BRISTOL-MYERS SQUIBB COMPANY

ABATACEPT

Final Clinical Study Report for Study IM101108

SYNOPTIC REPORT

A Phase 3, Multi-Center, Randomized, Placebo-Controlled Study to Evaluate the Clinical Efficacy and Safety of Induction and Maintenance Therapy with Abatacept in Subjects with Active Ulcerative Colitis (UC) Who Have Had an Inadequate Clinical Response and/or Intolerance to Medical Therapy

Indication:	Ulcerative Colitis
Phase:	3
Study Initiation Date:	21-Dec-2006
Study Completion Date for First Cohort of Induction Period:	25-May-2009
Study Termination Date:	19-Aug-2009
Last Observation for Any Period	19-Nov-2009
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THIS STUDY WAS CONDUCTED IN ACCORDANCE WITH GOOD CLINICAL PRACTICE

Sponsor's Responsible Medical Officer:

[redacted]

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SYNOPSIS

Final Clinical Study Report for Study IM101108

TITLE OF STUDY: A Phase 3, multi-center, randomized, placebo-controlled study to evaluate the clinical efficacy and safety of induction and maintenance therapy with abatacept in subjects with active Ulcerative Colitis (UC) who have had an inadequate clinical response and/or intolerance to medical therapy.

PURPOSE: This study was the first clinical evaluation of abatacept in ulcerative colitis (UC) and was designed to investigate the efficacy and safety of abatacept as induction and maintenance therapy in subjects with moderate to severe UC who have had an inadequate response and/or intolerance to standard medical therapy. Study IM101108 was terminated early due to a lack of efficacy in the first cohort of subjects in the Induction Period (IP1C). In addition, a higher proportion of subjects with severe UC at baseline reported serious adverse events (SAEs) of ulcerative colitis exacerbation in the abatacept treatment groups, as compared to placebo. At the time of this report, Bristol-Myers Squibb (BMS) has no plans for continuing the clinical development of abatacept for the treatment of patients with UC; therefore, data from all 3 periods (Induction Period (IP): first cohort [IP1C] plus second cohort [IP2C]; Maintenance Period [MP]; and Open-label Extension Period [OLE]) of this study are summarized herein a synoptic clinical study report format.

NUMBER OF SUBJECTS: Of the 636 subjects that were planned to be randomized in the IP, 490 were to be randomized in the IP1C and an additional 146 subjects in the IP2C. A total of 490 subjects were randomized into the IP1C (140 placebo, 350 abatacept) and an additional 101 subjects were randomized into the IP2C. A total of 131 subjects from the IP (IP1C or IP2C) were randomized and treated in the MP and (65 abatacept, 66 placebo); and 349 subjects were treated with abatacept in the OLE.

DISPOSITION, DEMOGRAPHICS, AND OTHER PERTINENT BASELINE CHARACTERISTICS: A total of 107 subjects (21.8%) were discontinued from the IP1C (20/140, 14.3% placebo, 87/350, 24.9% abatacept), with lack of efficacy being the most common reason for early withdrawal in all groups. A total of 131 subjects completed the IP (IP1C or IP2C) and entered the MP, of whom only 19.8% of subjects completed the MP. The percentage of subjects withdrawn due to study termination by the Sponsor was 42.6% for the IP2C, 35.1% for the MP, and 41.5% for the OLE. Lack of efficacy was the other major reason for premature discontinuation from the MP (37.4%) and OLE (46.1%). Demographic and baseline disease characteristics were generally comparable across treatment groups for the IP and MP. Of the 490 subjects entering the IP1C, 41% were female and 32.7% had an inadequate response or were intolerant to prior therapy with anti-tumor necrosis factor (TNF) therapy. Across all subjects entering the IP1C, the overall mean age was 41.9 years and the mean duration of UC was 6.5 years.

SUMMARY OF EFFICACY RESULTS: The study failed to demonstrate a clinically meaningful and statistically significant treatment effect of abatacept relative to placebo as measured by the primary endpoint of the proportion of subjects in clinical response at Day IP-85 (Week 12) (rates in placebo and abatacept 30/~10 mg/kg groups were 29.5% and 21.4%, respectively; p-value for the comparison was 0.124). Given the pre-specified hierarchical testing procedure, statistical testing of clinical response at Day IP-85 was not performed for abatacept ~ 10 mg/kg versus placebo or for any of the key secondary endpoints (clinical remission and mucosal healing at Day IP-85 [Week 12]) for either abatacept 30/~10 mg/kg versus placebo or abatacept ~10 mg/kg versus placebo. The proportion of subjects in clinical remission for the placebo and abatacept (30/~10 mg/kg, ~10 mg/kg, and 3 mg/kg) treatment groups was 10.8% and 2.1 to 5.8%, respectively. The proportion of subjects with mucosal healing at Day IP-85 for the placebo and abatacept (30/~10 mg/kg, ~10 mg/kg, and 3 mg/kg) treatment groups was 25.9% and 14.6 to

17.1%, respectively. Analyses of other efficacy endpoints, as well as subgroup analyses, also consistently failed to demonstrate any clinically meaningful treatment efficacy for abatacept.

SUMMARY OF SAFETY RESULTS: Overall, a higher proportion of subjects reported SAEs across all abatacept groups compared to the placebo group for the IP1C (see Safety Summary Table below). Additional non-prespecified safety analyses were conducted and indicated that this was primarily driven by the higher proportion of subjects that reported an SAE of ulcerative colitis in the abatacept groups (9.2%, 11.5%, and 7.1% in the 30/~10 mg/kg, ~10 mg/kg, and 3 mg/kg groups, respectively) compared to the placebo group (2.9%). The majority of SAEs of UC exacerbation occurred in subjects entering the study with severe UC (Mayo score of ≥ 10). The safety profiles for the IP1C and the IP2C, MP, and OLE are summarized in the following tables.

Safety Summary: Induction Period

	First Cohort (IP1C)				Second Cohort (IP2C)	
No. (%) of subjects with:	**Abatacept 30/~10 mg/kg (N=141)**	**Abatacept ~10 mg/kg (N=139)**	**Abatacept 3 mg/kg (N=70)**	**Placebo (N=140)**	**Abatacept 30/~10 mg/kg (N=51)**	**Abatacept ~10 mg/kg (N=50)**
Deaths	1 (0.7)	0	0	0	0	0
SAEs[a]	22 (15.6)	20 (14.4)	8 (11.4)	7 (5.0)	6 (11.8)	4 (8.0)
Related SAEs[a,b]	4 (2.8)	1 (0.7)	1 (1.4)	3 (2.1)	1 (2.0)	0
SAEs leading to discontinuation[a]	1 (0.7)	2 (1.4)	1 (1.4)	3 (2.1)	1 (2.0)	0
AEs	85 (60.3)	92 (66.2)	39 (55.7)	86 (61.4)	26 (51.0)	27 (54.0)
Related AEs[b]	48 (34.0)	46 (33.1)	23 (32.9)	37 (26.4)	10 (19.6)	11 (22.0)
AEs leading to discontinuation	4 (2.8)	6 (4.3)	2 (2.9)	5 (3.6)	1 (2.0)	0

[a] SAEs include hospitalizations for elective surgical procedures.

[b] Relationship of AE or SAE to study drug is certain, probable, possible, or missing.

Safety Summary: Maintenance Period and Open Label Period

	Maintenance Period		Open Label Period
No. (%) of subjects with:	**Abatacept ~10 mg/kg (N=65)**	**Placebo (N=66)**	**Abatacept ~10 mg/kg (N=349)**
Deaths	1 (1.5)	0	1 (0.3)
SAEs[a]	7 (10.8)	4 (6.1)	66 (18.9)
Related SAEs[a,b]	2 (3.1)	2 (3.0)	9 (2.6)
SAEs leading to discontinuation[a]	1 (1.5)	1 (1.5)	4 (1.1)
AEs	39 (60.0)	36 (54.5)	241 (69.1)
Related AEs[b]	12 (18.5)	13 (19.7)	100 (28.7)
AEs leading to discontinuation	1 (1.5)	3 (4.5)	7 (2.0)

[a] SAEs include hospitalizations for elective surgical procedures.

[b] Relationship of AE or SAE to study drug is certain, probable, possible, or missing.

CONCLUSIONS:

- Abatacept, at dose regimens of 3 mg/kg, ~10 mg/kg, and 30/~10 mg/kg, failed to demonstrate efficacy in UC as an induction therapy. Noting the small number of subjects treated and assessed during the MP, abatacept failed to demonstrate any evidence for clinical activity in UC during the MP.
- Abatacept, administered IV on Days 1, 15, and 29 and then every 28 days, at a dose regimen of up to 30/~10 mg/kg for 12 weeks in the IP, or at a weight-tiered dose of ~10 mg/kg for up to 12 months in the MP, or up to ~26 months in OLE, was generally well tolerated in subjects with UC.
- During the IP, subjects in the abatacept treatment groups with severe UC (Mayo score of ≥ 10) at baseline experienced higher frequency of SAE of UC exacerbation as well as SAE of UC exacerbation requiring surgery compared to the subjects with severe UC at baseline in the placebo treatment group.
- The incidence of immunogenicity during treatment with abatacept was low. Although rates increased upon withdrawal of abatacept during the MP, with prolonged withdrawal beyond 4 months, immunogenicity titer either decreased or became non-detectable. Seropositive responses were not associated with changes in AE profile or clinically relevant events.
- Further clinical development of abatacept in UC will not be pursued by the Sponsor.

DATE OF REPORT: 20-Apr-2010