



2.0 Synopsis

Abbott Laboratories	Individual Study Table Referring to Part of Dossier: Volume: Page:	(For National Authority Use Only)
Name of Study Drug: Adalimumab		
Name of Active Ingredient: Adalimumab		
Title of Study: A Multi-Center, 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 Crohn's Disease		
Coordinating Investigator: [REDACTED] [REDACTED] redacted information 01Oct2014		
Study Sites: Multicenter; 92 sites in Europe, United States, Canada, Australia, and South Africa		
Publications: None		
Studied Period (Years): First Subject First Visit: 31 Jul 2003 Last Subject Last Visit: 06 Sep 2005	Phase of Development: 3	
<p>Objective: The objective of this study was to assess the efficacy and safety of 40 mg weekly (ew) or 40 mg every other week (eow) subcutaneous (sc) doses of adalimumab for the induction and maintenance of clinical remission in subjects with moderate to severe Crohn's disease.</p> <p>The objective of this study was delineated in the protocol as noted above. Following the completion of the study and prior to unblinding, the objective was modified to reflect the intent of this study to evaluate adalimumab as maintenance therapy. The efficacy and safety of adalimumab for the induction of clinical remission in subjects with moderate to severe Crohn's disease was evaluated in a separate study (Study M02-403). All subjects in this study received the same open-label (OL) induction regimen prior to the randomized, double-blind (DB), placebo-controlled evaluation of adalimumab as maintenance therapy. Therefore, the objective of the study was modified per the statistical analysis plan (SAP) as follows:</p> <p>The objective of this study was to assess the efficacy and safety of 40 mg ew or 40 mg eow sc doses of adalimumab for the maintenance of clinical remission in subjects with moderate to severe Crohn's disease.</p>		
<p>Methodology:</p> <p>This was a randomized, DB, placebo-controlled, multicenter, efficacy and safety study in subjects with moderate to severe Crohn's disease (Crohn's Disease Activity Index [CDAI] ≥ 220 and ≤ 450 with confirmation by endoscopic or radiologic evaluation). Study medication was administered by sc injection. All subjects received OL 80 mg adalimumab at Baseline (Week 0) and 40 mg adalimumab at Week 2. At Week 4, subjects were stratified by their responder status and previous anti-tumor necrosis factor (TNF) use (no, yes) and randomized to one of three blinded treatment groups: adalimumab 40 mg ew, adalimumab 40 mg eow, or placebo.</p>		



If subjects in the randomized portion of the study experienced a disease flare (*i.e.*, an increase in CDAI of ≥ 70 points and a CDAI above 220 when compared to Week 4) at or after Week 12, they could be switched to the OL portion of the study in which they would receive 40 mg adalimumab sc eow. If subjects flared on this dose schedule, they could be switched to OL 40 mg adalimumab ew. If subjects continued to demonstrate a lack of improvement after the dose frequency was increased, they were to be withdrawn from the study. In addition, if subjects did not meet the definition of flare, but were consistent non-responders (did not attain a CDAI decrease of ≥ 70 points compared to Baseline) at or after Week 12, they could also be switched to the OL portion of the study after a discussion with the Abbott Medical Monitor.

The duration of the study was up to 62 weeks, which included a 2-week screening and a 4-week follow-up period. Efficacy and safety measurements were performed throughout the study.

Number of Subjects (Planned and Analyzed):

Planned: Approximately 830 subjects were planned at Week 0 in order for 480 subjects to be randomized in a 1:1:1 ratio to one of the three treatment groups at Week 4. Up to 778 subjects were analyzed for efficacy (ITT dataset) and 778 subjects were analyzed for safety. Subjects were analyzed by the following datasets:

	Treatment Group n (%)			Not Randomized N=76
	Placebo N=261	Adalimumab eow N=260	Adalimumab ew N=257	
ITT Dataset	261 (100.0)	260 (100.0)	257 (100.0)	0
mITT Dataset	170 (65.1)	172 (66.2)	157 (61.1)	0
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Safety Dataset	261 (100.0)	260 (100.0)	257 (100.0)	76 (100.0)

ITT = intent-to-treat; mITT = modified intent-to-treat; ██████████

Note: The ITT dataset included all randomized subjects who received at least one dose of randomized study drug, while the safety dataset included all subjects who received at least one dose of any study drug (including OL induction). The mITT dataset included all randomized subjects who received at least one dose of randomized study drug and achieved clinical response (CR-70) at Week 4 (defined as a CDAI decrease of ≥ 70 compared to the Baseline CDAI). This was the population for the primary efficacy analysis. ██████████

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Diagnosis and Main Criteria for Inclusion:

- Subject had a diagnosis of Crohn's disease for > 4 months.
- Subject had a diagnosis of Crohn's disease confirmed by endoscopy or radiologic evaluation.
- Subject had a CDAI score of ≥ 220 and ≤ 450 .
- Males and females between 18 and 75 years of age, inclusive.
- Subjects who used infliximab or any anti-TNF agent could have been enrolled if they had: a) responded and then stopped the agent, b) responded and lost their response, c) responded and became intolerant, or d) did not tolerate the anti-TNF agent.



Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:			
Subjects received OL 80 mg adalimumab at Baseline (Week 0) and 40 mg adalimumab at Week 2.			
Test Product	Dose	Mode of Administration	Lot Number
Adalimumab	40 mg ew or 40 mg eow	sc injection	[REDACTED]
Duration of Treatment:			
Four weeks OL adalimumab followed by up to 52 weeks of randomized study drug.			
Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:			
Placebo sc injection to match test product. Lot numbers were [REDACTED]			
Criteria for Evaluation			
<p>Efficacy: The primary efficacy variable was clinical remission (CDAI <150). There were two co-primary endpoints. The first co-primary endpoint was the proportion of subjects in clinical remission (CDAI <150) at Week 26 who had at least a CR-70 (decrease in CDAI score ≥ 70 points when compared to Baseline) at Week 4, and the second co-primary endpoint was the proportion of subjects in clinical remission at Week 56 who had at least a CR-70 at Week 4. Secondary variables were CR-70 and CR-100 (decrease in CDAI score ≥ 100 points when compared to Baseline), [REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>			
Safety: Adverse events (AEs), clinical laboratory data, and vital signs were assessed.			
Statistical Methods			
<p>Efficacy: The primary analysis was the hypothesis tests for adalimumab treatment effect at Week 26 and 56 in the mITT study population. The mITT dataset included all randomized subjects who received at least one dose of randomized study drug and achieved CR-70 at Week 4. The difference between each adalimumab group and the placebo group in the proportion of subjects achieving clinical remission was assessed with the Cochran-Mantel-Haenszel (CMH) test stratified by previous anti-TNF use (no, yes). [REDACTED]</p> <p>[REDACTED]</p> <p>Hypothesis testing for the co-primary endpoints was carried out in a hierarchical order. The Week 26 clinical remission rate was tested first. While testing the hypothesis for the two dose arms at the Week 26 endpoint, the Hochberg procedure was applied to control for multiplicity. The Week 56 clinical remission rate was tested only after the null hypothesis of no difference between adalimumab and placebo for Week 26 clinical remission rate was rejected. If the null hypothesis was rejected at Week 26, then the Week 56 clinical remission rate was tested using the Hochberg procedure to control for multiplicity.</p> <p>Secondary variables were divided into two groups. The first group includes major secondary endpoints, which were ranked by importance as specified by the SAP. Statistical significance was assessed at 0.050 in ranked endpoint order until the significance level exceeded 0.05. No additional statistically redacted information 01Oct2014</p>			



significant treatment differences could be declared after the first ranked endpoint failed to achieve 0.05. The second group included all other secondary variables.

For secondary variables that were proportions, the CMH test was used to test for treatment group differences. Treatment group differences for mean responses were assessed with the analysis of covariance with factors for Baseline score, treatment, and previous anti-TNF use. [REDACTED]

Safety: The safety dataset included all subjects who received at least one dose of any study drug (including OL induction), while the ITT dataset included all randomized subjects who received at least one dose of randomized study drug.

The incidence and prevalence of treatment-emergent AEs were summarized for each Medical Dictionary for Drug Regulatory Affairs (MedDRA) system organ class and preferred term (PT). Treatment group differences in the overall incidence of treatment-emergent AEs were assessed with Fisher's Exact test for each PT. [REDACTED]

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Summary/Conclusions

Efficacy Results:

The proportions of mITT subjects who achieved the protocol-specified primary efficacy endpoint of clinical remission (CDAI < 150) at Weeks 26 and 56 were statistically significantly greater ($p < 0.001$) in the adalimumab 40 mg eow (39.5% and 36.0%, respectively) and 40 mg ew (46.5% and 41.4%, respectively) groups compared to the placebo group (17.1% and 11.8%, respectively). Furthermore, the clinical remission rate for each of the adalimumab groups was statistically significantly greater than placebo at each visit from Week 8 through Week 56, although the difference between the adalimumab 40 mg eow group and placebo group was statistically significant only at Week 6. The proportion of subjects achieving clinical remission at Weeks 26 and 56 was greater in previous and concomitant non-users of immunosuppressants for the adalimumab 40 mg ew group, as well as previous non-users of anti-TNF agents for both adalimumab groups. The proportion of mITT subjects who were previous users of anti-TNF agents (predominantly infliximab) achieved clinical remission at Weeks 26 and 56 were 30.2% and 41.9%, respectively, in the adalimumab 40 mg eow group; 33.8% and 47.7%, respectively, in the 40 mg ew group; and 9.9% and 13.5%, respectively, in the placebo group. These clinical remission rates demonstrate that subjects previously treated with anti-TNF agents responded well to adalimumab maintenance therapy. In the mITT dataset, the median time to clinical remission from Week 0 was shorter in the adalimumab 40 mg eow and adalimumab 40 mg ew groups (42 and 43 days, respectively) compared to the placebo group (57 days). The difference between the adalimumab 40 mg eow and placebo groups was statistically significant ($p = 0.010$). Among subjects achieving clinical remission in the mITT dataset, the median time in clinical remission was statistically significantly greater in the adalimumab 40 mg eow group (378 days) compared to the placebo group (127 days) ($p = 0.002$). The median time in remission could not be estimated in the adalimumab 40 mg ew group because more than 50% remained in clinical remission at the end of the study.

Primary evidence for the effect of adalimumab dose on efficacy response is provided by the primary efficacy endpoint for which no statistically significant difference was observed between adalimumab 40 mg eow and adalimumab 40 mg ew in clinical remission (36.0% and 41.4%, respectively) at Week 56.



Supportive evidence for a restoration of clinical response as a result of dose titration is derived from a subgroup of 40 mITT subjects. These subjects were randomized to the adalimumab eow group and switched to OL dosing. For these 40 subjects, clinical remission was observed in 35% of subjects at Week 12 (prior to dose escalation). OL Dosing began with adalimumab 40 mg eow and increased to adalimumab 40 mg ew for recurrent flare or nonresponse. At the time of switch to OL adalimumab 40 mg eow, no subjects were in remission. Also, at the time of dose escalation to OL adalimumab 40 mg ew, no subjects were in remission. At the final visit (after dose escalation to adalimumab 40 mg ew OL), 13 (32.5%) subjects were in clinical remission. Dose escalation to ew dosing for recurrent flare or continued nonresponse appears to have restored response, as measured by clinical remission, in these mITT subjects.

Temporary interruption of adalimumab dosing (drug holiday) did not appear to affect clinical efficacy response to subsequent adalimumab exposure. Subjects who received DB placebo followed by OL adalimumab provided information about the effect of drug holiday because they were exposed to adalimumab from Week 0 until randomization at Week 4 (initial induction exposure) and to placebo from Week 4 until OL adalimumab was initiated at or after Week 12 (the drug holiday). Among mITT subjects who achieved clinical remission at Week 4, the clinical remission rate for the 28 subjects who received DB placebo/OL adalimumab 40 mg eow was 78.6% at the final visit. This is similar to the clinical remission rate for the 54 subjects who achieved clinical remission at Week 4 and remained on DB adalimumab 40 mg eow for the entire study (85.2%). The remission rate was 55.0% at the final visit for the 20 subjects who achieved clinical remission at Week 4 and received DB placebo/OL adalimumab 40 mg eow/OL adalimumab 40 mg ew. Because escalation to ew dosing occurred for subjects who did not respond to eow dosing (OL), the lower clinical remission rate is expected. Overall, for the 48 subjects who achieved clinical remission at Week 4 and were randomized to placebo, 33 subjects (68.8%) regained remission after receipt of OL adalimumab.

Statistically significant superiority of each adalimumab dose *vs.* placebo in the mITT dataset was observed for the first two ranked major secondary endpoints: proportion of subjects with CR-100 at Weeks 26 and 56 and proportion of subjects with CR-70 at Weeks 26 and 56. A summary of the major secondary efficacy endpoints is presented below.



Endpoint	Evaluation Timepoint	Placebo	Adalimumab 40 mg eow	Adalimumab 40 mg ew
		N = 170	N = 172	N = 157
		n (%)		
CR-100	Week 26	45 (26.5)	89 (51.7)*	82 (52.2)*
	Week 56	28 (16.5)	71 (41.3)*	75 (47.8)*
CR-70	Week 26	48 (28.2)	93 (54.1)*	88 (56.1)*
	Week 56	30 (17.6)	74 (43.0)*	77 (49.0)*
Median days in CR-70	Double-blind	94	298*	381*
Steroid-free at least 90 days and in clinical remission		N=66 ^a	N=58 ^a	N=74 ^a
	Week 26	2 (3.0)	11 (19.0)	11 (14.9)
	Week 56	3 (4.5)	17 (29.3)	15 (20.3)
Median days in clinical remission	Double-blind	127	378*	NE*
Mean change from Baseline in IBDQ total score		N=32	N=77	N=81
Baseline Mean (SD)		127.4 (26.78)	128.0 (30.26)	126.7 (28.02)
Mean Change (SD)	Week 56	45.9 (31.90)	59.8* (29.64)	59.7* (32.27)
NE Could not be estimated since > 50% of subjects were still in clinical remission at study completion				
a. Number of mITT subjects on corticosteroids at Baseline.				
* Statistically significant difference versus placebo, $p \leq 0.050$				
<p>CR-100 was observed for 26.5%, 51.7%, and 52.2% of subjects in the placebo, adalimumab 40 mg eow, and adalimumab 40 mg ew groups, respectively, at Week 26. CR-100 was observed for 16.5%, 41.3%, and 47.8% of subjects in the placebo, adalimumab 40 mg eow, and adalimumab 40 mg ew groups, respectively, at Week 56. The differences between each of the adalimumab groups and the placebo group in the proportion of mITT subjects achieving CR-100 were statistically significant at Week 26 and Week 56. Significant treatment differences were noted early (Week 8) and remained throughout the DB phase (Week 56).</p> <p>CR-70 was observed for 28.2%, 54.1%, and 56.1% of subjects in the placebo, adalimumab 40 mg eow, and adalimumab 40 mg ew groups, respectively, at Week 26. CR-70 was observed for 17.6%, 43.0%, and 49.0% of subjects in the placebo, adalimumab 40 mg eow, and adalimumab 40 mg ew groups, respectively, at Week 56. The differences between each of the adalimumab groups and the placebo group in the proportion of mITT subjects achieving CR-70 were statistically significant at Week 26 and Week 56. Significant treatment differences were noted early (Week 8) and remained throughout the DB phase (Week 56).</p> <p>These findings for CR-100 and CR-70 demonstrate that both doses of adalimumab provide superior efficacy to placebo as measured by prespecified clinical response criteria.</p> <p>Time in CR-70 (the third major secondary endpoint) was statistically significantly greater in each of the adalimumab groups compared to the placebo group. The median number of days in CR-70 was 94, 298, and 381 days for the placebo, adalimumab 40 mg eow, and adalimumab 40 mg ew groups, respectively.</p>				



The proportion of subjects who discontinued steroid use for at least 90 days and were in clinical remission at Week 56 (the fourth ranked major secondary endpoint) was statistically significantly greater for each of the adalimumab groups compared to the placebo group. The proportion of subjects who were steroid-free for at least 90 days and in clinical remission at Week 56 were 4.5%, 29.3%, and 20.3% for the placebo, adalimumab 40 mg eow, and adalimumab 40 mg ew groups, respectively.

As noted previously, time in clinical remission (fifth ranked major secondary endpoint) was statistically significantly greater in each of the adalimumab groups compared to the placebo group.

The sixth ranked major secondary endpoint was mean change from Baseline to Weeks 26 and 56 in IBDQ total score. Each adalimumab group was statistically significantly superior to placebo for this endpoint at Weeks 26 and 56 using observed cases and Last Observation Carried Forward methodology.

The seventh ranked major secondary endpoint was mean change from Baseline to Weeks 26 and 56 in the SF-36 Physical Component Summary. Although each adalimumab group was numerically superior to placebo at Weeks 26 and 56, only the difference at Week 26 was statistically significant ($p = 0.022$).

Two other major secondary endpoints were ranked after the SF-36 Physical Component Summary. The eighth ranked major secondary endpoint was the proportion of subjects with no draining fistulas at the last two evaluations. Numerical results are discussed under other supportive evidence. The ninth ranked major secondary endpoint was the proportion of subjects with complete healing of ulcers at Weeks 12 and 56; however, this endpoint was not evaluated due to the small sample size of the endoscopic dataset.

Other supportive evidence of adalimumab's efficacy in Crohn's disease included a larger proportion of ITT subjects for the combined adalimumab groups vs. the placebo group who had no draining cutaneous fistulas at the last two DB evaluations (32.9% vs. 12.8%, respectively) and smaller mean number of fistula days per month for the combined adalimumab group (24.73) vs. placebo (37.51) in the ITT dataset. In addition, greater improvements in each of the adalimumab groups compared to placebo in the mITT dataset were noted for the mean change from Baseline to Week 12, to Week 26, and to Week 56 for IBDQ social function score, emotional function, and bowel symptoms (except at Week 56 for the adalimumab 40 mg eow group).

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Safety Results:

Adalimumab was generally safe and well tolerated in subjects with moderate to severe Crohn's disease. No statistically significant treatment differences were observed for the proportions of subjects reporting a treatment-emergent or treatment-related AE. Treatment-emergent AEs were predominantly mild to moderate in severity. A summary of the overall incidence of treatment-emergent AEs, AEs at least possibly related to study drug (treatment-related AEs), any serious adverse event (SAE), and any AE leading to study discontinuation during DB treatment is presented below.

	Placebo	Adalimumab eow	Adalimumab ew
	N=261	N=260	N=257
	n (%)		
Any adverse event	221 (84.7)	231 (88.8)	220 (85.6)
Any adverse event with probable or possible relation to study drug	86 (33.0)	99 (38.1)	97 (37.7)
Any serious adverse event	40 (15.3)	24 (9.2)*	21 (8.2)*
Any adverse event leading to study discontinuation ^a	35 (13.4)	18 (6.9)*	12 (4.7)*
Any adverse event leading to death	0	0	0

* Statistically significant difference versus placebo ($p \leq 0.05$).

a. Denotes subjects who discontinued from the study during DB treatment at least in part due to an AE.

The most frequently reported ($\geq 5\%$ of subjects in any group) treatment-emergent AEs by MedDRA PT included Crohn's disease, arthralgia, nasopharyngitis, headache, nausea, fatigue, abdominal pain, pyrexia, upper respiratory tract infection, injection site reaction, urinary tract infection, influenza, diarrhoea, and pharyngolaryngeal pain.

A statistically significantly greater proportion of placebo subjects reported the treatment-emergent AE of Crohn's disease (32.2%) compared to adalimumab 40 mg eow and adalimumab 40 mg ew subjects (19.6% and 18.7%, respectively). Statistically significantly greater proportions of subjects in the adalimumab 40 mg eow and adalimumab 40 mg ew groups reported treatment-emergent injection site reaction (4.2% and 5.8%, respectively) compared to subjects in the placebo group (0.4%). Statistically significant differences were also observed between the adalimumab 40 mg ew and placebo groups in the proportions of subjects reporting treatment-emergent headache (11.7% and 5.7%, respectively), fatigue (7.8% and 2.3%, respectively), and urinary tract infection (5.8% and 1.5%, respectively).

Crohn's disease (6.5% placebo, 3.6% adalimumab 40 mg eow, and 4.1% adalimumab 40 mg ew) and small intestinal obstruction (2.1% adalimumab 40 mg eow) were the only commonly reported SAEs reported after randomization. All other SAEs after randomization were reported by $< 2.0\%$ of subjects in any group.

Crohn's disease was the only commonly reported AE after randomization that led to premature discontinuation from the study (7.7% placebo, 3.2% adalimumab 40 mg eow, and 4.6% adalimumab 40 mg ew). All other AEs that led to premature discontinuation from the study after randomization were reported by $< 2.0\%$ of subjects in any group.



The statistically significantly greater proportions of placebo subjects with SAEs and AEs that led to premature discontinuation during DB treatment compared to the proportions observed for the adalimumab groups was primarily due to a greater number of subjects with events related to active Crohn's disease. Similar proportions of subjects in each group experienced SAEs and AEs leading to discontinuation that were considered by the Investigator to be possibly or probably related to study drug.

One subject died during the study (OL induction) due to pulmonary embolism (not related). The subject had underlying risk factors of history of pulmonary embolism, hypertension, and atrial fibrillation. One subject developed a malignant neoplasm (breast cancer; probably not related) while receiving placebo during DB treatment.

During DB treatment, 36.8%, 46.2% and 44.4% of subjects in the placebo, adalimumab 40 mg eow, and adalimumab 40 mg ew groups, respectively, reported at least one infectious AE. The difference between the placebo and adalimumab 40 mg eow groups was statistically significant (p -value = 0.033).

However, no treatment differences were observed when normalized for length of patient exposure. The number of treatment-emergent infectious AEs per 100 patient-years during DB treatment was 167.7, 150.1, and 145.9 in the placebo, adalimumab 40 mg eow, and adalimumab 40 mg ew groups, respectively. Statistically significant differences between adalimumab and placebo were observed in the proportions of subjects reporting treatment-emergent urinary tract infection and vaginal infection, with higher incidences in the adalimumab 40 mg ew group and adalimumab 40 mg eow, respectively.

Similar proportions of subjects in the placebo, adalimumab 40 mg eow, and adalimumab 40 mg ew groups reported serious infectious AEs (3.4%, 2.7%, and 2.7%, respectively). There were two serious infectious AEs of tuberculosis reported during OL treatment. Both subjects were PPD negative and had a normal chest x-ray at Baseline.

One subject (during OL induction) reported moderate hypersensitivity that led to premature discontinuation from the study. Additionally, two subjects (one during DB placebo treatment and one during OL adalimumab 40 mg ew) reported moderate drug hypersensitivity that led to premature discontinuation from the study.

Two subjects (during OL induction) reported a severe injection site reaction that led to premature discontinuation from the study. One of these subjects also reported moderate injection site rash that led to premature discontinuation from the study. Additionally, two subjects (1 during OL induction and one during DB adalimumab 40 mg ew treatment) reported injection site pain and one subject (during OL induction) reported mild injection site irritation, each of which led to premature discontinuation from the study.

Clinical laboratory changes generally reflected improvement in Crohn's disease activity. Specifically, albumin, total protein, and calcium increased relative to placebo and alkaline phosphatase decreased. Hematocrit, hemoglobin, and red blood cell count increased relative to placebo, while white blood cell count and platelets decreased. Other treatment differences observed in mean laboratory changes were not clinically relevant. The incidence rate of patients experiencing Common Toxicity Criteria Grade 3 or higher abnormalities was similar between placebo and adalimumab groups for all clinical laboratory parameters.



Conclusions:

Adalimumab 40 mg eow and adalimumab 40 ew dosing were both shown to be efficacious and well tolerated as maintenance therapy for subjects with moderate to severe Crohn's disease. Efficacy differences between eow and ew dosing for clinical remission were not statistically significant. Subjects previously treated with anti-TNF agents responded well to adalimumab maintenance therapy. Supportive evidence indicated that escalation from eow to ew dosing restored clinical remission for some subjects. Ability to achieve clinical remission was not affected by a drug holiday. The results from this study support the selection of adalimumab 40 mg eow as the starting maintenance dose, with the option to dose escalate to adalimumab 40 mg ew, as maintenance therapy for subjects with moderate to severe Crohn's disease, including subjects who were previously treated with other anti-TNF agents.