 400 mg SC/200 mg SC N=18	Claza 600 mg IV/100 mg SC N=18	Claza arms combined N=54
mITT[a]: Clinical Remission[b]						
n/m (%)	3/17 (17.6)	3/9 (33.3)	0/8	3/16 (18.8)	2/16 (12.5)	8/49 (16.3)
95% CI	(3.8, 43.3)	(7.5, 70.1)	NA	(4.0, 45.6)	(1.6, 38.3)	(6.0, 26.7)
mITT[a]: Clinical Response[c]						
n/m (%)	5/17 (29.4)	3/9 (33.3)	2/8	5/16 (31.3)	4/16 (12.5)	14/49 (28.6)
95% CI	(7.8, 51.1)	(7.5, 70.1)	(3.2, 65.1)	(8.5, 54.0)	(7.3, 52.4)	(15.9, 41.2)
As-Observed: Clinical Remission[b]						
n/m (%)	3/15 (20.0)	3/7 (42.9)	0/9	4/12 (33.3)	2/13 (15.4)	9/41 (22.0)
95% CI	(4.3, 48.1)	(9.9, 81.6)	NA	(9.9, 65.1)	(1.9, 45.4)	(9.3, 34.6)
As-Observed: Clinical Response[c]						
n/m (%)	5/15 (33.3)	3/7 (42.9)	2/9 (22.2)	6/12 (50.0)	4/13 (30.8)	15/41 (36.6)
95% CI	(9.5, 57.2)	(9.9, 81.6)	(2.8, 60.0)	(21.7, 78.3)	(9.1, 61.4)	(21.8, 51.3)
Change from Baseline in CDAI score						
n	15	7	9	12	13	41
Mean (SD)	-70.3 (120.0)	-61.1 (129.5)	-39.2 (66.4)	-123.0 (120.8)	-38.3 (104.9)	-67.2 (110.0)

[a] mITT(modified Intent-To-Treat) analysis population: all randomized and treated subjects who had a chance to reach Day 57 by the date of study termination

[b] Clinical remission defined by CDAI score ≤150 at Week 8

[c] Clinical response defined by a reduction in CDAI score ≥100 or an absolute CDAI score <150 at Week 8

Table -5: Summary Statistics of MaRIA and its Mean Change from Baseline Over Time - Induction Period, All Randomized and Treated Subjects

MARIA SCORE	PBO (IP) N=18	150 IV/100 SC N=9	300 IV/100 SC N=9	600 IV/200 SC N=18	400 SC/200 SC N=18	Total N=72
IP-1 (Baseline)						
N	3	4	0	3	7	17
Mean	88.997	87.990		69.650	59.193	73.074
IP-85						
N	3	4	0	3	7	17
Change from Baseline, mean	-24.670	-9.335		6.627	0.059	-5.356

Abbreviations: IP, induction period; IV, intravenous; PBO, placebo; SC, subcutaneous

CONCLUSIONS:

Safety

- The study was terminated due to two reasons: 1) three cases of GI perforations (two of which were confirmed by MRE), one case was associated with peritonitis, septic shock and death, and 2) the inability to justify the high doses being used in this study given new data from the Phase 2b study in RA suggesting that lower doses could be utilized effectively with lower risk of AEs.
- Beside GI perforation that can spontaneously occur in Crohn's disease, there were no new safety signals compared to that reported in the Phase 2 studies in RA (IM133001) and PsA (IM133004).
- The rate of infections was slightly higher in clazakizumab-treated groups compared to placebo.
- Laboratory abnormalities were consistent with the mechanism of action (IL-6 inhibition).
- The few ALT elevations that were observed occurred mostly in the post-treatment period, were asymptomatic and transient. There were no cases of Hy's Law.
- There were no cases of tuberculosis or opportunistic infections observed.

Efficacy

- No dose-response of clazakizumab was apparent.
- No apparent efficacy of clazakizumab was observed vs. placebo in disease activity measures, although this is based on limited amount of information secondary to premature termination and a small number of subjects evaluated. In addition, it must be noted that almost 85% subjects in the analysis were TNF-IR that are known to be refractory to treatment as compared with biologic-naive patients.
- No treatment benefit of clazakizumab was observed on MRE assessments based on MaRIA scores.

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