Synopsis

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

Title of Study:

A Multi-center, Randomized, Double-Blind (DB), Placebo-controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab Endoscopy Trial to Evaluate the Effects on Mucosal Healing in Subjects with Crohn's Disease (CD) Involving the Colon

Investigator:

Paul Rutgeerts, MD

Study Sites:

Multicenter; 19 sites in Europe, the United States, and Canada.

Publications:

None

Studied Period (Years): First Subject First Visit: 28 August 2006 Last Subject Last Visit: 17 September 2008	**Phase of Development:** 3

Objectives:

The objectives of this study were to demonstrate the efficacy of therapy with adalimumab 40 mg every other week (eow), starting at Week 4 after a 160 mg/80 mg induction dose, on mucosal healing in subjects with moderate to severe ileocolonic CD, and to delineate the safety of adalimumab when administered to subjects with CD.

Methodology:

This was a randomized, DB, placebo-controlled, multicenter, efficacy and safety study. The study included a 1 to 3 week screening period, a 4-week induction period during which all subjects received adalimumab, a 48-week period in which subjects received either adalimumab or placebo, an open-label extension (OLE) period (duration up to ~ 80 weeks), and a 70-day follow-up phone call.

All doses of study medication were by subcutaneous (SC) injection. Study drug was to be administered SC using sterile technique by the research staff, by the subject, or by a designee (friend, family member, or healthcare professional) at the study site or at home.

Methodology (Continued):

At Baseline (Week 0), subjects were to have received an open-label (OL) dose of 160 mg adalimumab followed by an OL dose of 80 mg adalimumab at Week 2 (induction dose). At Week 4, subjects were randomized to either adalimumab 40 mg eow or placebo eow. Subjects were to be stratified at randomization by responder status so that subjects with a decrease ≥ 70 points in CD Activity Index (CDAI) score from Baseline to Week 4 were to be randomized in a 1:1 ratio in 2 treatment groups (adalimumab or placebo), and similarly, subjects with a decrease < 70 points in CDAI score from Baseline to Week 4 were to be randomized in a 1:1 ratio in 2 treatment groups (adalimumab or placebo).

While all subjects began blinded study drug (placebo or adalimumab), subjects could have switched to an OL dose of adalimumab upon disease flare or non-response at or after Week 8. Flare was defined as an increase in Crohn's Disease Activity Index (CDAI) of ≥ 70 points compared to Week 4 and a CDAI above 220. Non-response was defined as a lack of a CDAI decrease of ≥ 70 points compared to Baseline. If a subject on blinded study drug experienced disease flare at or after Week 8, or a subject was a non-responder for 2 consecutive visits at least 2 weeks apart on or after Week 8, the subject could have been switched to OL adalimumab (40 mg eow).

If a subject who switched to OL adalimumab (40 mg eow) experienced a flare or was a continued non-responder on the OL adalimumab dose, they could have been switched once more to OL adalimumab 40 mg weekly (ew). This switch was not to be made less than 2 weeks after the first switch to OL 40 mg eow dosing and was to first have been discussed with the Abbott Medical Monitor. If, after the dose frequency was increased, the subject continued to demonstrate a lack of improvement, they may have been withdrawn from the study.

If the CDAI was not completed but symptoms were indicative of a flare or non-response, the Medical Monitor was to be contacted before a switch to OL or dose escalation from eow to ew could be made.

Subjects who completed the Week 52 visit on blinded therapy were to be switched to OL adalimumab 40 mg eow at the Week 52 visit (for these subjects, the duration of OL therapy after Week 52 could have lasted up to 36 weeks). These subjects were permitted to switch to adalimumab 40 mg ew therapy for flare or non-response.

Efficacy and safety measurements were performed throughout the study. Subjects were to have undergone up to four endoscopies to evaluate the presence or absence of mucosal ulceration at Screening, at Week 12 (subjects who moved to OL drug between Week 8 and Week 12 were evaluated by endoscopy prior to OL dosing), at the time of switch from blinded study drug to OL adalimumab, at any time after Week 12, and at Week 52 or Early Termination. Subjects who remained blinded for the entire trial or switched to OL adalimumab at or between Week 8 and Week 12 were to have undergone only 3 endoscopies.

For subjects who switched to OL therapy between Week 8 and Week 12, the unscheduled endoscopy was to have replaced the scheduled Week 12 endoscopy.

Number of Subjects (Planned and Analyzed):

A total of 135 subjects were enrolled across 19 sites with 2 to 18 subjects per site. All subjects received the induction dose. A total of 129 subjects entered the DB phase (received DB study drug) and 100 subjects from the DB phase entered the OL phase of the study (received OL study drug) (76 subjects switched to OL prior to Week 52 and 24 subjects entered the OL phase at Week 52).

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

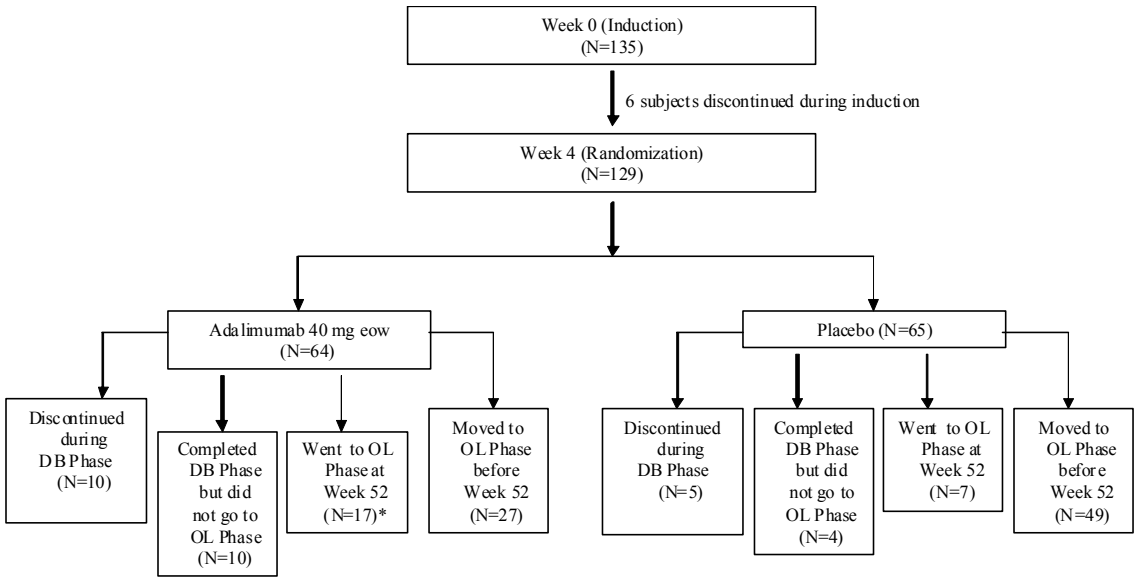
	Treatment Group n (%)		
	Placebo	Adalimumab	Total
Phase	**n (%)**		**N**
Received Induction dose[a]	--	--	135
Received DB study drug[b]	65 (50.4)	64 (49.6)	129
Received OL study drug	56 (56.0)	44 (44.0)	100
Switched prior to Week 52[c]	49 (64.5)	27 (35.5)	76
Entered at Week 52[c]	7 (29.2)	17 (70.8)	24

a. A total of 135 subjects entered the induction phase and received OL loading dose of 160 mg adalimumab at Week 0 and 80 mg adalimumab at Week 2.

b. At Week 4, subjects were randomized to receive injections of adalimumab 40 mg eow or placebo eow. Six subjects discontinued after receiving the induction dose and were not randomized.

c. Of the 100 subjects who entered the OL phase, 76 subjects switched from DB therapy to OL therapy prior to Week 52 and 24 subjects entered the OL phase at Week 52.

Figure 1. Disposition of Subjects



* Two adalimumab subjects did not have last dose of DB medication at Week 50 but received OL medication at Week 52 and are thus not considered DB completers.

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

All subjects were analyzed for efficacy and safety. Subjects were analyzed by the following populations:

- Subjects who received at least one dose of study medication (all treated population).
- The intent-to-treat (ITT) population included all subjects who were randomized at Week 4 and received at least one dose of blinded therapy.
- All ITT subjects who did not have a significant protocol deviation were considered to be the per-protocol population.
- The DB Completer population included ITT subjects who completed the DB phase and had Week 52 visit evaluations while still on blinded therapy.
- The OL population included ITT subjects who switched to OL therapy from the DB phase and received at least one dose of OL adalimumab 40 mg dose.

	Treatment Group			
	Placebo	Adalimumab 40 mg eow	Non-randomized	Total
Data Sets Analyzed		**N**		
All Subjects	65	64	6	135
All Treated	65	64	6	135
ITT	65	64	0	129
Per Protocol	60	63	0	123
DB Completer	11	25	0	36
OL	56	44	0	100

Diagnosis and Main Criteria for Inclusion:

Eligible subjects were male and female ≥ 18 and ≤ 75 years of age at the Baseline visit with a diagnosis of CD for ≥ 4 months. Eligible subjects had a diagnosis of ileocolonic CD confirmed by endoscopy or radiologic evaluation within 3 years of Baseline. For subjects that had operations in the ileocolonic region of the intestine after documented diagnosis of ileocolonic disease, postoperative recurrence of the disease was to have been documented. Eligible subjects had endoscopic documentation of ulceration at Screening corresponding to a score of 2 or 3 in at least one of the five segments of the colon on the Ulcerated Surface subscore of the Simple Endoscopic Score for CD (SES-CD). In addition, eligible subjects had a CDAI score of ≥ 220 and ≤ 450.

If female, subject was either not of child bearing potential, defined as post menopausal for at least one year, surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or was of child bearing potential and practiced one of the following methods of birth control during the study and for 150 days after the last dose: condoms, sponge, foam, jellies, diaphragm, or intrauterine device; oral or parenteral contraceptives for three months prior to study drug administration; or a vasectomized partner. Eligible female subjects were not breast-feeding throughout the study and for 150 days after the last dose.

Diagnosis and Main Criteria for Inclusion (Continued):

An eligible subject or his/her legal representative had voluntarily signed and dated an informed consent in conformity with the study protocol, which had been approved by an IRB/IEC. Eligible subjects had adequate cardiac, renal, and hepatic function as determined by the Principal Investigator and demonstrated by Screening laboratory evaluations, questionnaires, and physical examination results that did not indicate an abnormal clinical condition which would have placed the subject at undue risk and thus precluded subject participation in the study. Subjects must have been able to self-inject study medication or have had a designee or healthcare professional who could inject the study medication. Eligible subjects also must have agreed to undergo up to 4 endoscopies.

Subjects may have been included if they used infliximab or any anti-TNF agent (except adalimumab) and 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:

Adalimumab 40 mg eow or 40 mg ew SC

Lot numbers:

Blinded drug: 05-002082 and 05-001228

OL drug: 05-002082 and 07-010526

Duration of Treatment:

Induction: OL adalimumab 160 mg at Week 0 followed by OL adalimumab 80 mg at Week 2.

DB: At Week 4, subjects were randomized to receive either adalimumab 40 mg eow or placebo eow for up to 48 weeks.

OL: Subjects could continue into the OL arm, thereafter, for up to 137 weeks.

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

Placebo SC injection to match test product. Lot numbers: 05-001549 and 06-004100

Criteria for Evaluation

Efficacy:

The primary efficacy variable was the presence or absence of mucosal ulceration by endoscopy. The primary outcome analysis was a comparison of the proportions of subjects without mucosal ulceration on endoscopy between the adalimumab and the placebo group at Week 12. A subject was considered to have mucosal ulceration at a given time point if the final outcome of the endoscopy review determined that there was ulceration present in any one of the five segments of the colon.

Secondary efficacy variables included the number of subjects without mucosal healing, CD Endoscopic Index of Severity (CDEIS) scores, the SES-CD and ulcer counts, CDAI score, number of subjects discontinued from steroids, total Inflammatory Bowel Disease Questionnaire (IBDQ) scores, Work Productivity and Activity Impairment Questionnaire (WPAI) scores, SF-36 dimension scores, fistula counts, histology assessments, histochemistry assessments, and Healthcare Resource Utilization (HRCU; unscheduled outpatient visits, emergency room (ER) visits, and hospitalizations questionnaire).

Safety:

Safety was assessed from adverse event (AE) monitoring and results from laboratory tests, vital signs, and physical examinations.

Statistical Methods

Efficacy:

The primary analysis was the hypothesis test for adalimumab treatment effect at Week 12 in the ITT population. It encompassed the comparison of the proportion of subjects without mucosal ulceration on endoscopy between the adalimumab arm and the placebo arm at Week 12 in the ITT population using the Cochran-Mantel-Haenszel (CMH) test to adjust for CR-70 responder status at Week 4. Non-responder imputation (NRI) method was used to impute missing information on mucosal ulceration. This efficacy analysis was carried out for the per-protocol analysis set as supportive evidence.

Secondary variables were divided into two groups. The first group included major secondary endpoints which were ranked by importance as specified by the Statistical Analysis Plan. The ranked secondary variables were to be tested in a hierarchical order. Testing for statistical significance for each secondary endpoint was inferential only of the tests of all preceding ranked secondary endpoints were statistically significant. The CMH test, to adjust for the subjects' responder status at Week 4, was used to compare the proportions of subjects in the two treatment groups, for the ranked secondary variables 1 through 7. The second group included all other secondary variables.

For secondary variables that were proportions, the CMH test to adjust for the subjects' responder status at Week 4 was used to test for treatment group differences. Treatment group differences for mean responses were assessed with the analysis of covariance (ANCOVA) with factors for treatment and CR-70 responder status (a decrease of ≥ 70 points in CDAI from Baseline [CR-70]) status at Week 4, and Baseline values as a covariate.

Safety:

A treatment-emergent AE (TEAE) is an AE with an onset date on or after the first study drug dose and up to 70 days after the last dose of study drug. For this study, TEAEs are defined by administration (induction, DB, OL, and Any adalimumab):

Induction TEAE

An induction TEAE is an AE with onset on or after the first induction dose and prior to the first DB dose, or up to 70 days after the last induction dose if the subject prematurely discontinued during induction dose administration.

DB TEAE

A DB TEAE is an AE with onset on or after the first DB dose and prior to the first OL dose, or up to 70 days after the last DB dose if the subject prematurely discontinued during DB administration.

OL TEAE

An OL TEAE is an AE with onset on or after the first OL dose and up to 70 days after the last dose of study drug.

Safety (Continued):

Any Adalimumab TEAE

An Any Adalimumab TEAE is an AE with onset on or after the first dose of adalimumab and up to 70 days after the last dose of adalimumab (for subjects randomized to adalimumab).

For subjects who were randomized to placebo, an Any adalimumab TEAE is any AE with onset on or after the first dose of adalimumab and up to 70 days after the last dose of adalimumab, excluding events during the placebo period.

The incidence and prevalence of TEAEs were summarized for each Medical Dictionary for Drug Regulatory Affairs (MedDRA v11.0) system organ class and preferred term (PT). In addition to the evaluation of TEAEs, deaths, and serious adverse events (SAEs), the following categories of TEAEs of special interest were specifically examined: AEs leading to premature discontinuation from the study, infections, serious infections, opportunistic infections, malignancies, injection site reactions, hepatic AEs, congestive heart failure (CHF), demyelinating disorders, allergic reactions, and lupus like syndrome. These events are of special interest because they have been identified as safety concerns for the anti-TNF agent class of drugs. Treatment group differences in the overall incidence of TEAEs were assessed with Fisher's exact test for each PT. Clinical laboratory data were summarized with mean change from Baseline to the minimum, maximum, and final values during DB treatment, and with the proportion of subjects who changed to potentially clinically significant (PCS) values during DB treatment from Baseline values that were not PCS. Vital signs were analyzed similarly.

Summary/Conclusions

Efficacy Results:

For the primary efficacy analysis, the proportions of subjects without mucosal ulceration at Week 12, subjects who did not have endoscopy at Week 12 were considered to have mucosal ulceration at Week 12 (non-responder imputation). If subjects did not have endoscopy at Week 12, but had endoscopy between Week 8 and Week 12, the endoscopy results before Week 12 were carried forward to Week 12 for the primary efficacy analysis. ITT subjects who had mucosal ulceration at Screening were included in the primary analysis.

As per the primary analysis mentioned above, at Week 12 a larger proportion of subjects in the adalimumab group were without mucosal ulceration compared to placebo (27.4% versus 13.1%), respectively. The observed difference between the two groups was not statistically significant ($P = 0.056$).

However, results of a similar analysis using the per-protocol analysis set for subjects who had mucosal ulceration at Screening, were statistically significant in favor of adalimumab (adalimumab 27.9% versus placebo 12.5%; $P = 0.046$).

In an analysis of observed cases, a larger proportion of subjects in the adalimumab group were without mucosal ulceration compared to placebo (28.8% versus 14.3%, respectively). The observed difference between the two groups was not statistically significant ($P = 0.071$).

Efficacy Results (Continued):

Subjects without mucosal ulceration	Placebo N	Placebo n (%)	Adalimumab N	Adalimumab n (%)	*P* value[a]
Primary efficacy analysis					
ITT Set[b,c]	61	8 (13.1)	62	17 (27.4)	0.056
Sensitivity analyses of the primary variable					
As observed[c]	56	8 (14.3)	59	17 (28.8)	0.071
PP Set[b,c]	56	7 (12.5)	61	17 (27.9)	0.046

a. The *P* value is from CMH test with CR-70 responder status at Week 4 as the stratification factor.

b. Only subjects with mucosal ulceration (according to the review committee) at Screening were included in this analysis. Six subjects were excluded from the analysis because they did not have mucosal ulceration at Screening.

c. Subjects who did not have endoscopy at Week 12 were considered to have mucosal ulceration at Week 12 (NRI). If subjects did not have endoscopy at Week 12, but had endoscopy between Week 8 and Week 12, the endoscopy results before Week 12 were carried forward to Week 12 for the primary efficacy analysis. Among 123 subjects who had mucosal ulceration at Screening, 8 subjects did not have endoscopy at Week 12.

As the primary efficacy analysis was not statistically significant, the following secondary efficacy analyses are considered exploratory. Seven secondary variables were to be tested in a hierarchical order. Except for ranked endpoint No. 4, all ranked endpoints demonstrated statistical significance ($P < 0.05$) in favor of adalimumab when compared to placebo.

Ranked Endpoint No. 1 - A between treatment group comparison at Week 12 (ITT) demonstrated that a statistically significantly greater proportion of subjects in the adalimumab group achieved clinical remission (CDAI < 150) compared to the placebo group (46.9% versus 27.7%, respectively; $P = 0.021$).

Ranked Endpoint No. 2 - At Week 52 (ITT), a statistically significantly greater proportion of subjects in the ITT population who received adalimumab were without mucosal ulceration compared to subjects in the placebo group (24.2% versus 0%, respectively; $P < 0.001$).

Ranked Endpoint No. 3 - At Week 52 (ITT), a statistically significantly greater proportion of subjects in the adalimumab group achieved clinical remission (CDAI < 150) compared to the placebo group (32.8% versus 9.2%, respectively; $P = 0.001$).

Ranked Endpoint No. 4 - At both Week 12 and Week 52 (DB completer set) a greater proportion of subjects in the adalimumab group achieved mucosal healing compared to the placebo group (28.0% versus 0% respectively). No statistically significant difference was observed ($P = 0.150$).

Ranked Endpoint No. 5 - A between treatment group comparison at both Week 12 and Week 52 (ITT) demonstrated that a statistically significantly greater proportion of subjects in the adalimumab group achieved clinical remission (CDAI < 150) compared to the placebo group (29.7% versus 4.6%, respectively; $P < 0.001$).

Efficacy Results (Continued):

Ranked Endpoint No. 6 - A statistically significantly greater proportion of subjects in the adalimumab group achieved CDEIS remission (CDEIS ≤ 4) at Week 12 (ITT) compared to the placebo group (51.6% versus 27.7%, respectively; $P = 0.006$).

Ranked Endpoint No. 7 - A statistically significantly greater proportion of subjects in the adalimumab group achieved CDEIS remission (CDEIS ≤ 4) at Week 52 (ITT) compared to the placebo group (28.1% versus 3.1% respectively; $P < 0.001$).

Efficacy of adalimumab on mucosal disease was supported by the following secondary efficacy analyses:

- At Week 52, a statistically significantly greater proportion of subjects in the ITT Set in the adalimumab group were without mucosal ulceration compared to subjects in the placebo group (24.2% versus 0%, respectively; $P < 0.001$ [ranked endpoint No. 2]).
- A statistically greater proportion of subjects in the adalimumab group achieved CDEIS remission (CDEIS ≤ 4) at Week 12 (33/64, 51.6% of adalimumab subjects versus 18/65, 27.7% of placebo subjects; $P = 0.006$ [ranked endpoint No. 6]) and at Week 52 (18/64, 28.1% of adalimumab subjects versus 2/65, 3.1% of placebo subjects; $P < 0.001$ [ranked endpoint No. 7]) compared to subjects in the placebo group.
- At Week 52, a statistically significantly greater proportion of subjects in the adalimumab group achieved a > 75% decrease in CDEIS from Baseline compared to the placebo group (21.9% versus 1.5%, respectively; $P < 0.001$).
- Mean change from Baseline in CDEIS score was statistically significantly higher in the adalimumab group compared to the placebo group at Week 12 (4.736 versus 2.110, respectively; $P = 0.020$) and at Week 52 (6.282 versus 3.441, respectively; $P = 0.022$).
- Subjects in the adalimumab group demonstrated a statistically significantly higher mean change in total SES-CD from Baseline to Week 12 compared to subjects in the placebo group (8.44 versus 4.09, respectively; $P < 0.001$) and from Baseline to Week 52 (11.58 versus 6.4, respectively; $P < 0.001$).
- A majority of adalimumab group subjects who were without mucosal ulceration at both Week 12 and Week 52 (N = 15) were without mucosal ulceration at Week 52 (53.3%; 8/15). There were no placebo subjects without mucosal ulceration at Week 52. All 8 adalimumab subjects who were without mucosal ulceration were CR-70 responders at Week 4.

Efficacy of adalimumab on CD activity was supported by the following secondary efficacy analyses:

- A between treatment group comparison at Week 12 (46.9% versus 27.7%, $P = 0.021$ [ranked endpoint No. 1]), at Week 52 (32.8% versus 9.2%, $P = 0.001$[ranked endpoint No. 3]), and at both Week 12 and Week 52 (29.7% versus 4.6%, $P < 0.001$ [ranked endpoint No. 5]), demonstrated that a statistically significantly greater proportion of subjects in the adalimumab group achieved clinical remission (CDAI < 150).

Efficacy Results (Continued):

- At Week 12, no statistically significant difference between both groups could be shown for clinical response CR-70 (CDAI decrease from Baseline ≥ 70) or clinical response CR-100 (CDAI decrease from Baseline ≥ 100). However, at Week 52, a statistically significantly greater proportion of subjects in the adalimumab group demonstrated clinical response when compared to subjects in the placebo group (CR-70: 40.6% versus 13.8%, respectively; $P < 0.001$ and CR-100: 35.9% versus 13.8%, respectively; $P = 0.004$).
- Thirteen subjects (5 placebo, 8 adalimumab) had fistulas at both Screening and Baseline. Of these, one subject in the placebo group and 5 subjects in the adalimumab group had no draining fistulas at the last 2 evaluations on or before Week 28. On or before Week 52, 6 subjects (2 placebo, 4 adalimumab) were without draining fistulas.
- Among subjects who took steroids at Baseline, a greater proportion of subjects in the adalimumab group (44.4%) were steroid-free for ≥ 90 days and achieved clinical remission (CDAI < 150) at Week 52 when compared to subjects in the placebo group (4.0%) ($P = 0.012$). Results were similar at Week 52 for those subjects who remained steroid-free and achieved clinical remission (CDAI < 150).

Moreover

- Although Week 12 data was not statistically significant, a statistically significant greater proportion of adalimumab subjects were without mucosal ulceration and on clinical remission (CDAI < 150) at Week 52 (19.4% versus 0, $P < 0.001$) and at both Week 12 and Week 52 (8.1% versus 0, $P = 0.027$).
- For within group comparison in DB completers, the odds ratios in two treatment groups for clinical remission (CDAI < 150) at both Week 12 and Week 52 were calculated using the logistic regression model with absence of mucosal ulceration at Week 12 as an independent variable. Due to the small sample size in the placebo group, the estimate of the odds ratio was not reliable. However, for the adalimumab group, the odds ratio of 2.1 (confidence interval: 0.324, 13.614) was found to be statistically non-significant.

Results of patient-reported outcomes:

- The mean changes in IBDQ score from Baseline to Week 12 and Week 52 in both treatment groups were higher than the MCID (16 points). Observed values at Week 12 and Week 52 include data from subjects who switched to OL. At Week 12, the improvement in IBDQ in the adalimumab group was statistically significantly greater than that in the placebo group, despite the fact that some of placebo subjects could move to OL adalimumab at or after Week 8 (–39.64 versus –27.13, respectively; $P = 0.038$). Mean change was comparable between treatment groups at Week 52 (–48.32 adalimumab versus –52.81 placebo; $P = 0.502$). However, given the fact that subjects could have moved to OL adalimumab at or after Week 8, the observed improvement in the placebo group could be explained by the efficacy of OL adalimumab therapy.
- At Week 12, the adalimumab group achieved clinical meaningful improvement in absenteeism, presenteeism, total work productivity impairment, and daily activity impairment. Improvements observed were significantly greater in the adalimumab group compared to the placebo group for presenteeism (33.47 versus 19.15, respectively; $P = 0.017$) and total work productivity impairment (34.28 versus 17.41, respectively; $P = 0.039$).

Efficacy Results (Continued):

Results of histology and histochemistry parameters (Observed values at Week 12 and Week 52 include data from subjects who switched to OL.):

- Numerical differences in favor of adalimumab compared to placebo were observed at Week 12, at the time of the switch, and at Week 52 for mean changes in both Ileal Global Histologic Disease Activity Score (IGHAS) and Colonic Global Histologic Disease Activity Score (CGHAS):
    - Week 12:
        - IGHAS (1.71 versus 1.35, respectively; $P = 0.371$)
        - CGHAS (2.97 versus 1.9, respectively; $P = 0.789$)
    - At the time of the switch to OL adalimumab:
        - IGHAS (1.44 versus 1.38, respectively; $P = 0.229$)
        - CGHAS (1.9 versus 1.08, respectively; $P = 0.315$).
    - Week 52:
        - IGHAS (2.24 versus 1.75, respectively; $P = 0.184$)
        - CGHAS (3.55 versus 3.10, respectively; $P = 0.337$)
- Numerical differences in favor of adalimumab compared to placebo were observed at Week 12 in regard to the proportion of subjects who moved to a lower category in the number of lamina propria cells for both mononuclear (67.9 versus 57.1, respectively; $P = 0.582$) and polymorphonuclear (84.6 versus 72.2, respectively; $P = 0.667$) cells in the ileum.
- Numerical differences in favor of adalimumab compared to placebo were observed at Week 12 and Week 52 for both mononuclear and polymorphonuclear cells in the colon (Week 12 mononuclear: 59.2 versus 50.9, respectively; $P = 0.432$; Week 52 mononuclear: 70.6 versus 66.7, respectively; $P = 0.806$; Week 12 polynorphonuclear 71.4 versus 60.5, respectively; $P = 0.571$; Week 52 polynorphonuclear: 83.3 versus 77.4, respectively; $P = 1.000$).
- Mean expression of MPO, TNF-α, and HLA-DR at Week 12 in the ileum and colon was numerically lower for subjects in the adalimumab group. Statistical significance was observed for all 3 markers at Week 12 in the colon (MPO: adalimumab 3.46 versus 5.98 placebo; $P = 0.029$; TNF-α: 3.26 adalimumab versus 5.43 placebo; $P = 0.016$; HLA-DR: 12.3 adalimumab versus 14.44 placebo; $P = 0.005$).
- The proportion of subjects with aberrant expression of HLA-DR in the ileum and colon were lower at Week 12 for subjects in the adalimumab group compared to subjects in the placebo group (ileum: 18.9 versus 21.3, respectively; $P = 0.818$; colon: 31.1 versus 48.4, respectively; $P = 0.066$).

Efficacy Results (Continued):

- The proportion of subjects with increased expression of subepithelial tenascin in the ileum and colon were lower at Week 12 for subjects in the adalimumab group compared to subjects in the placebo group (ileum: 7.5 versus 8.2, respectively; $P = 1.000$; colon: 4.9 versus 9.7, respectively; $P = 0.491$).
- At Week 12 and at Week 52, within group and between group treatment comparisons did not demonstrate statistically significant correlation between expression of IL13R in the ileum and colon at Baseline for most examined variables.

Post-hoc analysis:

A statistically significantly greater proportion of subjects in the adalimumab group were without mucosal ulceration at Week 12 ($P = 0.015$) in a comparison of subjects without mucosal ulceration when data from Week 8 was not carried forward.

	Placebo		Adalimumab		
Subjects without mucosal ulceration	**N**	**n (%)**	**N**	**n (%)**	***P* value[a]**
Post-hoc efficacy analysis					
ITT Set[b,c]	61	6 (9.8)	62	17 (27.4)	0.015

a. The *P* value is from CMH test with CR-70 responder status at Week 4 as the stratification factor.

b. Only subjects with mucosal ulceration (according to the review committee) at Screening were included.

c. Subjects who did not have endoscopy at Week 12 were considered to have mucosal ulceration at Week 12 (non-responder imputation). Among subjects who had mucosal ulceration at Screening, 8 subjects did not have endoscopy at Week 12.

Note: Week 8 ulceration information was not carried forward for missing Week 12 ulceration.

A post-hoc analysis was conducted to show the cumulative number of post-baseline all-cause hospitalizations prior to the switch to OL (maximum to Week 52). All-cause hospitalizations were reported as SAEs (treatment-emergent) that began on or after induction (post-baseline only) and prior to switching to OL, or up to 70 days after the end of the DB phase for subjects who did not switch. For the 10 subjects (6 placebo, 4 adalimumab) included in this analysis, mean ± SD, median, and range for cumulative number of hospitalizations per 100 days of study treatment before the switch to OL were 1.09 ± 1.196, 0.72, and 0.3 to 3.4, respectively, for the placebo group and 0.76 ± 0.482, 0.060, and 0.4 to 1.4, respectively, for the adalimumab group.

Safety Results:

In this study, adalimumab was demonstrated to be generally safe and well-tolerated as evidenced by the results of assessment of TEAEs, SAEs, and events of special interest during the induction phase, and during DB and OL administration:

TEAEs:

- During DB study drug administration, the proportions of subjects who reported AEs were comparable between groups: 84.6% of placebo subjects and 95.3% of adalimumab subjects experienced at least one TEAE. A higher proportion of subjects in the adalimumab group experienced TEAEs that were assessed by the Investigator as possibly related to study drug than did subjects in the placebo group (42.2% versus 32.3%, respectively). No statistically significant difference was detected. The proportions of subjects in the adalimumab and placebo groups who reported a severe TEAE were comparable.
- During OL administration, the majority (87%) of subjects reported at least one TEAE. A total of 35% of subjects reported a TEAE that was assessed by the Investigator as possibly related to study drug and 25.0% of subjects reported a TEAE that was considered severe by the Investigator.
- The most frequently reported TEAEs (≥ 5% of subjects in any treatment group) during DB study drug administration was CD. No statistically significant difference was observed between groups for any individual MedDRA PT.
- The most frequently reported TEAEs (≥ 5% of subjects) during OL adalimumab administration were CD and nasopharyngitis.
- The majority of subjects who reported TEAEs reported TEAEs that were mild to moderate in severity during both DB and OL study drug administration. Fourteen subjects in the placebo group and 10 subjects in the adalimumab group reported severe TEAES while receiving DB study drug. During administration of OL adalimumab, 25 subjects reported a severe TEAE. The most frequently reported severe TEAE was CD during both DB and OL adalimumab study drug administration.
- Most subjects reported events that were not related or probably not related to study drug treatment per the Investigator. During DB study drug administration, 48 subjects reported TEAEs that were assessed by the Investigator as at least possibly related to study drug with no statistically significant difference observed between groups. During OL study drug administration, 35 subjects reported TEAEs that were assessed as at least possibly related to study drug. No events at least possibly related were reported in > 3 subjects during DB or OL study drug administration.

SAEs:

- No subjects died during the study.
- SAEs were reported in 5 (7.7%) and 4 (6.3%) subjects treated with placebo and adalimumab, respectively, during DB study drug administration. During OL administration, 15 subjects (15%) reported SAEs.

Safety Results (Continued):

TEAES of special interest:

- Twenty-one subjects prematurely discontinued from the study due to a TEAE (9 subjects randomized to receive placebo, 10 subjects randomized to receive adalimumab, and 2 subjects who were never randomized) (Any Adalimumab Set).
- A statistically significant difference was observed between the adalimumab and placebo treatment group in the proportion of subjects who reported infections during DB study drug administration: 54.7% versus 33.8%, respectively; $P = 0.021$. No subject reported a serious infection during DB study drug administration. Most infections were not related or probably not related to study drug upon Investigator assessment.
- Five subjects reported serious infections at a rate of 4.4 E/100 PYs (Any Adalimumab Set). Three subjects reported abscesses (anal, vulvar, and perianal). The other two subjects reported tonsillitis and herpes zoster. With the exception of the vulvar abscess, all events were either possibly or probably related to study drug treatment per the Investigator.
- Three subjects reported opportunistic infections that were considered possibly related by the Investigator in 2 cases (Any Adalimumab Set). All 3 were mild cases of candidiasis. No TB was reported.
- Most of the injection site reaction events occurred during induction (17 subjects; 12.6%). During DB administration 3.1% (2/65) of placebo subjects and 6.3% (4/64) of adalimumab subjects reported at least one injection site reaction. A total of 4% (4/100) of subjects who received OL study drug reported injection site reactions. All but 3 subjects' events were considered by the Investigator to be at least possibly related to study drug.
- Three subjects reported hepatic related AEs, only one of which (liver function test abnormal) was assessed as possibly related to study drug by the Investigator with no statistically significant difference observed between the adalimumab and placebo groups.
- One subject reported a hematologic related AE (thrombocytopenia) (Any Adalimumab Set). The event was mild in severity and was assessed as possibly related to study drug, according to the Investigator.
- No subjects reported the following AEs of special interest: CHF, demyelinating disease, allergic reaction, lupus-like syndrome, or malignancies (Any Adalimumab Set).

Laboratory and vital signs assessments:

- Mean changes in laboratory values and vital signs values were clinically unremarkable.
- Shifts in laboratory assessments were few.
- Assessment of potentially clinically significant laboratory and vital signs values resulted in no new safety signals.
- Shifts in laboratory assessments were few.
- Assessment of laboratory and vital signs values resulted in no new safety signals.

Conclusions:

Although a larger proportion of subjects in the adalimumab group had mucosal healing at Week 12 compared to placebo, the difference between the two groups in the primary efficacy analysis using the ITT set narrowly missed statistical significance ($P = 0.056$). However, results using the per-protocol analysis were statistically significant ($P = 0.046$). A likely explanation for missing statistical significance in the primary efficacy analysis may be found in the high proportion of subjects with mucosal healing at Week 12 in the placebo group, due to the prolonged effect of the adalimumab OL induction dose. This explanation is supported by the high proportion of subjects with CR-70 and CR-100 response at Week 12, and by the drop in the proportion of subjects with mucosal healing thereafter between Week 12 and Week 52 in the placebo group. The statistically significantly greater proportion of subjects without mucosal ulceration at Week 12 ($P = 0.015$) in the adalimumab group compared to placebo when data from Week 8 was not carried forward also appears to support this likely explanation.

While a secondary endpoint, at Week 52, a statistically significantly greater proportion of subjects in the adalimumab group were without mucosal ulceration compared to subjects in the placebo group (24.2% versus 0, respectively; $P < 0.001$) using the ITT Set. This is an important and clinically relevant result since CD is a chronic disease.

In terms of other secondary endpoints, efficacy of adalimumab on mucosal disease was demonstrated by the proportion of subject with CDEIS remission (CDEIS ≤ 4) at Week 12 and at Week 52, the proportion of subjects with CDEIS response (decrease from Baseline > 75% in CDEIS) at Week 52, the mean change from Baseline to Week 12 and from Baseline to Week 52 in CDEIS score, and SES-CD.

The efficacy of adalimumab on CD activity was confirmed with a statistically significantly greater proportion of subjects achieving clinical remission (CDAI < 150) at Week 12 and Week 52 in the adalimumab group compared with placebo.

Adalimumab was generally well tolerated, and no new safety signals were identified in this study.

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