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 Maintenance of Clinical Remission in Subjects with Crohn's Disease		
Coordinating Investigator: [redacted] MD redacted information 14Nov2014		
Study Sites: Multicenter; 53 study sites in the United States, Canada, Belgium, the Netherlands, the Czech Republic, and Poland		
Publications: 9		
Studied Period (Years): First Subject First Visit: 28 August 2002 Last Subject Last Visit: 15 December 2008	**Phase of Development:** 3	
Objectives: The objectives of the open label extension phase of this study were: (1) To demonstrate the efficacy of adalimumab in the maintenance of clinical remission in subjects with Crohn's disease (CD) who participated in the open-label extension portion, called the long-term extension phase in this document, of Study M02-433, and (2) To delineate the safety of adalimumab when administered to subjects with CD who participated in the long-term extension phase of Study M02-433.		
Methodology: Study M02-433 was designed to evaluate the efficacy and safety of adalimumab in the maintenance of clinical remission in subjects with CD. The study consisted of 2 phases: 1) a multi-center, randomized, double-blind, placebo controlled phase (with an open-label [OL] arm) that lasted 56 weeks, and 2) a long-term extension phase that was to be up to 264 weeks in duration (Week 56 to Week 320). The study was terminated prior to Week 320 per the protocol once adalimumab was approved for CD , all applicable local reimbursement procedures were completed and the long term safety registry (Registry P06-134) was open for enrollment. Efficacy data were collected up to Week 289; dosing data up to Week 287, and safety data up to 70 days past last dose (Week 260). Subjects were enrolled in Study M02-433 from Study M02-403, the lead-in study for Study M02-433.		

Methodology (Continued):

The lead-in study, Study M02-403, was a dose-response, randomized, DB, placebo-controlled, 4-week study that excluded anti-TNF experienced subjects. This study was designed to evaluate the safety, efficacy, and pharmacokinetics of adalimumab, in comparison with placebo, as induction treatment for subjects with moderate to severe CD. Subjects who met the study eligibility criteria were randomized at Baseline (Week 0) to receive 1 of 4 treatment regimens. The investigational treatment consisted of subcutaneous (SC) injections of adalimumab 160 mg at Baseline (Week 0) followed by 80 mg at Week 2, adalimumab 80 mg at Baseline (Week 0) followed by 40 mg at Week 2, adalimumab 40 mg at Baseline (Week 0) followed by 20 mg at Week 2, or placebo at Baseline (Week 0) and Week 2. Subjects who completed Study M02-403 were eligible to enroll in Study M02-433 to evaluate the long-term safety and efficacy of adalimumab as maintenance therapy.

In Study M02-433, all subjects who completed Study M02-403 received 40 mg of adalimumab SC at Baseline (Week 4 of Study M02-403) and Week 2. At Week 4, subjects were randomized based on their clinical remission status at Baseline and Week 4 of Study M02-433. Subjects who demonstrated clinical remission, defined as a Crohn's Disease Activity Index (CDAI) score < 150 points, at Baseline of Study M02-433, and remained in clinical remission at Study M02-433 Week 4 (defined as Remitters at Baseline and Week 4 in this long-term extension study report) were randomized to receive 1 of 3 blinded treatments as follows: 1) adalimumab 40 mg every other week (eow), 2) adalimumab 40 mg every week (ew), or placebo ew. Remitters were subjects who demonstrated clinical remission, defined as a CDAI score < 150 points, at Baseline values of Study M02-433, and remained in clinical remission at Study M02-433 Week 4. Non-remitters were subjects who did not demonstrate clinical remission at Baseline values of Study M02-433, or who were no longer in clinical remission at Week 4 of Study M02-433.

Subjects who did not demonstrate clinical remission at Baseline of Study M02-433, or who were no longer in clinical remission at Week 4 (defined as Non Remitters at Baseline or Week 4 in this long-term extension study report) were assigned to receive OL adalimumab 40 mg eow. From Week 4 on, these subjects (i.e., subjects who did not demonstrate clinical remission at Baseline of Study M02-433 or who were no longer in clinical remission at Week 4) who developed a flare or were non-responders during OL treatment could have had his/her dose increased to 40 mg ew. Subjects receiving adalimumab 40 mg ew who developed another flare or were non-responders could have been withdrawn from the study. A flare was defined as a recurrence of very active disease, specifically an increase in CDAI of ≥ 70 points when compared to the subject's value at Week 4 of Study M02-433, and a CDAI above 220 points. A nonresponder was defined as a subject who did not attain a CDAI decrease of ≥ 70 points compared to the subject's value at the Study M02-403 Baseline.

After 1 year (Week 56), subjects participating in Study M02-433 who met entry criteria for the long-term extension phase of the study were able to rollover into the long-term extension phase of the study. During the long-term extension phase, subjects in the blinded treatment groups were switched to OL adalimumab 40 mg eow, and subjects previously in the OL treatment group continued on their previous OL adalimumab dose. At any time during the long-term extension phase of Study M02-433, subjects receiving OL adalimumab 40 mg eow who developed a flare or were non-responders during OL treatment could have had his/her dose increased to 40 mg ew. Subjects receiving adalimumab 40 mg ew who developed another flare or were non-responders could have been withdrawn from the study.

Number of Subjects (Planned and Analyzed):

270 subjects were planned for enrollment.

A total of 276 subjects entered the Study M02-433. Those subjects received at least 1 dose of study drug, ie adalimumab or placebo, in the lead-in study, Study M02-403, and 1 dose of adalimumab at any time in this study, Study M02-433, and were included in the analysis of safety and the analysis of efficacy. Analysis for efficacy included all 276 subjects, however, only 177 subjects had non-missing efficacy information on or after Week 56 of Study M02-433 (long-term extension phase of the study). Therefore, observed-case efficacy analysis for the long-term extension phase of Study M02-433 had data for 177 subjects.

Diagnosis and Main Criteria for Inclusion:

Subjects were required to have successfully enrolled in and completed the lead-in study, Study M02 403.

Female subjects must have:

- Continued to utilize a highly effective method of birth control throughout the study and for 150 days after the last dose of study drug,
- Not been of childbearing potential, defined as postmenopausal ≥ 2 years, surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy or hysterectomy), and
- Practiced an acceptable form of birth control, which could include hormonal contraceptives (i.e., oral, skin patch, injection or implant), contraceptive foam with barrier, intra- uterine contraceptive device, condom and diaphragm with spermicidal cream or jelly.

Subjects must have been able and willing to give written informed consent and to comply with the requirements of the protocol.

Subjects must have had adequate cardiac, renal, and hepatic function, as determined by the Investigator and demonstrated by Screening laboratory evaluations, questionnaires, and physical examination results within normal limits.

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

Adalimumab 40 mg/0.8 mL SC injection

Lot numbers: [redacted] redacted information 14Nov2014

Duration of Treatment:

The long-term extension phase of the study could have lasted up to 264 weeks (e.g., Week 56 through Week 320), plus a 4 week follow up period. The entire study was terminated on 15 December 2008.

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

None

Criteria for Evaluation

Efficacy:

The efficacy variables evaluated during the long-term extension phase were to assess the maintenance of adalimumab efficacy and included the following:

- Proportion of subjects achieving clinical remission (CDAI < 150 points) by visit
- Proportion of subjects achieving CR-100 (CDAI decrease of ≥ 100 points from the subject's Baseline in Study M02-403) by visit
- Proportion of subjects achieving CR-70 (CDAI decrease of ≥ 70 points from the subject's Baseline in Study M02-403) by visit
- Steroid-free clinical remission by visit for subjects with use of systemic corticosteroids at Baseline in Study M02-403
- Steroid-free CR-100 by visit for subjects with use of systemic corticosteroids at Baseline in Study M02-403
- Change from Baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) score by visit
- Fistula remission by visit for subjects with fistula at Baseline in Study M02-403

Safety:

Adverse events (AEs) were monitored throughout the study. Standard laboratory evaluations, vital signs determinations, physical examinations, electrocardiogram, and chest x-ray were performed at specified timepoints throughout the study. Treatment-emergent adverse events (TEAEs) were defined as any AE with an onset date on or after the first adalimumab dose (could have occurred in Study M02-403 or Study M02-433) and up to 70 days after the last adalimumab dose in Study M02-433 excluding events during the placebo re-randomization period of the Study M02-433.

Statistical Methods

Efficacy:

All statistical analyses were descriptive. Continuous data were summarized by mean, SD, median, minimum, and maximum values. Categorical data were summarized by frequency and percentage. Last-observation-carried-forward method was also used to impute the missing values for continuous and categorical data.

Safety:

A TEAE was defined as any AE with an onset date on or after the first adalimumab dose (during Study M02-403 or Study M02-433) and up to 70 days after the last adalimumab dose, excluding events during the placebo re-randomization period of the Study M02-433. [redacted]

Efficacy Results:

Using the efficacy data for 177 subjects who enrolled in the study M02-433 and also had efficacy information on or after Week 56 (of Study M02-433), the study demonstrated the long-term efficacy of adalimumab in the maintenance of clinical remission and response rates, maintenance of improvement in quality of life, and maintenance of fistula healing rates in subjects with CD through 5 years of exposure to adalimumab:

- Rates of clinical remission (defined as CDAI Score of < 150 points) observed at Year 1 of Study M02-433 were maintained through 5 years of adalimumab exposure. Clinical remission rates were consistently numerically higher among baseline remitters compared with baseline non-remitters, and among subjects < 40 years of age compared with subjects ≥ 40 years of age.
- CR-100 and CR-70 (CDAI decrease of ≥ 100 or 70 points from Baseline of Study M02-403, respectively) rates observed at Year 1 of Study M02-433 were maintained through 5 years of adalimumab exposure.
- A subject was considered to be in steroid-free clinical remission at a visit if the subject had a CDAI score < 150 points at the visit and stopped taking steroid before the visit. Rates of steroid-free clinical remission observed at Year 1 of Study M02-433, among subjects with systemic corticosteroid use at Baseline, were maintained through 5 years of adalimumab exposure.
- A subject was considered to have achieved steroid-free CR-100 at a visit if the subject stopped taking steroids before the visit and was also CR-100 (decrease in CDAI score ≥ 100 points from the Baseline of Study M02-403) at that visit. Rates of steroid-free clinical remission and CR-100 observed at Year 1 of Study M02-433, among subjects with systemic corticosteroid use at Baseline, were maintained through 5 years of adalimumab exposure.
- Rates of fistula healing observed at Year 1 of Study M02-433, among subjects with draining fistula at Baseline (Week 0 of Study M02-403), were maintained through 5 years of adalimumab exposure. Although the total number of subjects decreased throughout follow-up, the absolute number of subjects who demonstrated fistula healing was fairly stable, varying from between 8 and 13 subjects.
- Improvements (increases) in IBDQ scores observed at Year 1 were maintained through 5 years of adalimumab exposure.

Number (%) of Subjects Achieving Efficacy Endpoints (Observed Cases Analyses)			
	Remitters at Baseline and Week 4 (Study M02-433) **N = 55**	**Non-Remitters at Baseline or Week 4 (Study M02-433)** **N = 221**	**Total** **N = 276**
Timepoint (during Study M02-433)	**n/N (%)**		
Clinical Remission (CDAI < 150 points)			
Year 1 (Week 56)	40/45 (88.9)	75/132 (56.8)	115/177 (65.0)
Year 2 (Week 104)	29/34 (85.3)	71/103 (68.9)	100/137 (73.0)
Year 3 (Week 152)	26/30 (86.7)	62/87 (71.3)	88/117 (75.2)
Year 4 (Week 212)	21/25 (84.0)	45/69 (65.2)	66/94 (70.2)
Year 5 (Week 260)	8/10 (80.0)	21/27 (77.8)	29/37 (78.4)
CR - 100			
Year 1 (Week 56)	39/45 (86.7)	102/132 (77.3)	141/177 (79.7)
Year 2 (Week 104)	28/34 (82.4)	87/103 (84.5)	115/137 (83.9)
Year 3 (Week 152)	28/30 (93.3)	74/87 (85.1)	102/117 (87.2)
Year 4 (Week 212)	23/25 (92.0)	58/69 (84.1)	81/94 (86.2)
Year 5 (Week 260)	8/10 (80.0)	27/27 (100.0)	35/37 (94.6)
CR - 70			
Year 1 (Week 56)	41/45 (91.1)	112/132 (84.8)	153/177 (86.4)
Year 2 (Week 104)	31/34 (91.2)	92/103 (89.3)	123/137 (89.8)
Year 3 (Week 152)	30/30 (100.0)	77/87 (88.5)	107/117 (91.5)
Year 4 (Week 212)	24/25 (96.0)	63/69 (91.3)	87/94 (92.6)
Year 5 (Week 260)	10/10 (100.0)	27/27 (100.0)	37/37 (100.0)
Steroid-free Clinical Remission[a]			
Year 1 (Week 56)	9/21 (42.9)	14/36 (38.9)	23/57 (40.4)
Year 2 (Week 104)	8/18 (44.4)	12/31 (38.7)	20/49 (40.8)
Year 3 (Week 152)	8/18 (44.4)	14/30 (46.7)	22/48 (45.8)
Year 4 (Week 212)	5/14 (35.7)	10/23 (43.5)	15/37 (40.5)
Year 5 (Week 260)	2/6 (33.3)	4/12 (33.3)	6/18 (33.3)
Steroid-free CR – 100[a]			
Year 1 (Week 56)	8/21 (38.1)	17/36 (47.2)	25/57 (43.9)
Year 2 (Week 104)	9/18 (50.0)	15/31 (48.4)	24/49 (49.0)
Year 3 (Week 152)	9/18 (50.0)	15/30 (50.0)	24/48 (50.0)

		Remitters at Baseline and Week 4 (Study M02-433) N = 55	Non-Remitters at Baseline or Week 4 (Study M02-433) N = 221	Total N = 276
Timepoint (during Study M02-433)		**n/N (%)**		
Year 4 (Week 212)		6/14 (42.9)	12/23 (52.2)	18/37 (48.6)
Year 5 (Week 260)		2/6 (33.3)	5/12 (41.7)	7/18 (38.9)
Fistula Healing[b]				
Year 1 (Week 56)		1/3 (33.3)	10/17 (58.8)	11/20 (55.0)
Year 2 (Week 104)		1/3 (33.3)	11/15 (73.3)	12/18 (66.7)
Year 3 (Week 152)		2/3 (66.7)	11/14 (78.6)	13/17 (76.5)
Year 4 (Week 212)		1/3 (33.3)	10/11 (90.9)	11/14 (78.6)
Year 5 (Week 260)		2/2 (100.0)	6/7 (85.7)	8/9 (88.9)
IBDQ Score		**Baseline**	**Visit**	**Change**
	N	**Mean ± SD**		
Year 1 (Week 56)	180	129.9 ± 29.78	172.2 ± 34.82	42.3 ± 35.13
Year 2 (Week 104)	142	130.6 ± 28.73	173.0 ± 34.16	42.4 ± 36.27
Year 3 (Week 152)	114	128.7 ± 28.98	176.6 ± 32.01	47.9 ± 33.70
Year 4 (Week 200)	99	129.0 ± 29.24	180.0 ± 31.51	51.0 ± 32.77
Year 5 (Week 248)	69	126.6 ± 27.97	178.3 ± 32.22	51.7 ± 32.67

Note: Results are from the observed cases analyses. Total number (N) reflects only subjects with non-missing data at each timepoint.

a. Among subjects with use of systemic corticosteroids at Study M02-403 Baseline. At each visit, only subjects who demonstrated steroid-free clinical remission at the specified time point were counted.

b. Among subjects with draining fistula at Study M02-403 Baseline.

Safety Results:

Adalimumab was generally safe and well tolerated following long-term administration up to 5 years as evaluated by the incidence, severity, and relationship of TEAEs:

- A total of 271 subjects (98.2%) reported at least 1 TEAE. Other than CD, which occurred in 39.9% of subjects, subjects most frequently reported nasopharyngitis (23.9%), nausea (21.4%), and headache (20.7%).
- Most subjects reported TEAEs that were mild or moderate in severity; 42.4% reported a severe TEAE. The rate of severe TEAEs was higher among non-remitters (45.7%) compared with remitters (29.1%). The most frequently reported severe TEAEs were CD (10.5%), headache (4.3%), and abdominal pain (3.6%).
- A total of 175 subjects (63.4%) reported a TEAE that was considered by the Investigator to be at least possibly related to study drug. The most frequently reported TEAEs considered at least possibly related to study drug were injection site irritation (10.9%), injection site reaction

(8.7%), headache (6.9%), injection site pain (5.4%), and arthralgia (5.4%).

Safety Results (Continued):

Adalimumab was generally safe and well-tolerated following long-term administration up to 5 years as evaluated by the incidence of deaths, other SAEs, and TEAEs of special interest.

- No deaths were reported.
- A total of 75 subjects (27.2%) reported at least 1 SAE. The rate of SAEs was higher among non-remitters (31.2%) compared with remitters (10.9%) across SAE MedDRA preferred terms. The most frequently reported SAEs were CD (6.2%) and small intestinal obstruction (2.9%).
- A total of 70 subjects (25.4%) reported at least 1 TEAE that led to discontinuation from the study. The rate of TEAEs leading to discontinuation was higher among non-remitters (28.1%) compared with remitters (14.5%) across AE PTs. In general, the proportions of subjects reporting individual TEAEs leading to discontinuation was low (< 1.5%), with the exception of CD (8.0%). The most frequently reported TEAE leading to discontinuation was CD (8.0%). All other TEAEs leading to discontinuation were reported by ≤ 4 subjects.
- A total of 193 subjects (69.9%) reported at least 1 infection. The most frequently reported infections were nasopharyngitis (23.9%), sinusitis (14.9%), upper respiratory tract infection (13.8%), and influenza (13.0%). Fifty-seven subjects (20.7%) experienced infections considered by the Investigator to be at least possibly related to adalimumab treatment.
- Eighteen subjects (6.5%) reported at least 1 serious infection. Overall, the incidence of serious infections was low. There were two serious infections reported by ≥ 2 subjects: abdominal abscess and rectal abscess. All other serious infections occurred in only 1 subject. Six subjects (2.2%) reported serious infections considered by the Investigator to be at least possibly related to adalimumab treatment. The rate of serious infections was higher among non-remitters (7.7%) compared with remitters (1.8%); only 1 serious infection (pneumonia) occurred in remitters. No cases of TB were reported.
- Seven subjects (2.5%) reported at least 1 opportunistic infection (candidiasis [2], nocardiosis [1], esophageal candidiasis [1], oral candidiasis [1], oropharyngeal candidiasis [1]). Four subjects had events that were considered by the Investigator to be at least possibly related to adalimumab treatment (oral candidiasis [1], oropharyngeal candidiasis [1], nocardiosis with adenopathy and erythematous nodule of right forearm and fever [1], esophageal candidiasis [1])
- Four subjects (1.4%) reported at least 1 malignancy (basal cell carcinoma [2], neoplasm prostate [1], non-Hodgkin's lymphoma [1], and squamous cell carcinoma [1]). The event of non-Hodgkin's lymphoma was considered possibly related to study drug by the Investigator. However, the subject received azathioprine during study.
- A total of 68 subjects (24.6%) reported at least 1 injection site reaction. Subjects most frequently reported injection site irritation (10.9%), injection site reaction (8.7%), injection site pain (5.4%), and injection site erythema (3.6%). All other injection site reactions occurred in < 1% of subjects.
- Two subjects reported AEs associated with CHF (cardiac failure congestive and ventricular dysfunction). Both events were considered not related to adalimumab treatment by the Investigator. Both subjects were smokers and had cardiovascular events in their medical histories.

Safety Results (Continued):

- One subject (0.4%) reported a demyelinating disorder (optic neuritis). The event, which resolved after 93 days, was considered by the Investigator to be probably related to adalimumab treatment.
- Twenty-six subjects (9.4%) reported at least 1 hepatic-related TEAE. The most frequently reported hepatic-related TEAEs were ALT increased and AST increased. All other hepatic-related TEAEs occurred in ≤ 3 subjects. Thirteen subjects (4.7%) reported hepatic-related TEAEs considered by the Investigator to be at least possibly related to adalimumab treatment. None of the hepatic-related TEAEs led to discontinuation from study.
- Four subjects (1.4%) reported allergic reactions (drug hypersensitivity [1], hyper sensitivity [2], and urticaria [1]), all of which were considered by the Investigator to be at least probably not related to adalimumab treatment except for urticaria (possibly related) for which the subject received concomitant medication treatment with diphenhydramine. Study medication was continued, the event resolved and no new episode of urticaria was reported.
- One subject reported a lupus-like syndrome TEAE (systemic lupus erythematosus) with positivity of anti-DNA and anti nuclear antibodies. The event was considered by the Investigator to be possibly related to adalimumab treatment.
- Six subjects (2.2%) reported at least 1 hematology-related TEAE (leucopenia [4], neutropenia [2], and pancytopenia [1]). In 5 cases, the hematology-related TEAE was considered at least probably not related by the investigator, the alternative etiology being concomitant immunosuppressive therapy, underlying Crohn's disease or infection. One event of neutropenia was considered by the Investigator to be possibly related to adalimumab treatment. Nasopharyngitis was reported during during the episode of neutropenia. It resolved while continuing adalimumab. Resolution of the neutropenia occurred simultaneously to the switching from mercaptopurin to azathioprine.

Adalimumab was generally safe and well-tolerated as evaluated by assessments of serum chemistry and hematology values and vital signs.

Conclusions:

- In conclusion, long-term administration of adalimumab 40 mg up to 5 years to subjects with CD resulted in maintained remission and clinical response rates (as assessed by CDAI < 150, CR-100, CR-70, and steroid-free clinical remission, steroid-free CR-100 and CR-70), maintenance of previously observed improvements in quality of life as assessed by the IBDQ, and maintained rates of fistula healing. Long-term administration of adalimumab 40 mg was generally safe and well-tolerated; no new safety findings were observed.