



## Synopsis

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| <b>Abbott Laboratories</b>  | <b>Individual Study Table Referring to Part of Dossier:</b><br><br><b>Volume:</b><br><br><b>Page:</b> | <b>(For National Authority Use Only)</b> |
| <b>Name of Study Drug:</b><br>Adalimumab  |   |  |
| <b>Name of Active Ingredient:</b><br>adalimumab   |   |  |
| <b>Title of Study:</b><br>A Multicenter, Randomized, Double-blind, Placebo controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction and Maintenance of Clinical Remission in Subjects with Moderately to Severely Active Ulcerative Colitis  |   |  |
| <b>Coordinating Investigator:</b><br>William J. Sandborn, MD, Vice Chair, Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN 55905   |   |  |
| <b>Study Sites:</b><br>One hundred and three (103) sites in the US, Canada, Austria, Belgium, Denmark, France, Germany, Israel, Norway, Portugal, Spain, Switzerland, the Czech Republic, Hungary, Poland, Australia, and New Zealand.  |   |  |
| <b>Publications:</b><br>None.   |   |  |
| <b>Studied Period (Years):</b><br>First Subject First Visit: 20 November 2006<br>Last Subject Last Visit: 02 March 2010   | <b>Phase of Development: 3</b>  |  |
| <b>Objectives:</b><br>The primary objective of this study was to assess the efficacy and safety of adalimumab for the induction and maintenance of clinical remission in subjects with moderately to severely active ulcerative colitis (UC). The secondary objective of this study was to assess the pharmacokinetics (PK) of adalimumab following subcutaneous (SC) administration. |   |  |



### Methodology:

Adult subjects with moderate to severe UC (Mayo score of 6 to 12 points with endoscopy subscore of 2 to 3 points), confirmed by colonoscopy with biopsy or flexible sigmoidoscopy with biopsy, were to be enrolled at approximately 120 sites worldwide.

Subjects were to be stratified by prior exposure to infliximab and/or other anti-TNF agents, and randomized in a 1:1 ratio to receive adalimumab or placebo by SC injection. Subjects assigned to the adalimumab treatment arm were to receive an induction dose of 160 mg at Week 0 and 80 mg at Week 2, and 40 mg every other week (eow) starting at Week 4. Subjects assigned to the placebo treatment arm were to receive matching placebo during the same period of time. At or after Week 10, subjects who met the criteria for inadequate response could have been switched to open-label (OL) adalimumab 40 mg eow beginning at Week 12. Inadequate response was defined as:

- Partial Mayo score greater than or equal to their Baseline score on 2 consecutive visits at least 14 days apart (for subjects with a partial Mayo score of 4 to 7 at Baseline).
- Partial Mayo score  $\geq 7$  on 2 consecutive visits at least 14 days apart (for subjects with a partial Mayo score of 8 or 9 at Baseline).

Subjects who demonstrated inadequate response at 2 consecutive visits at least 14 days apart while on OL adalimumab 40 mg eow were permitted to dose escalate to adalimumab 40 mg weekly (ew). Subjects with persistent inadequate response while on adalimumab 40 mg ew may have been discontinued from the study at the Investigator's discretion. Upon completion of the study, subjects had the option to enroll into OLE Study M10-223 in which they could receive adalimumab treatment.

### Number of Subjects (Planned and Analyzed):

Enrollment was planned for 500 subjects. A total of 494 subjects comprised the ITT analysis set used for primary efficacy analyses; 24 subjects (14 randomized to adalimumab and 10 to placebo) from 3 sites (Sites 22635, 36809, and 27010) were excluded from the ITT analysis due to site noncompliance. A total of 517 subjects (including subjects at non-compliant sites) were analyzed as part of the Safety analysis set (518 subjects were randomized into the study, 1 subject did not receive study drug).

### Diagnosis and Main Criteria for Inclusion:

Subjects at least 18 years of age with moderately to severely active UC (Mayo score of 6 to 12 points and an endoscopy subscore of 2 to 3 points, despite concurrent treatment with corticosteroids and/or immunosuppressants) confirmed by colonoscopy with biopsy or flexible sigmoidoscopy with biopsy.

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

| <u>Study Drug</u>      | <u>Dose/Strength/Concentration/Mode</u>  | <u>Lot Number</u>                                   |
|------------------------|--|---|
| Adalimumab             | 40 mg/0.8 mL - 160 mg at Baseline (Week 0), 80 mg at Week 2, and 40 mg eow starting at Week 4 as a SC injection solution in 1-mL pre-filled syringes | 06-006764,<br>07-011196,<br>07-014216,<br>08-015939 |
| Placebo for Adalimumab | 40 mg/0.8 mL - 4 injections at Baseline (Week 0), 2 injections at Week 2, and 1 injection eow starting at Week 4                                     | 06-006518,<br>06-009051,<br>08-018846               |



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| <b>Duration of Treatment:</b><br>The duration of the study was up to 65 weeks, including a Screening Period of up to 3 weeks, a double-blind (DB), placebo-controlled treatment period of up to 52 weeks, and a 70 day follow-up phone call for subjects who prematurely discontinued or who did not enroll in the extension study (Study M10 223).   |
| <b>Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:</b><br>See Test Product information above.   |
| <b>Criteria for Evaluation</b><br><b>Efficacy:</b><br>The ranked co-primary efficacy endpoints were: <ul style="list-style-type: none"><li>• The proportion of subjects who achieved remission at Week 8 and</li><li>• The proportion of subjects who achieved remission at Week 52.</li></ul> Ranked secondary efficacy variables as described in the protocol were as follows: <ul style="list-style-type: none"><li>• Proportion of subjects with remission (sustained) per Mayo score at both Weeks 8 and 52.</li><li>• Proportion of subjects who achieved response per Mayo score at Week 8; at Week 52 (No. 3); at both Weeks 8 and 52 (No. 4).</li><li>• Proportion of subjects who achieved mucosal healing at Week 8; at Week 52 (No. 6); at both Weeks 8 and 52 (No. 7).</li><li>• Proportion of subjects who discontinued corticosteroid use before Week 52 and achieved remission at Week 52.</li><li>• Proportion of subjects with PGA subscore indicative of mild disease (<math>\leq 1</math>) at Week 8.</li><li>• Proportion of subjects with stool frequency subscore (SFS) indicative of mild disease (<math>\leq 1</math>) at Week 8.</li><li>• Proportion of subjects with rectal bleeding subscore (RBS) indicative of mild disease (<math>\leq 1</math>) at Week 8.</li><li>• Proportion of subjects who discontinued corticosteroid use for at least 90 days before Week 52 and achieved remission at Week 52.</li><li>• Proportion of subjects who discontinued corticosteroid use and achieved remission at both Weeks 32 and 52.</li><li>• Proportion of subjects who were inflammatory bowel disease questionnaire (IBDQ) responders at Week 52; and at Week 8 (No. 15).</li></ul> Non-ranked secondary variables as described in the protocol were as follows: <ul style="list-style-type: none"><li>• Proportion of subjects who achieved remission at Week 32 and (sustained) throughout Weeks 8, 32, and 52.</li><li>• Proportion of subjects who achieved response per Mayo score at Week 32 and throughout Weeks 8, 32, and 52.</li><li>• Proportion of subjects who achieved response per partial Mayo score at each time point separately.</li></ul> |



**Efficacy (Continued):**

- Time to response per partial Mayo score.
- Duration of response per partial Mayo score.
- Proportion of subjects who discontinued corticosteroid use for  $\geq 90$  days and achieved remission at Week 32.
- Proportion of subjects who discontinued corticosteroid use and achieved remission at Week 32.
- Proportion of subjects who have discontinued corticosteroid use at each time point after Week 8 separately.
- Duration of steroid-free response per partial Mayo score for subjects who were using corticosteroids at Baseline.
- Proportion of subjects who were IBDQ responders at Week 32, at both Weeks 8 and 52, and throughout Weeks 8, 32 and 52.
- Proportion of subjects with IBDQ score  $\geq 170$  at each time point separately.
- Change from Baseline in IBDQ score, SF-36 score, Mayo score, endoscopy score, SFS, RBS, and PGA subscore at each time point separately.
- Proportion of subjects who achieved mucosal healing at each time point separately.
- Proportion of subjects with RBS indicative of mild disease ( $\leq 1$ ) at each time point separately.
- Time in minimal rectal bleeding (RBS  $\leq 1$ ).
- Proportion of subjects with PGA subscore indicative of mild disease ( $\leq 1$ ) at each time point separately.
- Proportion of subjects with SFS indicative of mild disease ( $\leq 1$ ) at each time point separately.
- Proportion of subjects requiring dose escalation to 40 mg ew.
- Proportion of subjects achieving response (per Mayo score and per partial Mayo score) 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.
- Change from Baseline in WPAI at each time point separately.
- Health care resource utilization at each time point separately.
- Colectomy rates during the study.



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**Pharmacokinetic:**

Blood samples were to be collected at Weeks 0, 2, 4, 8, 32, and 52 for the adalimumab trough serum concentration assay. Mean concentration versus time plots by treatment group were to be provided. Adalimumab apparent clearance (CL/F) and apparent volume of distribution (V/F) were estimated for subjects in the study population. Blood samples were to be collected at Weeks 0, 8, 32, and 52 for the anti adalimumab antibody (AAA) assay. Additionally, blood samples were collected at Week 0 for infliximab and human anti-chimeric antibody (HACA) assay.

**Safety:**

Adverse events (including AEs of special interest for adalimumab), clinical laboratory tests (hematology, chemistry, urinalysis, and liver function tests), vital signs and physical examination were assessed.

**Statistical Methods****Efficacy:**

The primary efficacy analysis was performed on the ITT analysis set and consisted of two ranked efficacy endpoints: (1) proportion of subjects achieving clinical remission at Week 8 and (2) proportion of subjects achieving clinical remission at Week 52. Hypothesis testing for the ranked endpoints was carried out in a hierarchical order using a two-sided Cochran Mantel Haenszel (CMH) test adjusted for prior exposure to infliximab or other anti-TNF agents. The remission rate at Week 8 was tested first. If the null hypothesis of no difference between adalimumab and placebo in remission rate at Week 8 was rejected at  $\alpha = 0.05$ , then the remission rate at Week 52 was to be tested at a significance level of 0.05. However, in order to claim maintenance of remission, it was necessary to reject not only both hypotheses on the two ranked co-primary endpoints but also to reject the hypothesis on the first ranked secondary endpoint (proportion of subjects in remission at both Week 8 and Week 52). This first ranked secondary endpoint was incorporated in the confirmatory testing procedure conducted in hierarchical order from the first to the second ranked co-primary efficacy endpoint, and then to the ranked secondary endpoints, and stopped whenever a hypothesis could not be rejected at a significance level of 0.05. If a ranked endpoint did not meet the criteria for statistical significance, the analyses of the rest of the ranked secondary endpoints would be considered exploratory. This ensured that the multiple significance level was controlled at 0.05.

Non-responder imputation was used in the analysis. Subjects who discontinued the study for any reason and subjects with a missing Mayo Score were counted as non-remitters. Subjects who switched to OL drug were counted as non-remitters from the time of switching onward.

The last observation carried forward (LOCF) method was used for sensitivity analyses. For subjects who switched to OL drug, the non-missing value at the visit when the subject switched to the OL drug was to be carried forward in the LOCF analysis.

The secondary efficacy analysis was performed on the ITT analysis set. The testing of ranked secondary endpoints was initiated only in case of statistically significant differences between the treatment groups for both ranked co-primary endpoints. The statistical tests for the ranked secondary variables were carried out in hierarchical order.



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**Efficacy (Continued):**

The difference in proportions of subjects between treatment groups was analyzed using the Cochran-Mantel-Haenszel test adjusted for prior exposure to infliximab or other anti-TNF agents. Non-responder imputation was used in the analysis of the ranked dichotomous secondary variables. LOCF was used as a sensitivity analysis.

Non-ranked categorical secondary efficacy variables were analyzed by non-responder imputation and by LOCF as a sensitivity analysis using the CMH test. Change from Baseline in Mayo Score, IBDQ, SF-36, and WPAI were analyzed using an ANCOVA model including factors of treatment, prior exposure to infliximab or other anti-TNF agents, and Baseline values. For changes, both LOCF and as observed cases were used as imputation methods.

Duration of response and time to response data were analyzed using Kaplan-Meier curves and a proportional hazards model, including treatment factors and prior exposure to infliximab or other anti-TNF agents.

**Pharmacokinetic:**

Population pharmacokinetic analyses were to be performed based on actual sampling times, rather than protocol times. Pharmacokinetic models were to be built with the Non-Linear Mixed Effect Modeling (NONMEM) software (Version V or higher).

The structure of the starting pharmacokinetic model was to be based on observations from a population pharmacokinetic analysis performed with data collected from studies with adult rheumatoid arthritis subjects. From these studies, it is known that a one compartmental model with first-order absorption from the depot compartment and first order elimination from the central compartment is appropriate for describing adalimumab pharmacokinetics when only trough concentrations are available. Estimation of adalimumab clearance and volume of distribution were to be the primary and secondary interest in NONMEM analyses, respectively. The estimated CL/F and V/F values obtained with the base-model were to be plotted against potential covariates (such as subject age, sex, and body weight); regression and analysis of covariance (ANCOVA) were to be performed using SAS.

**Safety:**

The number and percentages of subjects experiencing treatment-emergent adverse events (TEAEs) were to be tabulated using the Medical Dictionary for Regulatory Activities (MedDRA<sup>®</sup>) version 12.1 system organ class (SOC) and preferred term (PT). Summaries by severity and relationship to study drug were to be provided. Certain TEAEs, like serious or severe TEAEs, or TEAEs leading to premature withdrawal, were to be listed and described in detail.

Other safety variables, such as laboratory data, were to be described by descriptive statistics. In addition, shift tables and listings were to be provided for abnormal values based on the normal range of the analyzing laboratory.



## Summary/Conclusions

### Efficacy Results:

No significant differences in the demographics, medical history, presenting Baseline disease conditions, and prior and concomitant medications were observed between treatment groups in the study population.

With regard to the ranked co-primary efficacy endpoints, statistically significantly greater proportions of adalimumab than placebo recipients achieved clinical remission as assessed by Mayo score at Week 8 (induction) and at Week 52 (maintenance) in both the primary analysis (Week 8 - 16.5% versus 9.3%, respectively,  $P = 0.019$  and Week 52 - 17.3% versus 8.5%, respectively,  $P = 0.004$ ) and supportive sensitivity analyses.

The ranked secondary endpoints of this study were evaluated for statistical significance between the adalimumab and placebo groups. Fifteen secondary induction and maintenance variables were to be tested in a hierarchical order. The first 8 ranked endpoints met the criteria for statistical significance, specifically, sustained clinical remission per Mayo score at both Weeks 8 and 52 ( $P = 0.047$ ), clinical response per Mayo score at Week 8 ( $P < 0.001$ ) and at Week 52 ( $P = 0.002$ ), sustained clinical response per Mayo score at both Weeks 8 and 52 ( $P < 0.001$ ), mucosal healing (defined as endoscopy subscore  $\leq 1$ ) at Week 8 ( $P = 0.032$ ) and at Week 52 ( $P = 0.009$ ), sustained mucosal healing at both Weeks 8 and 52 ( $P = 0.013$ ), and (among subjects using corticosteroids at Baseline) steroid-free clinical remission per Mayo score at Week 52 ( $P = 0.035$ ). Ranked endpoint No. 9 (PGA  $\leq 1$  at Week 8 in the adalimumab treatment group versus placebo) narrowly missed statistical significance ( $P = 0.058$ ), although it exhibited a numerical benefit of the adalimumab treatment group versus placebo.

The adalimumab treatment group had a statistically significantly greater proportion of subjects meeting the remaining ranked endpoints ( $P$  value ranged from 0.002 to 0.035) compared with placebo: SFS  $\leq 1$  at Week 8, RBS  $\leq 1$  at Week 8, steroid-free clinical remission for at least 90 days at Week 52, sustained steroid-free clinical remission at Weeks 32 and 52, and IBDQ response at Week 8 and at Week 52.

Among subjects who were naive to anti-TNF agents at study entry, a statistically significantly higher proportion of those treated with adalimumab achieved the primary and ranked secondary endpoints compared with placebo, except for sustained clinical remission per Mayo score at both Weeks 8 and 52, and steroid free clinical remission at Week 52 with discontinued steroid use any time before Week 52 or for  $\geq 90$  days before Week 52.

Among subjects who had previously used anti-TNF agents, a statistically significantly greater proportion of adalimumab-treated subjects compared to placebo-treated subjects met 3 of these endpoints (clinical remission per Mayo score at Week 52, clinical response per Mayo score at Week 52, and sustained clinical response per Mayo score at both Week 8 and Week 52).

With regard to other clinically important subgroups analyzed for the ranked co-primary and first ranked secondary endpoints, in 3 subgroups, subjects in the adalimumab treatment group achieved clinical remission at Week 52 at a  $> 10\%$  higher rate than the placebo group: subjects with Baseline Mayo score  $\geq 10$ , weight  $< 70$  kg (including a difference  $> 10\%$  for sustained remission at both Week 8 and Week 52), and Baseline endoscopy subscore = 3.



### **Efficacy Results (Continued):**

Similarly, at Week 8, subjects in the adalimumab treatment group who did not use azathioprine/6-MP at Baseline and subjects who did use corticosteroids at Baseline achieved clinical remission at a > 10% higher rate than the placebo group.

With regard to non-ranked secondary measures, statistically significant differences were observed in favor of the adalimumab dosing regimen compared with placebo administration for the endpoints of clinical remission and clinical response as assessed by Mayo score, partial Mayo score (except remission per partial Mayo score at Week 38 and response per partial Mayo score at Week 32 and 44), RBS  $\leq 1$  (except Week 44), SFS  $\leq 1$ , PGA subscore  $\leq 1$  (except Week 8 and 44), mucosal healing (endoscopy score  $\leq 1$ ), CRP levels (significant only for Week 4 and 8), and proportion of IBDQ responders. Statistically significantly greater reductions in Mayo score and partial Mayo score were seen with adalimumab treatment compared with placebo treatment at most study visits. The time to clinical response per partial Mayo score was statistically significantly shorter for the adalimumab treatment group than for the placebo group (median time 4 weeks vs. 10 weeks), which supports the efficacy of adalimumab as well as the induction regimen used in this study.

When analyzed using the NRI (non-responder imputation) method, at Week 52, 17.3% of subjects in the adalimumab group were in remission per Mayo score and 22.2% were in remission per partial Mayo score.

Among subjects in the adalimumab group, the steroid-free remission rate per Mayo score at Week 32 was 14.0% compared to 7.1% for placebo-treated subjects.

Twenty-two subjects underwent colectomies (12 had been randomized to placebo and 10 to adalimumab) during the 70-day follow-up phase of the study.

Subjects were permitted to escalate the dose of adalimumab to 40 mg ew in the case of inadequate response. Over the course of the study, fewer subjects originally randomized to the adalimumab treatment group (27.4%) required dose escalation compared to subjects originally randomized to placebo (34.1%). Of the subjects who dose escalated, a larger proportion of subjects previously in the placebo group (34.1%) than in the adalimumab group (12.2%) achieved remission per Mayo score at Week 52.

The proportion of dose escalators who had not achieved clinical response per partial Mayo score prior to dose escalation, but who achieved remission per Mayo score at Week 52 was greater in subjects previously in the placebo group (33.3% of subjects) than in those previously in the adalimumab group (6.7% of subjects).

Based on the achievement of statistically significant results for both primary efficacy endpoints and the first 8 ranked secondary endpoints related to sustained clinical remission and clinical response, evidence suggests that adalimumab is clinically effective in inducing and sustaining clinical remission in subjects with moderately to severely active UC.

### **Pharmacokinetic Results:**

The pharmacokinetic variables assessed in this study are described in a separate report (R&D/10/462).





### Safety Results:

Adalimumab was generally safe and well tolerated throughout the study. During DB administration, the following results were found:

- No deaths occurred during the study.
- Serious TEAEs occurred infrequently. During DB administration, approximately 12% of subjects in both treatment groups reported SAEs. Incidence rates of SAEs were 36.6 events/100 PYs for the placebo group and 30.8 events/100 PYs for the adalimumab group. The most frequently reported SAEs were colitis ulcerative, pyoderma gangrenosum, and anaemia, and deep vein thrombosis.
- During DB administration, more than 82% of subjects reported at least 1 TEAE. The incidence rate of TEAEs was 846.1 events/100 PYs in the placebo group and 743.3 events/100 PYs in the adalimumab group.
- During DB administration, the most frequently reported TEAEs were colitis ulcerative, nasopharyngitis, headache, nausea, arthralgia, abdominal pain, fatigue, anaemia, pyrexia, and upper respiratory tract infection. Incidence rates of anaemia, colitis ulcerative, pyrexia, upper respiratory tract infection, and headache were greater in placebo- than adalimumab-treated subjects. Nasopharyngitis, iron deficiency anaemia, injection site erythema, injection site reaction, and gastroenteritis were reported in a statistically significantly greater proportion of subjects in the adalimumab than placebo treatment group.
- During DB administration, the majority of TEAEs reported were mild to moderate in severity, and the majority of severe AEs were reported by 3 subjects or less in either group. The most frequently reported severe TEAEs were colitis ulcerative, anaemia, abdominal pain, and pyoderma gangrenosum. A total of 14.2% and 16.0% of subjects in the placebo and adalimumab groups, respectively, had severe TEAEs.
- During DB administration, the majority of TEAEs reported were considered not related or probably not related to study drug by the Investigator. AEs considered possibly or probably related to study drug were reported in 33.1% and 39.3% of subjects in the placebo and adalimumab groups, respectively. A statistically significantly greater proportion of adalimumab-treated than placebo-treated subjects experienced injection site erythema and injection site reaction considered possibly or probably related to study drug. The most frequently reported AEs that were considered by the Investigator to be possibly or probably related to study drug included colitis ulcerative, headache, injection site erythema, nausea, injection site reaction, injection site pain, nasopharyngitis, fatigue, upper respiratory tract infection, and arthralgia.
- More subjects in the placebo group prematurely discontinued from the study due to a TEAE (13.1%) than did subjects in the adalimumab treatment group (8.9%) during DB administration. The most frequently reported TEAE leading to discontinuation was colitis ulcerative (38/517 [7.4%]), which was reported by more placebo subjects (7.7%) than adalimumab subjects (7.0%).



### Safety Results (Continued):

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

- **Infections:** Treatment-emergent infections were reported by more than 39% of subjects in both treatment groups. The overall incidence rates of infectious TEAEs were similar between placebo and adalimumab groups (147.4 events/100 PYs versus 145.1 events/100 PYs, respectively). Infectious TEAEs of nasopharyngitis, pharyngitis, and gastroenteritis were reported in a statistically significantly greater proportion of subjects in the adalimumab group than in the placebo group. The most frequently reported treatment-emergent infections were nasopharyngitis, upper respiratory tract infection, sinusitis, and influenza. The majority of infectious TEAEs were not serious and were considered probably not or not related to study drug, as assessed by the Investigator. These TEAEs were common infections that were generally easily medically managed.
- **Serious Infections:** During DB administration, serious treatment-emergent infections were reported by 4 (1.6%) and 5 (1.9%) subjects in the adalimumab and placebo treatment groups, respectively, with no statistically significant overall or PT differences observed between treatment groups. Serious infections were predominantly abscesses. Four subjects in the placebo treatment group had serious infections that were considered at least possibly related to study drug by the Investigator, while all subjects in the adalimumab treatment group had serious infections that were considered probably not or not related to study drug. All of the placebo subjects and one of the adalimumab subjects prematurely discontinued from the study. Serious infections in all but 1 placebo-treated subject resolved prior to the last study evaluation. No cases of tuberculosis were observed in this study.
- **Opportunistic Infections:** Eight subjects reported treatment-emergent opportunistic infections during DB administration (3 in the placebo group and 5 in the adalimumab group) with no statistically significant overall or individual PT differences between treatment groups. The TEAEs of 5 subjects were considered by the Investigator to be possibly or probably related to study drug. All but 1 of these subjects had a TEAE of candidiasis.
- **Malignancies:** Two subjects in the adalimumab group reported treatment-emergent malignancies during DB administration (squamous cell carcinoma and gastric cancer; both were considered at most probably not related to study drug as assessed by the Investigator); no subjects in the placebo group experienced a malignancy-related TEAE. Both subjects underwent surgery to excise the lesions. No lymphomas were reported during the study.
- **Injection Site Reactions:** Injection site reactions overall (3.8% versus 12.1% in the placebo and adalimumab group, respectively), and PTs of injection site erythema and injection site reaction, were reported in a statistically significantly greater proportion of subjects in the adalimumab than placebo treatment group. The majority of subjects reported injection site reactions considered by the Investigator to be possibly or probably related to study drug.



#### Safety Results (Continued):

- **Congestive Heart Failure:** One CHF-related event was reported. The event was not serious, mild in severity, and considered not related to study drug.
- **Demyelinating Disorders:** No cases of demyelinating disorders were reported.
- **Hepatic-related TEAEs:** Seven subjects in the placebo group and 10 subjects in the adalimumab group had hepatic-related AEs during DB administration. No statistically significant overall or individual PT differences were observed between treatment groups. The most frequently observed TEAEs were ALT and AST increased. Most events were considered probably not or not related to study drug. Hepatic-related TEAEs resolved during study treatment in approximately half of the subjects.
- **Allergic Reactions:** During DB administration, 1 subject in the placebo group and 4 subjects in the adalimumab group reported allergic reactions (drug hypersensitivity and urticaria), with no statistically significant overall or individual PT differences observed between groups. All subjects had events that were mild or moderate in severity, none were serious, and all TEAEs were not related or probably not related to study drug, as assessed by the Investigator.
- **Lupus-like syndrome:** During DB administration, a single subject in the adalimumab treatment group had a lupus-like syndrome-related AE (systemic lupus erythematosus rash). The event was not serious, was moderate in severity, was considered probably related to study drug, did not resolve during the study, and led to premature discontinuation.
- **Hematology-related AEs:** Hematology-related TEAEs during DB administration were reported in 5 adalimumab-treated and no placebo-treated subjects ( $P = 0.030$ ); the only TEAE reported by more than 1 subject in any treatment group was leukopenia, which was reported by 4 adalimumab-treated subjects. No statistically significant differences between groups in individual PTs were observed. Two subjects discontinued study drug due to leukopenia. One SAE was reported, the majority of subjects had hematology-related TEAEs that were not related to study drug, and all events resolved during the study.

#### Conclusions:

In Study M06-827, adalimumab was effective in inducing and sustaining clinical remission in subjects with moderate to severe UC who did not adequately respond to conventional therapy with oral corticosteroids and/or immunosuppressants. This conclusion is supported by the achievement of statistically significant results for both primary efficacy endpoints and the first 8 ranked secondary endpoints related to sustained clinical remission and clinical response.

The safety profile observed throughout the study was consistent with previous clinical trials for adalimumab, and no new safety signals were observed.

**Date of Report:** 16Mar2012