2.0 Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:**	**(For National Authority Use Only)**
Name of Study Drug: Adalimumab	**Volume:**	
Name of Active Ingredient: Adalimumab	**Page:**	

Title of Study: A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction of Clinical Remission in Subjects with Moderate to Severe Crohn's Disease who Have Lost Response or are Intolerant to Infliximab

Coordinating Investigator: William J. Sandborn, M.D. (Mayo Clinic Research, Rochester, MN)

Study Sites: Multicenter; 52 study sites in United States, Canada, Belgium, and France

Publications: None

Studied Period (Years): First Subject First Visit: 23 Nov 2004 Last Subject Last Visit: 26 Jan 2006	**Phase of Development:** 3

Objectives: The objectives of this study were to demonstrate the efficacy of adalimumab in the treatment of subjects with Crohn's disease who either initially responded to administration of infliximab but stopped responding or were intolerant to infliximab; to delineate the safety of adalimumab when administered to subjects with Crohn's disease; and to assess the pharmacokinetics (PK) of adalimumab following subcutaneous (sc) administration.

Methodology:

This was a randomized, double-blind, placebo-controlled, multicenter, efficacy, safety, and PK study designed to demonstrate the effectiveness of adalimumab in the treatment of moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] ≥ 220 and ≤ 450 with confirmation by endoscopic or radiologic evaluation) in subjects who either initially responded to infliximab and lost response or were intolerant to infliximab. Study medication was administered by sc injection. Subjects were randomized to one of two blinded treatment groups: adalimumab 160/80 mg or placebo. All subjects received a loading dose at Baseline (Week 0), followed by a second dose at Week 2.

The duration of the study was up to 6 weeks, and included a 2-week Screening period and a 4-week treatment period. Efficacy and safety measurements were performed throughout the study. Blood samples were obtained for the measurement of adalimumab and anti-adalimumab antibody concentrations at Baseline and Week 4/early termination. Blood samples were also obtained for measurement of human anti-chimeric antibody to infliximab at Baseline.

Number of Subjects (Planned and Analyzed):

300 subjects (150 in each treatment group) were planned; 159 adalimumab 160/80 mg subjects and 166 placebo subjects received at least one dose of study medication; 325 subjects were analyzed for efficacy and safety.

Diagnosis and Main Criteria for Inclusion:

- Subject had a diagnosis of Crohn's disease confirmed by endoscopy or radiologic evaluation.
- Subject had a CDAI score of ≥ 220 and ≤ 450.
- Males and females between 18 and 75 years of age, inclusive.
- Subject had lost an initial response to or had adverse reactions to infliximab.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Subjects received 160 mg adalimumab at Baseline (Week 0) and 80 mg adalimumab at Week 2. Lot numbers were 13191HK and 24264HK.

Duration of Treatment:

Two doses of study drug were administered two weeks apart.

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

Placebo sc injection to match test product. Lot numbers were 13195HK and 90014HK.

Criteria for Evaluation

Efficacy: The primary efficacy variable was the induction of clinical remission (CDAI <150) at Week 4. The major secondary efficacy variable measurements were: (1) clinical response (decrease in CDAI score ≥ 70 points when compared to Baseline [CR-70]) at Week 4; (2) clinical response (decrease in CDAI score ≥ 100 points when compared to Baseline [CR-100]) at Week 4; (3) changes from Baseline Inflammatory Bowel Disease Questionnaire (IBDQ) scores at Week 4; (4) proportion of subjects with CR-70 at Week 2; (5) proportion of subjects with CR-70 at Week 1; (6) change from Baseline in Short Form-36 (SF-36) Physical Component Summary (PCS) score at Week 4; (7) change from Baseline in visual analogue scale score for joint pain at Week 4; (8) proportion of subjects with no draining fistulas at last two evaluations; (9) change from Baseline in C-reactive protein (CRP) at Week 4; (10) change from Baseline in SF-36 Mental Component Summary score at Week 4; and (11) proportion of subjects with remission at Week 2. Other secondary outcomes included improvement in the number of draining fistulas at Week 4 (where improvement was defined as a decrease of ≥ 50% in the number of fistulas that were draining at Screening and Baseline for at least two consecutive visits); mean change from baseline in CRP; and mean change from baseline in CDAI.

Safety: Adverse events (AEs), clinical laboratory data, and vital signs were collected and physical examinations were performed.

Statistical Methods

Efficacy: The primary analysis was the comparison of the induction of clinical remission of adalimumab 160/80 mg *vs.* placebo at Week 4. Those with missing primary endpoint data at Week 4 were classified in the "no induction of clinical remission" category. The treatment comparison was performed using Pearson's Chi-square test.

Summary statistics included point estimates of the induction rate of clinical remission for each treatment group, the difference in proportion between the adalimumab and placebo groups, and the corresponding 2-sided 95% confidence intervals. A supportive analysis of the primary variable was performed using the Last Observation Carried Forward (LOCF) approach to impute missing values at Week 4.

Secondary efficacy analyses were conducted on Week 4 LOCF data and included the following: the proportions of subjects with CR-70 at Week 4 were compared using the Chi-square test between the adalimumab and placebo groups. Summary statistics were displayed as the frequency and proportion of subjects who achieved clinical response in both groups, the difference in clinical response rate between the adalimumab and placebo groups, and the corresponding 95% confidence intervals of the difference.

Other summary statistics were conducted for the following efficacy variables: CR-100 and changes in Baseline IBDQ scores.

Safety: The incidence of treatment-emergent AEs was summarized for each Medical Drug Regulatory Affairs (MedDRA) system organ class and preferred term. Treatment group differences in the overall incidence of treatment-emergent AEs were assessed with Fisher's Exact test for each preferred term. Clinical laboratory data were summarized with mean change from Baseline to the minimum, maximum, and final values, and with the proportion of subjects who changed to potentially clinically significant (PCS) values from Baseline values that were not PCS. Vital signs were analyzed similarly.

Summary/Conclusions

Efficacy Results:

The proportion of subjects who achieved the protocol-specified primary efficacy endpoint of clinical remission (CDAI < 150) at Week 4 was statistically significantly greater in the adalimumab 160/80 mg group compared to the placebo group (21.4% *vs.* 7.2%; $p < 0.001$). The clinical remission rate for the adalimumab group was statistically significantly greater than placebo at Week 2.

Subgroup analyses of clinical remission at Week 4 showed no clinically important differences between the following subgroups: subjects who had loss of response to infliximab *vs.* those who did not have loss of response to infliximab; subjects who had intolerance to infliximab *vs.* those who did not have intolerance to infliximab; subjects with both loss of response to and intolerance to infliximab *vs.* those without both conditions; and subjects who were human anti-chimeric antibody (HACA) positive *vs.* subjects who were HACA negative.

The primary endpoint results were supported by the secondary endpoint results as outlined in the table below.

Endpoint	Evaluation Time	Placebo N=166	Adalimumab 160/80 mg N=159
		n (%)	
CR-100	Week 2	30 (18.1)	58 (36.5)*
	Week 4	41 (24.7)	61 (38.4)*
CR-70	Week 1	34 (20.5)	55 (34.6)*
	Week 2	54 (32.5)	83 (52.2)*
	Week 4	56 (33.7)	82 (51.6)*
Change from Baseline in IBDQ total score	Week 4		
Baseline Mean ± SD		123.5 ± 27.45	119.7 ± 27.43
Mean Change ± SD		15.1 ± 26.99	30.2* ± 30.75
Change from Baseline in SF-36 Physical Component Summary	Week 4	N=159	N=153
Baseline Mean ± SD		35.2 ± 8.02	34.9 ± 7.90
Mean Change ± SD		3.5 ± 6.76	5.7 ± 8.15

IBDQ = Inflammatory Bowel Disease Questionnaire

* Statistically significant difference *vs.* placebo, $p \leq 0.050$

The statistically significant superiority of adalimumab 160/80 mg *vs.* placebo in the full analysis set was observed for the proportion of subjects with CR-100 at Week 2 and Week 4; with CR-70 at Week 1, Week 2, and Week 4; change from Baseline in IBDQ total score at Week 4; and change from Baseline in SF-36 in PCS at Week 4. CR-100 was observed for 24.7% and 38.4% of placebo and adalimumab 160/80 mg subjects, respectively, at Week 4. CR-70 was observed for 33.7% and 51.6% of placebo and adalimumab 160/80 mg subjects, respectively, at Week 4. These findings demonstrate that adalimumab provides superior clinical efficacy to placebo as demonstrated by a range of clinical response endpoints.

Safety Results:

Adalimumab was generally safe and well tolerated in study subjects with moderate to severe Crohn's disease. A summary of the overall incidence of treatment-emergent AEs, AEs at least possibly related to study drug (treatment-related AEs), any serious adverse event, and any AE leading to study discontinuation is presented below.

	Placebo	Adalimumab 160/80 mg
	N=166	N=159
	n (%)	
Any adverse event	121 (72.9)	91 (57.2)*
Any adverse event with probable or possible relation to study drug	53 (31.9)	43 (27.0)
Any serious adverse event	8 (4.8)	2 (1.3)
Any adverse event leading to death	0	0
Any adverse event leading to study discontinuation[a]	4 (2.4)	2 (1.3)

* Statistically significant difference *vs.* placebo ($p \leq 0.05$).

a. Denotes subjects who discontinued at least in part due to an AE

With the exception of AEs related to underlying Crohn's disease having been reported more frequently in the placebo group compared to the adalimumab group, AEs were similar in frequency and character in the two treatment groups. There were four serious infectious AEs in the placebo group (three events reported as various gastrointestinal-related abscesses) and none in the adalimumab 160/80 mg treatment group. No subject died nor experienced a malignant neoplasm during the study.

Infectious AEs reported by study subjects were typical of those seen in the Crohn's disease population. Although not statistically significantly different, the percentage of placebo subjects with treatment-emergent infectious AEs was greater than that of adalimumab 160/80 mg subjects, indicating that there is no evidence of increased risk of infection with short-term adalimumab therapy. No cases of tuberculosis were observed during the study.

Clinical laboratory changes generally reflected improvement in Crohn's disease activity as well. Specifically, albumin and total protein increased relative to placebo and alkaline phosphatase decreased. Hematocrit, hemoglobin, and red blood cell count increased relative to placebo, while platelets decreased. The incidence rate of patients experiencing Common Toxicity Criteria Grade 3 or higher abnormalities was similar between placebo and adalimumab treatment groups for all clinical laboratory parameters.

Conclusions:

The results of this study demonstrated that adalimumab given as induction therapy at sc doses of 160 mg at Week 0 and 80 mg at Week 2 to subjects with moderately to severely active Crohn's disease who had lost an initial response to or had adverse reactions to infliximab was effective, safe, and well tolerated. These results suggest that adalimumab as induction therapy offers a therapeutic option to patients with moderate to severe Crohn's disease who have failed treatment with infliximab.