Synopsis

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

Title of Study:

A Multi-Center, Open-Label Study of the Human Anti-TNF Monoclonal Antibody Adalimumab to Evaluate the Long-term Safety and Tolerability of Repeated Administration of Adalimumab in Subjects with Crohn's Disease

Coordinating Investigator:

Remo Panaccione, MD (Health Science Centre, Calgary, AB, Canada)

Study Sites:

Multicenter, 114 sites in Australia, Belgium, Canada, Denmark, France, Germany, Greece, Hungary, Italy, The Netherlands, Norway, Poland, the Republic of South Africa, Spain, Sweden, United Kingdom, and US.

Publications:

3 manuscripts, 27 abstracts (poster presentations)

Studied Period (Years):	**Phase of Development:** 3
First Subject First Visit: 23 September 2004 Last Subject Last Visit: 15 December 2008	

Objective:

The objective of this study was to evaluate the long-term maintenance of response, safety, and tolerability of repeated administration of adalimumab in subjects with Crohn's disease (CD) who participated in and successfully completed Study M02-404 or Study M04-691.

Methodology:

Subjects who entered this study from a blinded cohort in the previous study were to be assigned to open-label adalimumab, 40 mg every other week (eow). Subjects who entered this study from an open-label cohort in the previous study were to continue their regimen of eow or every week (ew) dosing. Subjects who developed a flare of CD while receiving 40 mg eow of adalimumab could have had their dose frequency increased to 40 mg every week (ew). In addition, if subjects did not meet the definition of flare but were consistent nonresponders while receiving 40 mg eow, they could have also had their dose of study medication increased to 40 mg ew after a discussion with the Abbott Medical Monitor. Subjects who entered this study from a blinded cohort should not have increased their dose of study medication to 40 mg ew prior to the Week 8 Visit. Subjects who received 40 mg ew dosing who continued to have a disease flare or developed another flare could have been withdrawn from the study.

Methodology (Continued):

In addition, if subjects did not meet the definition of flare but were consistent nonresponders while receiving 40 mg ew, they could have been withdrawn from the study after a discussion with the Abbott Medical Monitor.

A disease flare was defined in this study as a recurrence of active disease, specifically an increase in the subject's Crohn's Disease Activity Index (CDAI) score of ≥ 70 points when compared to his/her CDAI score at Week 4 of the preceding study and a CDAI score ≥ 220. A repeated nonresponder was defined as a subject not attaining a CDAI score decrease of ≥ 70 points compared to the Baseline Visit of the previous study (M02-404 or M04-691).

Reductions in concomitant therapy were to be allowed for Crohn's treatment-related toxicities (i.e., leukopenia) of Grade 3 or higher. Subjects were to be allowed to adjust Crohn's-specific concomitant medications if they met the criteria specified in the protocol. Subjects were to be allowed to decrease prednisone (or equivalent) and budesonide if qualifications specified in the protocol were met.

Efficacy and safety measurements were performed throughout the study.

Number of Subjects (Planned and Analyzed):

Enrollment was limited to subjects who had completed Study M02-404 or Study M04-691. It was estimated a total of 960 subjects would enroll into the study. A total of 777 subjects actually enrolled and received at least 1 dose of study drug.

Diagnosis and Main Criteria for Inclusion:

Subjects must have successfully enrolled in and completed either Study M02-404 or Study M04-691.

Female subjects must have:

- Practiced an acceptable method of birth control during the study and for 150 days after the last dose of study medication, if subject was of childbearing potential. Acceptable forms of birth control included condoms, sponge, foam, jellies, diaphragm, intrauterine device, or oral or parenteral contraceptives (for 3 months prior to start of study drug administration in the previous study)
- Not been of childbearing potential, defined as postmenopausal ≥ 2 years, surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or hysterectomy).
- Not been breastfeeding.

Subjects must have been able and willing to give written informed consent and comply with the requirements of the protocol and be able to self-inject study medication or have a designee perform the injections.

Subjects must have been judged to be in generally good health as determined by the Investigator.

Subjects could not receive > 40 mg/day prednisone (or equivalent) or > 9 mg/day budesonide; concurrent administration of prednisone and budesonide was also prohibited.

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

Adalimumab 40 mg/0.8 mL subcutaneous injection.

Lot Numbers: 15339S2, 17561S2, 27025S2, 05-002543, 06-006976, 08-016836, 21768S2, 27027S2, 05-002546, 07-010749, 08-015251, 21772S2, 27418HT, 05-002881, 06-009556, 08-015827, 08-016632

Duration of Treatment:

This open-label study could have lasted up to 240 weeks. 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 analyzed for this study included:

- Proportion of subjects achieving clinical remission, defined as a CDAI score of < 150 points, by visit
- Proportion of subjects achieving clinical response-100 (CR-100), defined as a CDAI score decrease of ≥ 100 points, by visit
- Proportion of subjects achieving clinical response-70 (CR-70), defined as a CDAI score decrease of ≥ 70 points, by visit
- Proportion of subjects achieving steroid-free clinical remission, defined as a CDAI score of < 150 points and the discontinuation of steroid use, by visit
- Proportion of subjects achieving steroid-free CR-100, defined as a CDAI score decrease of ≥ 100 points and the discontinuation of steroid use, by visit
- Proportion of subjects with fistula remission by visit, defined as the absence of draining fistulas for subjects with fistula present at the preceding study's Baseline Visit.

Safety:

Adverse events (AEs) were monitored throughout the study. Standard laboratory evaluations, vital sign determinations, and physical examinations were performed at specified time points throughout the study.

Statistical Methods

Efficacy:

Efficacy analyses were conducted on the following populations:

- **Intent-to-treat (ITT) population:** All subjects who received as least 1 dose of adalimumab in the current study. Analyses were also conducted on 3 additional populations:
- **M02-404 randomized to eow (EOW404) population:** All subjects from Study M02-404 who were randomized to receive adalimumab 40 mg eow, completed Study M02-404, and enrolled into the current study (M04-690).
- **M02-404 double-blind eow in clinical remission completer (404DBEOWCR) population:** All subjects from Study M02-404 who were randomized to receive adalimumab 40 mg eow, completed Study M02-404 without the open-label portion of the study, were in clinical remission at Week 56 of Study M02-404, and enrolled into the current study (M04-690).

Efficacy (Continued):

- **M02-404 double-blind eow randomized responders in clinical remission completer (404RREOWCR) population:** All randomized responder subjects from Study M02-404 who were randomized to receive adalimumab 40 mg drug eow, completed Study M02-404 without the open-label portion of the study, were in clinical remission at Week 56 of Study M02-404, and enrolled into the current study (M04-690).

A CDAI score was calculated from the subject's diary and appropriate laboratory values at all study visits beginning with the Week 2 Visit. Summary statistics were provided for each study visit using 2 analyses: observed cases (OC) and last observation carried forward (LOCF).

Safety:

Safety analyses were conducted using the safety population, which was equivalent to the ITT population for this study. A treatment-emergent AE is defined as any AE with onset on or after the first dose of adalimumab in the previous study (M02-404 or M04-691) or the current study (M04-690), up to 70 days after the last dose of adalimumab in the current study, excluding 1) events with onset after 70 days during the administrative gaps between the preceding study and the current study (for subjects who received their first dose of adalimumab in the previous study) and 2) events with onset during the placebo period (for subjects randomized to placebo in Study M02-404). The number and percent of subjects experiencing AEs tabulated by body system and Medical Dictionary for Regulatory Activities (MedDRA, version 11.1) preferred term. In addition, a summary of AEs by severity and relationship to study drug was presented. Adverse events that were serious, severe, or that led to premature study discontinuation were listed and described in detail. Changes in hematology, blood chemistry, and urinalysis were described by statistical characteristics. Shift tables were provided. When performing the statistics, abnormal laboratory values were flagged in reference to the normal range and also according to Common Toxicity Criteria (CTC).

Summary/Conclusions

Efficacy Results:

The proportion of subjects in the ITT population who achieved clinical remission gradually increased through Week 24 and was maintained through the remainder of the study, as shown by both the OC and LOCF analyses. By the end of Year 1 (Week 48 Visit), Year 2 (Week 108), Year 3 (Week 156), and Year 4 (Week 204), the proportion of subjects who had achieved clinical remission was 59.4%, 68.8%, 69.5%, and 46.7%, respectively, using the OC analysis. The gradual increase in clinical remission achieved in the overall population appeared to be influenced primarily by subjects who entered the current study (M04-690) from Study M04-691. At Week 2, the proportion of subjects from Study M04-691 who had achieved clinical remission was 24.3%; this proportion gradually increased through Week 24 and then remained stable (OC analysis). At Week 2, the proportion of subjects from Study M02-404 who had achieved clinical remission was 68.9%; this proportion of subjects with clinical remission was maintained throughout the study.

In general, clinical remission rates were higher for subjects who enrolled from Study M02-404 compared to subjects who enrolled from Study M04-691. The analyses performed on the EOW404, 404DBEOWCR, and 404RREOWCR populations supported the finding of the analysis performed on the ITT population from Study M02-404. Clinical remission rates were higher for subjects in the 404DBEOWCR, and 404RREOWCR populations compared to the EOW404 population.

Efficacy Results (Continued):

The results of a nonresponders imputation (NRI) analysis in the 404RREOWCR population were similar to findings for the analysis of clinical remission in the ITT population and suggested clinical remission was maintained throughout the majority of the study.

Regardless of age (< 40 years and ≥ 40 years), sex, or race category (White or non-White), the proportion of subjects who achieved clinical remission followed a pattern similar to that noted for the ITT population overall using both the OC analysis and LOCF analysis. At a majority of time points, a greater proportion of subjects < 40 years of age had achieved clinical remission compared to subjects ≥ 40 years of age. Within the EOW404, 404DBEOWCR, and 404RREOWCR populations, the proportion of subjects who achieved clinical remission reflected the results observed in the ITT population from Study M02-404, regardless of age, sex, or race category or analysis.

Overall, the proportion of subjects in the ITT population who achieved CR-100 followed patterns similar to the results observed for clinical remission. The proportion of total subjects who achieved CR-100 increased from Week 2 through approximately Week 12, at which time the proportion of subjects achieving CR-100 remained relatively steady through the end of the study. By the end of Year 1 (Week 48 Visit), Year 2 (Week 108), Year 3 (Week 156), and Year 4 (Week 204), the proportion of subjects who had achieved CR-100 was 77.5%, 84.4%, 85.7%, and 93.3%, respectively, using the OC analysis. In general, CR-100 rates were higher for subjects who enrolled from Study M02-404 compared to subjects who enrolled from Study M04-691. The analyses performed on the EOW404, 404DBEOWCR, and 404RREOWCR populations supported the findings of the analysis performed on the ITT population from Study M02-404, and suggested the proportion of subjects with CR-100 was maintained throughout the study.

Overall, the proportion of subjects in the ITT population who achieved CR-70 gradually increased from Week 2 through the end of the study. By the end of Year 1 (Week 48 Visit), Year 2 (Week 108), Year 3 (Week 156), and Year 4 (Week 204), the proportion of subjects who had achieved CR-70 was 85.6%, 89.6%, 91.2%, and 93.3%, respectively, using the OC analysis. Although the proportion of subjects who enrolled into the current study (M04-690) from Study M04-691 and had achieved CR-70 at Week 2 (61.7%) was notably less than for subjects from Study M02-404 (88.1%), approximately 80% of all subjects had attained CR-70 by Week 24 using the OC analysis. In general, CR-70 rates were higher for subjects who enrolled from Study M02-404 compared to subjects who enrolled from Study M04-691. Within the EOW404, 404DBEOWCR, and 404RREOWCR populations, the proportion of subjects who achieved CR-70 generally remained with a range of 83% to 95%, regardless of analysis (OC or LOCF) or population.

In the ITT population, the proportion of subjects who achieved steroid-free clinical remission followed a pattern similar to the results for the proportion of subjects who achieved clinical remission (regardless of steroid administration). The proportion of patients who achieved steroid-free clinical remission steadily increased through approximately Week 48 to 48.9% (OC), and then fluctuated above this value through the remainder of the study. By the end of Year 1 (Week 48 Visit), Year 2 (Week 108), Year 3 (Week 156), and Year 4 (Week 204), the proportion of subjects who had achieved steroid-free clinical remission was 48.9%, 55.7%, 63.1%, and 20.0%, respectively, using the OC analysis. In contrast, at Week 2, 59.5% of subjects from Study M02-404 had achieved steroid-free clinical remission, this proportion remained relatively steady throughout the study. In general, steroid-free clinical remission rates were higher for subjects who enrolled from Study M02-404 compared to subjects who enrolled from Study M04-691.

Efficacy Results (Continued):

The proportion of subjects who achieved steroid-free clinical remission in the EOW404, 404DBEOWCR, and 404RREOWCR populations reflected the overall results observed in subjects in the ITT population from Study M02-404.

The proportion of subjects achieving steroid-free CR-100 in the ITT population followed a pattern similar to the results observed for steroid-free clinical remission. The proportion of subjects who achieved steroid-free CR-100 gradually increased from Week 2 through approximately Week 48, and then remained steady throughout the rest of the study. By the end of Year 1 (Week 48 Visit), Year 2 (Week 108), Year 3 (Week 156), and Year 4 (Week 204), the proportion of subjects who had achieved steroid-free CR-100 was 59.2%, 65.9%, 74.8%, and 80.0%, respectively, using the OC analysis. In general, steroid-free CR-100 rates were higher for subjects who enrolled from Study M02-404 compared to subjects who enrolled from Study M04-691. The proportion of subjects who achieved steroid-free CR-100 in the EOW404, 404DBEOWCR, and 404RREOWCR populations reflected the overall results observed in subjects from Study M02-404 in the ITT population.

The proportion of subjects with fistula remission remained relatively constant throughout the study.

Safety Results:

Adalimumab was generally safe and well-tolerated following long-term administration as evaluated by the incidence of AEs overall, severe AEs, and study drug-related AEs.

- A total of 764 subjects (98.3%) reported a total of 11,751 AEs during the study, corresponding to 555.3 events per 100 patient-years. Other than CD flares, which occurred in 51.6% of subjects, the most frequently reported AEs were nasopharyngitis, arthralgia, and abdominal pain.
- The majority of subjects reported AEs that were mild or moderate in intensity, and the majority of severe AEs (reported by 364 subjects) were reported by 1 subject each. Other than CD flares (97 subjects), the most frequently reported severe AEs included abdominal pain (50 subjects) and small intestine obstruction (27 subjects).
- A total of 514 subjects (66.2%) reported study drug-related treatment-emergent AEs during the study. The most frequently reported AEs considered to be possibly or probably related to study drug by the Investigator included injection site reaction (7.6%), headache (6.6%), injection site irritation (5.8%), injection site pain (5.3%), and CD flares (5.3%).

Adalimumab was generally safe and well-tolerated following long-term administration, as evaluated by the incidence of deaths, other SAEs, and AEs leading to withdrawal.

- Two deaths were reported during the study. One subject was diagnosed with acute myeloid leukemia on Day 416 (relative to the subject's first dose of adalimumab) and died on Day 681. The Investigator considered the leukemia to be possibly related to study drug; however, it was noted that this subject had also received Imuran® (azathioprine) during the study. The second death was due to severe pancytopenia. The Investigator considered the pancytopenia to be probably not related to study drug.
- A total of 296 subjects (38.1%) reported at least 1 SAE during the study. With the exception of CD flares (11.8%), the most frequently reported SAE was small intestinal obstruction (3.9%). Other SAEs were reported by < 2% of subjects. A total of 70 (9.0%) of subjects reported at least 1 SAE considered by the Investigator to be at least possibly related to study drug.

Safety Results (Continued):

- A total of 156 subjects (20.1%) reported an AE that led to discontinuation. Other than CD flare (8.1%), the most frequently reported AEs leading to discontinuation were small intestinal obstruction (0.8%), abdominal pain (0.6%), and anal abscess (0.5%). All other AEs leading to discontinuation were reported by < 0.5% of subjects. There was a higher incidence of AEs that led to discontinuation in subjects who enrolled from Study M04-691 (25.8%) compared to subjects who enrolled from Study M02-404 (16.3%). The majority of AEs that led to discontinuation each occurred in 1 subject only.

Adalimumab was generally safe and well-tolerated following long-term administration as evaluated by AEs of special interest.

- A total of 623 subjects (80.2%) reported at least 1 infection during the study, a majority of which were considered by the Investigator to be mild or moderate in intensity and not related or probably not related to study drug. The most frequently reported infections included nasopharyngitis (26.1%), upper respiratory infection (19.3%), influenza (17.6%), sinusitis (15.3%), bronchitis (12.2%), and urinary tract infection (10.7%). One subject was diagnosed with pulmonary tuberculosis (TB) during the study; and another was treated for a latent TB infection.
- A total of 82 subjects (10.6%) reported at least 1 serious infection during the study, the majority of which were considered by the Investigator to be not related or probably not related to study drug. The most frequently reported serious infections were anal abscess (1.9%) and pneumonia (1.0%). The rate of serious infections was estimated to be 5.3 events/100 patient-years.
- A total of 38 subjects (4.9%) reported at least 1 opportunistic infection (excluding TB) during the study, the majority of which were considered by the Investigator to be possibly or probably related to study drug. The most frequently reported opportunistic infections were candidiasis (2.3%) and oral candidiasis (2.1%).
- A total of 32 subjects (4.1%) reported at least 1 malignancy during the study, the majority of which were not considered by the Investigator to be related to study drug. The most frequently reported malignancies were basal cell carcinoma (1.0%) and squamous cell carcinoma (0.5%). Skin cancer, breast cancer, and thyroid cancer were each reported by 2 subjects (0.3%); the remaining malignancies were each reported by 1 subject, including a single case of lymphoma which was considered by the Investigator to be probably not related to study drug.
- A total of 177 subjects (22.8%) reported at least 1 injection-site reaction during the study, the majority of which were considered by the Investigator to be possibly or probably related to study drug. The most frequently reported injection-site reactions were injection site reaction (7.7%), injection site irritation (5.9%), and injection site pain (5.5%). The incidence of injection-site reactions was higher in subjects who enrolled from study M02-404 (26.6%) compared with subjects who enrolled from Study M04-691 (17.1%).
- There were no cases of congestive heart failure reported during the study.
- Two subjects reported a demyelinating disease during the study (optic neuritis; demyelination). All demyelinating disease events were considered by the Investigator to be possibly related to study drug.

Safety Results (Continued):

- A total of 63 subjects reported at least 1 hepatic-related AE during the study. The most frequently reported hepatic-related AEs were aspartate aminotransferase increased (1.8%), liver function test abnormal (1.7%), alanine aminotransferase increased (1.5%), and hepatic enzyme increased (1.3%). Eighteen subjects reported hepatic-related AEs considered by the Investigator to be possibly or probably related to adalimumab.
- A total of 21 subjects (2.7%) reported at least 1 allergic reaction-related AE during the study, the majority of which were considered by the Investigator to be possibly or probably related to study drug. The most frequently reported allergic reaction-related AE was hypersensitivity (1.3%).
- Three subjects (0.4%) reported lupus-like syndrome AEs; 2 subjects with lupus-like syndrome and 1 subject with systemic lupus erythematosus. The events of lupus-like syndrome were considered by the Investigator to be possibly or probably related to study drug; the systemic lupus erythematosus was considered not related to study drug.
- A total of 12 subjects (1.5%) reported at least 1 hematology-related AE during the study; 6 of these AEs were considered by the Investigator to be possibly related to study drug. The most frequently reported hematology-related AE was leukopenia (0.8%).

Adalimumab was generally safe and well-tolerated as evaluated by the assessment of clinical laboratory parameters.

- Mean changes from Baseline values to minimum, maximum, and final values for hematology parameters appeared to reflect normal inter-subject variability. At the final assessment, increases in mean change from Baseline were noted for hemoglobin, hematocrit, lymphocytes, monocytes, and eosinophils; decreases were noted for RBC count, platelet count, WBC count, neutrophils, and basophils. None of these changes were considered clinically meaningful.
- Mean changes from Baseline values to minimum, maximum, and final values for clinical chemistry parameters appeared to reflect normal inter-subject variability. At the final assessment, increases in mean change from Baseline were noted for AST, total bilirubin, CPK, creatinine, BUN, uric acid, potassium, glucose, albumin, total protein, and triglycerides; decreases were noted for alkaline phosphatase, inorganic phosphorus, calcium, sodium, chloride, cholesterol, and LDH. None of these changes were considered clinically meaningful.
- Mean changes from Baseline values to minimum, maximum, and final values for urinalysis parameters appeared to reflect normal inter-subject variability. At the final assessment, an increase in the mean change from Baseline value was noted for urine pH, while a decrease was noted for urine specific gravity. Neither of these changes was considered clinically meaningful.
- The proportion of subjects with shifts in hematology values from CTC Grade < 3 to CTC Grade ≥ 3 was low ($\leq 5.1\%$ of subjects for any given parameter).
- The proportion of subjects with shifts in clinical chemistry values from CTC Grade < 3 to CTC Grade ≥ 3 was low ($\leq 5.7\%$ of subjects for any given parameter).
- For subjects with values $< 1.5 \times$ the upper limit of normal (ULN) at Baseline, there were 101 subjects who had elevations in ALT values, 81 subjects who had elevation in AST values, 22 subjects who had elevations in alkaline phosphatase values, and 22 subjects who had elevations in total bilirubin values that met the potentially clinically significant criteria.

Safety Results (Continued):

- Mean changes from Baseline values to minimum, maximum, and final values for vital signs were not considered to be clinically meaningful, and the incidence of potentially clinically significant values for any given vital sign parameter was ≤ 5.7%.

Conclusions:

In conclusion, long-term administration of 40 mg adalimumab ew or eow resulted in maintenance of clinical remission, clinical response, and improvements in the quality of life in subjects with CD. Long-term administration of adalimumab was generally safe and well-tolerated; no new safety findings were observed.

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