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 multicenter, open-label treatment of the human anti-TNF monoclonal antibody adalimumab in patients with moderate to severe Crohn's disease with previous exposure to infliximab

Investigator: [redacted] MD redacted information 14Nov2014

Study Site(s): 96 sites in the US

Publications: None

Studied Period (Years): Date First Subject Dosed: 13 Jul 2006 Date Last Subject Completed Dosing: 25 May 2007	**Phase of Development:** 3

Objective(s): The primary objective of this study was to make adalimumab available to subjects suffering from moderately to severely active Crohn's disease (CD) who had failed to respond to, lost response to, or were intolerant to infliximab, and to evaluate safety by collecting serious adverse events (SAEs).

The secondary objective was to assess changes from Baseline in Health Economics Outcomes Questionnaires.

Methodology: This was a Phase 3b, multicenter, open-label study with an induction regimen of 160 mg at Baseline and 80 mg at Week 2, followed by maintenance dosing of 40 mg every other week (eow) starting at Week 4 in subjects with moderately to severely active CD who had failed to respond to, lost response to, or were intolerant to infliximab. Doses could be increased to 40 mg weekly (ew) at or after Week 8 in subjects with flares, as determined by the Investigator. Dose escalations prior to Week 8 required Abbott Medical Monitor approval. A subject who experienced a flare or who was a nonresponder (both as determined by the Investigator) while receiving adalimumab ew, could have been discontinued from the study. All doses were open-label and subcutaneously (SC) administered.

Number of Subjects (Planned and Analyzed): 1000 planned, 673 enrolled

Diagnosis and Main Criteria for Inclusion: Subjects with moderately to severely active CD who had been initially treated with infliximab and were primary nonresponders or either lost response to or discontinued its use as a result of intolerance to the drug.

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

Adalimumab 40 mg/0.8 mL administered SC. Lot Number: [redacted] redacted information 14Nov2014

Duration of Treatment: Subjects remained in the study for at least eight weeks. The trial was to continue for approximately nine months or until adalimumab became commercially available for the treatment of CD.

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

None

Criteria for Evaluation

Safety: Safety assessments performed throughout the study included physical examination and AE monitoring. The laboratory testing done at Screening was repeated if warranted.

Efficacy: Beginning at the Baseline visit, subjects completed the following Health Economics Outcomes questionnaires at each visit (Baseline, Weeks 4, 8, 12, and approximately every 12 weeks thereafter, until study termination):

1) Short Quality of Life in Inflammatory Bowel Disease Questionnaire (SIBDQ) – this questionnaire is a simple, validated, 10-item instrument that assesses health-related quality of life in inflammatory bowel disease patients. The SIBDQ is designed to find out how the subject has been feeling during the last 2 weeks. Increases in SIBDQ scores indicate improved overall quality of life, with larger increases indicating greater improvement. Of note, a 9-point change in the SIBDQ correlates with a 100-point change in CDAI.

2) Work Productivity and Activity Impairment questionnaire (WPAI) – this questionnaire, as adapted for CD, measures the percentage of overall impairment in work productivity and daily activity due to CD. Four scores are generated from WPAI: percent time work missed (absenteeism), percent impairment while working (presenteeism), overall work impairment, percent activity impairment score. A WPAI score of 0% = no impairment and a score of 100% = total loss of work productivity or activity. An absolute change in WPAI score of 7% is considered the minimal clinically meaningful change.

Beginning at the Baseline visit, study staff completed the Health Care Resource Utilization questionnaire (HCRU) at each visit. This questionnaire was designed to assess unscheduled outpatient visits, emergency room visits, and hospitalizations.

Fistula counts were performed as part of the physical examination.

Statistical Methods

Safety: Treatment-emergent, pre-and post-treatment SAEs were summarized and reported. Physical examination, including blood chemistry, urinalysis, and chest x-ray, was described statistically. For laboratory parameters, the normal range of the analyzing laboratory was used and all values outside the normal range were listed.

Efficacy: The null hypothesis of no change from Baseline was tested using a 95% confidence interval based on the t-statistic for quantitative efficacy variables. Supportive analysis including all post-Baseline measurements collected, regardless of the number of days after the last dose of study drug may also have been performed. Summary statistics for efficacy were performed by subgroups: Sex [male, female], Age [< 65 years, ≥ 65 years], Ethnicity [White, Black, Asian, Hispanic, Other], Weight [≤ 70 kg, > 70 kg], and use of corticosteroid or immunosuppressants [Yes, No].

Summary/Conclusions

Safety Results: In this study, adalimumab was found to be safe and well-tolerated in subjects with moderately to severely active CD who had failed to respond to, lost response to, or were intolerant to infliximab.

One treatment-emergent death was reported. Subject [redacted] died of unknown treatment-emergent causes three days post-treatment on Day 74. The Investigator considered the event probably not related to study drug. redacted information 14Nov2014

Another, non-treatment-emergent death was also reported. Subject [redacted] died of acute renal failure, methicillin-resistant *S. aureus* (MRSA) septicemia, *C. difficile* colitis, and pneumonia 130 days post-treatment on Day 300. The Investigator considered this probably not related to study drug, and the Abbott assessment was not related. redacted information 14Nov2014

In total, 88 subjects (13.1%) experienced SAEs with similar proportions reporting SAEs in both groups (13.0% of initial responders and 13.4% of primary nonresponders). The majority of these events were gastrointestinal in nature. Approximately 3% of subjects had an SAE that was considered by the Investigator to be at least possibly related to study drug.

Serious adverse events led to discontinuation from the study for approximately 3% of subjects. In total, 22 subjects (3.3%) had an infectious SAE. No SAEs in the following categories were reported: opportunistic infections, malignant SAE (including lymphoma and non-melanoma skin cancer), injection site reaction, congestive heart failure, demyelinating disease, allergic reaction-related, or lupus-like syndrome.

Laboratory toxicities ≥ Grade 3 were few.

Efficacy Results: Efficacy variables are secondary outcomes for this study and were assessed mainly from patient-reported outcomes data (SIBDQ scores, WPAI scores, HCRU) and fistula counts.

Clinically and statistically significant mean increases in total SIBDQ scores were demonstrated in All Treated Subjects at all study visits. Numerically greater mean increases in total SIBDQ scores were seen over time among initial responders than primary nonresponders in the intent-to-treat (ITT) group, and in subjects who dose-escalated compared to subjects who did not dose escalate, although the limited sample sizes preclude meaningful comparison. Greater increases were observed in the last assessed value (LAV) of mean total SIBDQ scores in primary nonresponders compared to initial responders when dosing was escalated from eow to ew. Mean SIBDQ Domain scores improved comparably in initial responders and primary nonresponders for each domain from Baseline to LAV. Increases in mean SIBDQ Domain scores tended to be higher among initial responders for all domains. Per-protocol analyses performed to explore the impact of major protocol violations and/or deviations on the results of this study showed results in total SIBDQ score by visit were consistent with results from the All Treated Subjects analyses.

Clinically meaningful and statistically significant mean increases in total and component WPAI scores were demonstrated in All Treated Subjects at all study visits. Numerically greater mean decreases in total WPAI impairment scores (absenteeism, presenteeism, percent overall work impairment, and percent activity impairment) were seen over time among initial responders than primary nonresponders in the ITT group, and in subjects who dose escalated compared to subjects who did not dose escalate, although the limited sample sizes preclude meaningful comparison. The large number of missing values among primary nonresponders led to a small sample size in this group; consequently, the results in this group should be viewed with caution. As with SIBDQ scores, dose escalators had continued improvements following dose escalation from eow to ew dosing.

In general, there were no marked differences in the number of any of the four types of healthcare resource visits between initial responders and primary nonresponders, or subjects who did not escalate compared to those that that did; however, the variation in duration of follow-up was different for each subject, therefore no conclusions may be drawn from these overall numbers.

Draining fistula counts showed similar decreases from Baseline to LAV in initial responders and primary nonresponders among all treated subjects and subjects who did not dose escalate. Among subjects who dose escalated, initial responders showed greater decreases in draining fistula counts from Baseline to LAV compared to primary nonresponders.

Conclusions: Safety data from this study confirm that adalimumab is generally well tolerated in subjects with moderate to severely active CD. Efficacy data from this study show a strong positive trend in favor of the use of adalimumab to improve quality of life and overall health outcome, including fistula response, in subjects with moderately to severely active CD who had failed to respond to, lost response to, or were intolerant to infliximab.