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, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction of Clinical Remission in Subjects with Moderately to Severely Active Ulcerative Colitis

Investigator: Walter Reinisch, MD, Medizinische Universität Wien, Vienna, Austria

Study Sites: A total of 80 sites participated in this study from Austria, Belgium, Canada, Czech Republic, Germany, Hungary, Italy, the Netherlands, Poland, Puerto Rico, Slovakia, Sweden, and the United States.

Publications: 2 abstracts

Studied Period (Years): First Subject First Visit: 13 November 2006 Last Subject Last Visit: 05 March 2010	**Phase of Development:** 3

Objective: The objective of this study as stated in the protocol was to assess the efficacy and safety of 2 dosing regimens of adalimumab for the induction of clinical remission in subjects with moderately to severely active ulcerative colitis.

In addition, supportive information was collected on the maintenance of clinical remission during the open-label period of the study.

Methodology:

This was a multicenter Phase 3 trial designed to evaluate the efficacy and safety of the human anti-TNF monoclonal antibody adalimumab in subjects with moderately to severely active UC. The study consisted of a randomized, double-blind, placebo-controlled period (DB Period) followed by an open-label period (OL Period). The primary efficacy analysis was conducted on the data set from the DB Period through Week 8.

Subjects enrolled in the study under the original protocol or Amendments 1 and 2 were randomized in a 1:1 ratio to receive adalimumab or placebo during the 12-week DB induction period. Subjects received 160 mg of adalimumab or placebo at Baseline; 80 mg adalimumab or placebo at Week 2; and 40 mg adalimumab or placebo at Weeks 4 and 6. At Week 8, subjects randomized to placebo received 160 mg adalimumab followed by 80 mg adalimumab at Week 10. Subjects randomized to adalimumab continued to receive 40 mg adalimumab at Weeks 8 and 10. All subjects continued to receive 1 injection of open-label (OL) adalimumab 40 mg eow beginning at Week 12 up to Week 52 (or the ET visit).

Number of Subjects (Planned and Analyzed):

Planned: 561 subjects

Analyzed: 576 subjects (safety); 575 subjects (efficacy [ITT-E Set]), 390 subjects (efficacy [ITT-A3 Set])

Diagnosis and Main Criteria for Inclusion:

Adult subjects with moderate to severe active UC (Mayo score of 6 to 12 points with endoscopy subscore of 2 to 3 points), confirmed by colonoscopy with biopsy or by flexible sigmoidoscopy with biopsy.

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

Adalimumab 40 mg/0.8 mL via subcutaneous (SC) injection

Bulk Product Lot Numbers: 06-006764, 07-011080, 07-010526, 07-014216, 08-017131

Duration of Treatment: 52 weeks

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

Matching placebo via SC injection

Bulk Product Lot Numbers: 06-006518, 06-009051, 06-006520, 08-018846

Criteria for Evaluation

Efficacy:

The primary efficacy endpoint of this study is the proportion of subjects with remission at Week 8.

Ranked secondary efficacy variables assessed at Week 8 included (in the order at which statistical test was to be conducted):

1. Proportion of subjects with clinical response per Mayo score at Week 8 (ADA 160/80/40 versus placebo).
2. Proportion of subjects with mucosal healing at Week 8 (ADA 160/80/40 versus placebo).
3. Proportion of subjects with Rectal Bleeding subscore indicative of mild disease (≤ 1) at Week 8 (ADA 160/80/40 versus placebo).
4. Proportion of subjects with Physician's Global Assessment subscore indicative of mild disease (≤ 1) at Week 8 (ADA 160/80/40 versus placebo).
5. Proportion of subjects with Stool Frequency subscore indicative of mild disease (≤ 1) at Week 8 (ADA 160/80/40 versus placebo).
6. Proportion of subjects with clinical response per Mayo score at Week 8 (ADA 80/40 versus placebo).
7. Proportion of subjects with mucosal healing at Week 8 (ADA 80/40 versus placebo).
8. Proportion of subjects with Rectal Bleeding subscore indicative of mild disease (≤ 1) at Week 8 (ADA 80/40 versus placebo).
9. Proportion of subjects with Physician's Global Assessment subscore indicative of "normal or mild disease" (or numerical score ≤ 1) at Week 8 (ADA 80/40 versus placebo).

Criteria for Evaluation

Efficacy (Continued):

10. Proportion of subjects with Stool Frequency subscore indicative of mild disease (≤ 1) at Week 8 (ADA 80/40 versus placebo).
11. Proportion of IBDQ responders at Week 8 (ADA 160/80/40 versus placebo).
12. Proportion of IBDQ responders at Week 8 (ADA 80/40 versus placebo).

Non-ranked secondary efficacy variables:

- Proportion of subjects with response per Partial Mayo Score at Weeks 2, 4, and 6.
- Proportion of subjects with Rectal Bleeding subscore indicative of mild disease (≤ 1) at Weeks 2, 4, and 6.
- Proportion of subjects with Physician's Global Assessment subscore indicative of mild disease (≤ 1) at Weeks 2, 4, and 6.
- Proportion of subjects with Stool Frequency subscore indicative of mild disease (≤ 1) at Weeks 2, 4, and 6.
- Change from Baseline in total Inflammatory Bowel Disease Questionnaire (IBDQ) score at Week 8.
- Change from Baseline in Short Form-36 Questionnaire (SF-36) at Week 8.
- Change from Baseline in Partial Mayo Score at Weeks 2, 4, 6, and 8.
- Change from Baseline in Mayo Score at Week 8.
- Time to clinical response per Partial Mayo Score (up to Week 8).

Descriptive statistics were to be presented for the OL period of the study through Week 52, including, but not limited to, the following efficacy variables:

- Proportion of subjects with remission at both Week 8 and at Week 52.
- Proportion of subjects with remission at Week 52.
- Proportion of subjects with response per Mayo Score at both Week 8 and Week 52.
- Time in clinical response per Partial Mayo Score.
- Proportion of subjects with mucosal healing at both Week 8 and Week 52.
- Proportion of subjects with mucosal healing at Week 52.
- Proportion of subjects using corticosteroids at Baseline in remission at Week 8 who had discontinued corticosteroids and were in remission at Week 52.
- Proportion of subjects using corticosteroids at Baseline who had discontinued corticosteroids and were in remission at Week 52.
- Proportion of subjects using corticosteroids at Baseline who had discontinued corticosteroids for at least 90 days and were in remission at Week 52.
- Time in steroid-free clinical response per Partial Mayo Score for subjects who were using corticosteroids at Baseline.
- Proportion of subjects requiring dose escalation to 40 mg ew.

Criteria for Evaluation

Efficacy (Continued):

- Proportion of subjects achieving response at Week 52 after dose escalation.
- Proportion of subjects achieving remission at Week 52 after dose escalation for a) subjects who had not achieved response per Partial Mayo Score prior to dose escalation and b) subjects who had achieved response per Partial Mayo Score but lost response (had inadequate response) prior to dose escalation.
- Proportion of subjects achieving minimal rectal bleeding (Rectal Bleeding subscore ≤ 1) at Week 52.
- Proportion of subjects achieving minimal rectal bleeding (Rectal Bleeding subscore ≤ 1) at both Week 8 and Week 52.
- Time in minimal rectal bleeding (Rectal Bleeding subscore ≤ 1).
- Proportion of subjects randomized to placebo who achieve clinical response by Partial Mayo Score at Week 16.
- Proportion of subjects who are IBDQ responders at Week 52.
- Change from Baseline in IBDQ at Week 52.
- Change from Baseline in SF-36 at Week 52.
- Change from Baseline in Mayo Score at Week 52.
- Change in Partial Mayo Score over time.
- Colectomy rates during the study.

Safety:

Adverse events, physical examination, vital signs and laboratory data were assessed throughout the study.

Statistical Methods

Efficacy:

The primary efficacy variable was remission rate, which was defined as the proportion of subjects with a total Mayo score ≤ 2 and no individual subscore > 1. The objective of the primary efficacy analysis was to demonstrate that adalimumab was statistically significantly better than placebo in efficacy at Week 8. The analyses were to be carried out in the following hierarchical order to handle the multiplicity issues induced by the 2 comparisons to placebo.

1. Compare the remission rates of adalimumab 160/80/40 mg group and placebo at Week 8. The superiority of adalimumab 160/80/40 mg treatment over placebo was to be established by the Chi-square test (two-sided) at an alpha level of 0.05.
2. Compare the remission rates of adalimumab 80/40 mg group and placebo at Week 8. The superiority of adalimumab 80/40 mg treatment over placebo was to be established by the Chi-square test (two-sided) at an alpha level of 0.05.

A *P* value ≤ 0.05 from Comparison 1 was necessary to initiate Comparison 2 at a significance level of 0.05. Since a hierarchical procedure was used, each comparison was to be tested at a significance level of 0.05 and overall alpha level of 0.05 could be preserved.

Statistical Methods

Efficacy (Continued):

The secondary efficacy analysis was to be performed in the ITT-A3 population. The statistical comparisons for the ranked secondary endpoints were to be carried out in hierarchical order. Statistically significant results (*P* value ≤ 0.05) had to be achieved for a comparison in the higher rank in order to initiate the next comparison in the lower rank.

1. Proportion of subjects with clinical response per Mayo score at Week 8 (ADA 160/80/40 versus placebo).
2. Proportion of subjects with mucosal healing at Week 8 (ADA 160/80/40 versus placebo).
3. Proportion of subjects with Rectal Bleeding subscore indicative of mild disease (≤ 1) at Week 8 (ADA 160/80/40 versus placebo).
4. Proportion of subjects with Physician's Global Assessment subscore indicative of mild disease (≤ 1) at Week 8 (ADA 160/80/40 versus placebo).
5. Proportion of subjects with Stool Frequency subscore indicative of mild disease (≤ 1) at Week 8 (ADA 160/80/40 versus placebo).
6. Proportion of subjects with clinical response per Mayo score at Week 8 (ADA 80/40 versus placebo).
7. Proportion of subjects with mucosal healing at Week 8 (ADA 80/40 versus placebo).
8. Proportion of subjects with Rectal Bleeding subscore indicative of mild disease (≤ 1) at Week 8 (ADA 80/40 versus placebo).
9. Proportion of subjects with Physician's Global Assessment subscore indicative of "normal or mild disease" (or numerical score ≤ 1) at Week 8 (ADA 80/40 versus placebo).
10. Proportion of subjects with Stool Frequency subscore indicative of mild disease (≤ 1) at Week 8 (ADA 80/40 versus placebo).
11. Proportion of IBDQ responders at Week 8 (ADA 160/80/40 versus placebo).
12. Proportion of IBDQ responders at Week 8 (ADA 80/40 versus placebo).

The proportion of subjects achieving response per Mayo score (yes/no), which was defined as a decrease in Mayo score of ≥ 3 points and a ≥ 30% decrease from Baseline plus a decrease in the rectal bleeding subscore [RBS] ≥ 1 or an absolute RBS of 0 or 1, was to be presented by randomized treatment group at Week 8. Subjects with a missing Mayo score were not to be considered as achieving response. The difference in proportion of subjects achieving response between adalimumab group and placebo group was to be assessed using the chi-square test, or Fisher's exact test as appropriate.

Other ranked dichotomous variables that included proportion of subjects with mucosal healing, proportion of subjects having mild disease indicated by components of the Mayo score (RBS, Physician's Global Assessment subscore [PGA] and Stool Frequency subscore), and proportion of IBDQ responders, were be analyzed using the same method used to analyze clinical response.

Statistical Methods

Efficacy (Continued):

Non-ranked dichotomous efficacy variables will be analyzed using the same methods listed above. Change from Baseline in the IBDQ scores; SF-36 scores; Mayo score and partial Mayo score were to be summarized using descriptive statistics. The treatment difference in mean change was to be analyzed using the ANOVA model including factors of treatment and Baseline scores, or non-parametric test, as appropriate. Both the data as-observed and the LOCF method could be used as appropriate. The median time to achieve response per partial Mayo score from Baseline was to be calculated using the Kaplan-Meier method.

Descriptive statistics were to be presented for the variables analyzed from the OL period of the study. The response rate based on Mayo score and the colectomy rate during the study was to be tabulated and could be tested using the chi-square test or Fisher's exact test, as appropriate.

Safety:

Safety analyses were to be performed separately for the DB, placebo-controlled period (Weeks 0 to 8) and the OL period. The safety variables were to be summarized by treatment group according to the treatment a subject actually received.

Treatment-emergent adverse events (AEs) were to be summarized. Treatment-emergent AEs were defined as events with an onset date on or after the first study drug injection and up to 70 days after the last injection of study drug. SAEs with onset date before the first study drug injection were to be considered as pre-treatment SAEs. In case of increasing severity of an existing AE, the worsening was to be considered as a new AE with a new onset date.

AEs were to be tabulated by system organ class and preferred term, whereby the most current implemented Medical Dictionary for Regulatory Activities (MedDRA®) was to be used. The number and percentage of subjects experiencing AEs were to be presented. Also, summaries by severity and relationship to study drug were to be provided. Certain AEs, such as serious or severe, leading to premature withdrawal from study, were to be listed and described in detail.

Other safety variables, such as laboratory data and vital signs, were to be described by statistical characteristics. In addition, shift tables and listings were to be provided for abnormal lab values, whereby the normal range of the analyzing laboratory was to be used.

Summary/Conclusions

Efficacy Results:

This study evaluated the efficacy of 2 adalimumab induction regimens compared to placebo in 575 subjects with moderate to severely active UC, as well as the maintenance of remission in subjects who were followed to 52 weeks in the open-label phase of the study. Owing to changes in study design introduced by Protocol Amendment 3, in which the adalimumab 80/40 treatment group was added, separate analysis sets were used for the induction and maintenance phases of the study. The primary analysis population for the induction phase of the study (DB period through Week 8) was the ITT-A3 Set (N = 390), a population comprising all randomized and treated subjects enrolled after Protocol Amendment 3. The primary analysis population for the maintenance phase of the study (OL period through Week 52) was the ITT-E Set (N = 575), a population comprising all subjects who received long-term adalimumab regardless of randomization group and amendment.

Summary/Conclusions

Efficacy Results (Continued):

No significant differences in the study population's demographics, medical history, presenting Baseline disease conditions, electrocardiograms, tuberculosis (TB), chest x-ray, and prior and concomitant medications were observed between treatment groups.

The primary efficacy endpoint of this study was clinical remission at Week 8 as assessed by Mayo score in the ITT-A3 Set. A statistically significantly greater proportion of subjects in the adalimumab 160/80/40 treatment group achieved this endpoint compared with placebo ($P = 0.031$, NRI analysis). A similar result was observed using the sensitivity analyses conducted on the Per Protocol Set ($P = 0.020$, NRI analysis), the ITT-E Set ($P = 0.005$, NRI analysis), as well as on the ITT-A3 set using LOCF imputation ($P = 0.033$). Among the subgroups analyzed for the primary endpoint, the following 4 subgroups had differences in clinical remission at Week 8 between either of the adalimumab treatment groups and placebo that were > 10%, with the lower bound of the 95% CI for the difference greater than zero: subjects in the adalimumab 160/80/40 treatment group with CRP < 10 mg/L at Baseline, tobacco smokers, use of azathioprine or 6-MP at Baseline, or no aminosalicylate use at Baseline; and subjects in the adalimumab 80/40 treatment group with no aminosalicylate use at Baseline.

The ranked secondary endpoints of this study were evaluated for statistical significance between the adalimumab and placebo groups. Twelve secondary induction variables were to be tested in a hierarchical order. Ranked endpoint No. 1 (clinical response per Mayo score at Week 8 in the adalimumab 160/80/40 treatment group versus placebo) did not meet the criteria for statistical significance.

The adalimumab 160/80/40 treatment group had a statistically significantly greater proportion of subjects meeting the endpoints of rectal bleeding subscore ≤ 1 at Week 8 ($P = 0.038$) and Physician's Global Assessment subscore ≤ 1 at Week 8 ($P = 0.035$). All other ranked secondary endpoints had numerically greater, but not statistically significant proportions of subjects in the adalimumab 160/80/40 treatment group meeting the ranked secondary endpoints compared with placebo.

The following results were observed for the unranked secondary induction endpoints during the DB period through Week 8:

- **Clinical response per partial Mayo score:** A statistically significantly greater proportion of subjects in the adalimumab 160/80/40 treatment group achieved clinical response as assessed by partial Mayo score compared with placebo at all time points (Weeks 2, 4, 6, and 8); in the adalimumab 80/40 treatment group statistically significant differences compared with placebo in clinical response as assessed by partial Mayo score were observed at Weeks 2, 4, and 6.
- **Rectal bleeding:** A statistically significantly greater proportion of subjects in the adalimumab 160/80/40 treatment group achieved an RBS ≤ 1 compared with placebo at all time points (Weeks 2, 4, 6, and 8).
- **Physician's Global Assessment:** A statistically significantly greater proportion of subjects in the adalimumab 160/80/40 treatment group achieved a PGA subscore ≤ 1 compared with placebo at Week 8.

Summary/Conclusions

Efficacy Results (Continued):

- **Stool frequency:** A statistically significantly greater proportion of subjects in the adalimumab 160/80/40 treatment group achieved a stool frequency subscore ≤ 1 compared with placebo at Weeks 4 and 6.
- **Change in Mayo score from Baseline:** A statistically significantly greater reduction in Mayo score observed in the adalimumab 160/80/40 treatment group compared with placebo at Week 8.
- **Change in partial Mayo score from Baseline:** Statistically significantly greater reductions in partial Mayo score observed in the adalimumab 160/80/40 treatment group compared with placebo at all time points (Weeks 2, 4, 6, and 8).
- **Health Care Resource Utilization:** Subjects in the adalimumab 80/40 treatment group reported statistically significantly more physician visits compared with placebo. Subjects in the adalimumab 160/80/40 treatment group reported numerically fewer physician visits compared with placebo, but the difference was not statistically significant. The rates per patient-year of emergency room visits, hospital admissions, and length of hospital stay were numerically lower in both adalimumab treatment groups compared with placebo, but the differences were not statistically significant or could not be tested due to non-convergence in the negative binomial model used to perform the analysis.

The following results were observed for the unranked secondary maintenance endpoints during the OL period through Week 52 (all analyses were conducted on the ITT-E Set unless otherwise noted):

- **Dose escalation:** Fewer subjects in the adalimumab 160/80/40 treatment group required dose escalation (from 40 mg eow to 40 mg weekly) as compared to the adalimumab 80/40 or placebo groups (22.9% versus 30.0% and 31.1%, respectively). Within the placebo group, a lower proportion of subjects who received adalimumab 160/80/40 at the start of the OL period dose escalated as compared to those who switched from placebo directly to adalimumab 40 mg eow (21.7% versus 37.7%, respectively).
- **Clinical remission per Mayo score:** When analyzed using the NRI method, the clinical remission rate per Mayo score at Week 52 among all subjects combined was 24.2% (139/575 subjects). When analyzed using the modified NRI method under which dose escalators were not considered non-responders, the clinical remission rate per Mayo score at Week 52 was 27.5% (158/575 subjects). In both adalimumab treatment groups and in the placebo group (who switched to OL adalimumab at Week 8 or 12), the proportion of subjects with clinical remission per Mayo score increased from Week 8 to Week 52. Similar improvements were observed in the ITT-A3 Set.
- Approximately 5% to 14% of subjects who had not achieved a clinical response per partial Mayo score on eow dosing achieved full clinical remission per Mayo score at Week 52 following dose escalation to weekly dosing.
- **Clinical remission per partial Mayo score:** When analyzed using the NRI method, the clinical remission rate per partial Mayo score at Week 52 among all subjects combined was 28.3% (163/575 subjects). When analyzed using the modified NRI method under which dose escalators were not considered non-responders, the clinical remission rate per partial Mayo score at Week 52 was 34.1% (196 subjects/575 subjects). In both adalimumab treatment groups, the proportion of subjects with clinical remission per partial Mayo score remained generally stable between Week 8 to Week 52. In the placebo treatment group, the proportion of subjects with clinical remission per partial Mayo score increased after subjects switched from placebo to adalimumab at Week 8.

Summary/Conclusions

Efficacy Results (Continued):

- **Clinical response per Mayo score:** When analyzed using the NRI method, the clinical response rate per Mayo score at Week 52 among all subjects combined was 42.6% (245/575 subjects). When analyzed using the modified NRI method under which dose escalators were not considered non-responders, the clinical response rate per Mayo score at Week 52 was 52.0% (299/575 subjects). In both adalimumab treatment groups, there was a numerical decrease in the proportion of subjects with clinical response per Mayo score increased from Week 8 to Week 52. At Week 8, > 51% of subjects in either adalimumab treatment group had a clinical response per Mayo score; at Week 52, > 38% of subjects in all treatment groups had a clinical response per Mayo score. Among all placebo-treated subjects, the proportion of subjects with clinical response per Mayo score increased after subjects switched from placebo to adalimumab at Week 8.
- **Clinical response per partial Mayo score:** When analyzed using the NRI method, the clinical response rate per partial Mayo score at Week 52 among all subjects combined was 41.6% (239/575 subjects). When analyzed using the modified NRI method under which dose escalators were not considered non-responders, the clinical response rate per partial Mayo score at Week 52 was 51.1% (294/575 subjects). In both adalimumab treatment groups and the placebo group, there was a numerical decrease in the proportion of subjects with clinical response per Mayo score between Week 8 and Week 52. At Week 8, > 52% of subjects in both adalimumab treatment groups had a clinical response per Mayo score; at Week 52, > 39% of subjects in all treatment groups had a clinical response per Mayo score. Clinical responses per Mayo score were observed after a median of 43 days in the placebo group, 43 days in the adalimumab 80/40 treatment group, and 29 days in the adalimumab 160/80/40 treatment group, and lasted a median of 99, 100, and 132 days, respectively.
- **Mucosal healing:** When analyzed using the NRI method, the mucosal healing rate at Week 52 among all subjects combined was 36.5% (210/575 subjects). When analyzed using the modified NRI method under which dose escalators were not considered non-responders, the mucosal healing rate at Week 52 was 44.2% (254/575 subjects). In both adalimumab treatment groups and the placebo group, the proportions of subjects with mucosal healing and complete mucosal healing remained generally stable between Week 8 to Week 52.
- **Rectal bleeding:** When analyzed using the NRI method, the rate of RBS ≤ 1 at Week 52 among all subjects combined was 47.0% (270/575 subjects). When analyzed using the modified NRI method under which dose escalators were not considered non-responders, the rate of RBS ≤ 1 at Week 52 was 60.5% (348/575 subjects). In both adalimumab treatment groups and the placebo group, there was a numerical decrease in the proportion of subjects with an RBS ≤ 1 between Week 8 and Week 52. At Week 8, ≥ 70% of subjects in both adalimumab treatment groups had RBS ≤ 1; at Week 52, > 43% of subjects in all treatment groups had RBS ≤ 1. The median time to RBS ≤ 1 was 43 days in the placebo group, 29 days in the adalimumab 80/40 treatment group, and 24 days in the adalimumab 160/80/40 treatment group. The median durations of RBS ≤ 1 were 211, 195, and 261 days, respectively.

Summary/Conclusions

Efficacy Results (Continued):

- **Physician's Global Assessment:** When analyzed using the NRI method, the rate of PGA ≤ 1 at Week 52 among all subjects combined was 41.7% (240/575 subjects). When analyzed using the modified NRI method under which dose escalators were not considered non-responders, the rate of PGA ≤ 1 at Week 52 was 52.0% (299/575 subjects). In both adalimumab treatment groups, there was a numerical decrease in the proportion of subjects with PGA subscore ≤ 1 between Week 8 and Week 52. At Week 8, ≥ 53% of subjects in both adalimumab treatment groups had PGA ≤ 1; at Week 52, > 39% of subjects in both adalimumab treatment groups had PGA ≤ 1. In the placebo group, the proportion of subjects with a PGA subscore ≤ 1 remained generally stable between Week 8 and Week 52.
- **Stool frequency:** When analyzed using the NRI method, the rate of SFS ≤ 1 at Week 52 among all subjects combined was 36.5% (210/575 subjects). When analyzed using the modified NRI method under which dose escalators were not considered non-responders, the rate of SFS ≤ 1 at Week 52 was 43.7% (251/575 subjects). In both adalimumab treatment groups and the placebo group, the proportion of subjects with an SFS ≤ 1 remained generally stable between Week 8 and Week 52.
- **Steroid-free clinical remission per Mayo score:** Among all subjects using corticosteroids at Baseline who were steroid-free at Week 52, the steroid-free remission rate at Week 52 was 42.3%. In both adalimumab treatment groups, among subjects who were steroid-free at Week 52, the proportion of subjects with remission per Mayo score increased from Week 8 (prior to steroid taper) to Week 52. In the placebo treatment group, among subjects who were steroid-free at Week 52, the proportion of subjects with clinical remission per Mayo score increased after subjects switched from placebo to adalimumab (and could begin steroid taper) at Week 8.
- **Steroid-free clinical remission per partial Mayo score:** The median time to steroid-free clinical remission per partial Mayo score among subjects using corticosteroids at Baseline was 43 days in the placebo group, 29 days in the adalimumab 80/40 treatment group, and 30 days in the adalimumab 160/80/40 treatment group. The median durations of steroid-free clinical remission per partial Mayo score were 30, 38.5, and 30 days, respectively.
- **Change in Mayo score from Baseline:** The median reduction in Mayo score from Baseline at Week 52 in all patients was 54.6% when LOCF was used and 71.4% on an observed cases basis. A numerically greater reduction in Mayo score was observed in the placebo group compared with both adalimumab treatment groups at Week 52 when LOCF was used. On an observed cases basis, the mean changes in Mayo score from Baseline to Week 52 were similar across treatment groups.
- **Change in partial Mayo score from Baseline:** Similar reductions in partial Mayo score were observed between the adalimumab treatment groups compared with placebo. The median reduction in partial Mayo score at Week 52 in all patients was 35.4% when LOCF was used and 71.4% on an observed cases basis.

Summary/Conclusions

Efficacy Results (Continued):

- **Colectomy rate:** Thirteen subjects (2.3%) underwent colectomies during the conduct of the study. Eight (3.6%) had been randomized to placebo and 5 subjects (1.4%) had been randomized to adalimumab at the onset of the study. No colectomies were performed on any subjects while on treatment. None of the subjects who underwent colectomies following the last dose of study drug enrolled in the open-label extension study.

Safety Results:

Adalimumab was generally safe and well tolerated during the induction phase of the study (DB period through Week 8):

- Approximately one-half of subjects reported at least 1 AE through Week 8. Aside from colitis ulcerative, which occurred in 9.4% of subjects in the placebo group, 7.7% of subjects in the adalimumab 80/40 treatment group, and 5.8% in the adalimumab 160/80/40 treatment group, the most frequently reported AE terms were headache, nasopharyngitis, abdominal pain, fatigue, upper respiratory tract infection, nausea, and injection site pain.
- The majority of AE terms reported by subjects were mild to moderate in severity, and the majority of severe AEs were reported by 1 subject each. Other than colitis ulcerative, the most frequently reported severe AEs were fatigue and abdominal pain.
- Adverse events considered possibly or probably related to study drug were reported by 21.5% of subjects in the placebo group, 21.5% of subjects in the adalimumab 80/40 treatment group, and 19.5% of subjects in the adalimumab 160/80/40 treatment group. The most frequently reported AEs that the investigator considered possibly or probably related to study drug included headache, injection site pain, pyrexia, colitis ulcerative, nausea, fatigue, and erythema.
- There were no deaths during the study. SAEs and other significant AEs were infrequent and consistent with the known safety profile of adalimumab.

Adalimumab was generally safe and well tolerated during the maintenance phase of the study (OL period through Week 52; any adalimumab exposure through Week 52):

- More than 75% of subjects reported at least 1 AE while receiving adalimumab. The most frequently reported AEs were colitis ulcerative, nasopharyngitis, headache, arthralgia, upper respiratory tract infection, fatigue, and nausea. All other AEs were each reported by < 5% of subjects.
- The majority of AE terms reported by subjects were mild to moderate in severity, and most severe events were reported by 1 subject each. The most frequently reported severe event was colitis ulcerative, fatigue, headache, colitis, deep vein thrombosis, abdominal pain, muscle strain, and depression. All other severe AEs were each reported by ≤ 2 subjects each.
- The most frequently reported SAEs were colitis ulcerative, deep vein thrombosis, abortion induced, appendicitis, perirectal abscess, and pneumonia. All other SAEs were reported by 1 subject each.
- The most frequently reported AE leading to discontinuation were colitis ulcerative, colitis, depression, drug hypersensitivity, frequent bowel movements, infection site reaction, and pharyngitis. All other AEs leading to discontinuation were reported by 1 subject each.

Summary/Conclusions

Safety Results (Continued):

The following results were observed for the AEs of special interest for adalimumab:

- **Infections:** The most frequently reported infections were nasopharyngitis and upper respiratory tract infection; all other infections were reported by < 5% of subjects each.
- **Serious infections:** During exposure to any adalimumab through Week 52, serious infections were reported by 17 subjects (3.1%; 4.0 events/100 PYs). The infections resolved in 16 subjects; 3 subjects were discontinued due to serious infections. One subject reported pneumonia Legionella. There were no cases of TB.
- **Opportunistic infections:** A total of 5 subjects reported opportunistic infections during the OL period through Week 52 or after the last dose of study drug. Four subjects reported oral or esophageal candidiasis and 1 subject reported cytomegalovirus colitis. Oral/oesophageal candidiasis resolved in 3 subjects, and 1 subject was discontinued due to oesophageal candidiasis.
- **Malignancies:** Two subjects in the placebo group (0.9%) reported malignancies during the DB period through Week 8, and 1 subject in the placebo group (0.5%), 1 subject in the placebo/OL adalimumab treatment group (0.3%), and 1 subject in the adalimumab/OL adalimumab treatment group (0.2%) reported malignancies during the OL period through Week 52. No lymphomas were reported during the study. Three of these malignancies were considered resolved during the course of this study, and 3 subjects, including 2 subjects with breast cancer and 1 subject with ongoing spindle cell sarcoma, discontinued adalimumab therapy as a result of their malignancy. One subject with basal cell carcinoma underwent surgery to excise the lesion but was not withdrawn from the study.
- **Injection site reactions:** During any adalimumab exposure through Week 52, the majority of subjects (45/48) reported injection site reactions that were considered possibly or probably related to adalimumab. The most frequently reported injection site reactions were injection site reaction, injection site erythema, injection site pruritus, and injection site pain.
- **Congestive heart failure:** One subject in the adalimumab 80/40 treatment group reported a CHF-related event of pulmonary congestion, which began on Day 198 (during the OL period) and was ongoing as of Day 307. The event was mild in severity and considered by the investigator to be not related to study drug.
- **Demyelinating disorders:** One subject in the adalimumab 80/40 treatment group reported leukoencephalopathy, which began on Day 251 (12 days after his last dose of adalimumab) and resolved on Day 290. The subject was discontinued as a result of this AE. The event was mild in severity and considered by the investigator to be possibly related to study drug.
- **Hepatic-related AEs:** Hepatic-related AEs were infrequent and mostly considered by the investigator to be not related to study drug. One subject reported hepatitis that resolved. No hepatic-related AEs led to interruption or discontinuation of adalimumab.
- **Allergic reactions:** Allergic reactions were infrequent and no AE terms were reported by more than 1 subject in any treatment group during the DB and OL periods. None of these events was serious. Two subjects reported drug hypersensitivity that was diagnosed as allergic reactions to adalimumab that led to their discontinuation from the study.

Summary/Conclusions

Safety Results (Continued):

- **Lupus-like syndrome:** No cases of lupus-like syndrome were reported during the study.
- **Hematology-related AEs:** Leukopenia was the only hematology-related AE reported by > 1 subject during the OL period through Week 52 and any adalimumab exposure through Week 52. No hematology-related AEs led to discontinuation of adalimumab.

There were no safety concerns identified in the analysis of clinical laboratory and vital signs parameters.

Conclusions:

Adalimumab was an effective, safe, and well-tolerated treatment for the induction of clinical remission in this population of subjects with moderate to severe UC despite concurrent treatment with oral corticosteroids or immunosuppressants. In addition, the results for the open-label period (through 52 weeks of therapy) provide supportive evidence for the maintenance of clinical remission. The safety profile observed throughout the study was consistent with previous clinical trials for adalimumab, and no new safety signals were observed.

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