# Synopsis

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

**Title of Study:** A Multicenter, Double-blind Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of the Human Anti-TNF Monoclonal Antibody Adalimumab in Pediatric Subjects with Moderate to Severe Crohn's Disease

**Coordinating Investigator:** Jeffrey Hyams, MD, Connecticut Children's Medical Center, Hartford, CT USA

**Study Sites:** A total of 45 sites in Belgium, Canada, Czech Republic, France, Italy, The Netherlands, Poland, the United Kingdom, and the United States participated in this study.

**Publications:** None

| **Studied Period (Years):** | **Phase of Development:** 3 |
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| First Subject First Visit: 04 May 2007<br>Last Subject Last Visit: 18 May 2010 | |

**Objectives:**

The objective of the study was to demonstrate the safety and efficacy of adalimumab for the induction and maintenance of clinical remission in pediatric subjects with moderate to severe Crohn's disease (CD) and to assess the pharmacokinetics (PK) of adalimumab administered by subcutaneous (SC) injection.

**Methodology:**

This was a multicenter, randomized, double-blind (DB), safety, efficacy, and PK study designed to evaluate the efficacy of 2 open-label (OL) induction dose regimens and 2 adalimumab maintenance dose regimens for the induction and maintenance of clinical remission in pediatric subjects between the ages of 6 and 17 (inclusive) with moderate to severe CD. Subjects must have either failed conventional therapy for CD or have previously received infliximab and lost response/had intolerance to infliximab.

All subjects received an induction regimen administered at Baseline (Week 0) and Week 2. The OL induction dose was based on the subject's Baseline body weight (BW). Subjects weighing ≥ 40 kg were to receive 160 mg at Week 0 and 80 mg adalimumab at Week 2. Subjects weighing < 40 kg were to receive 80 mg at Week 0 and 40 mg adalimumab at Week 2.

**Methodology (Continued):**

At Week 4, subjects were to be randomized 1:1 to one of 2 maintenance treatment groups (Low-Dose or High-Dose), stratified by Week 4 clinical responder status (clinical response was defined as decrease in Pediatric Crohn's Disease Activity Index [PCDAI] of ≥ 15 points from the Baseline score), and prior exposure to infliximab. Subjects randomized to the High-Dose treatment group were to receive either 40 mg adalimumab SC eow (if Week 4 BW ≥ 40 kg) or 20 mg adalimumab SC eow (if Week 4 BW < 40 kg). Subjects randomized to the Low-Dose treatment group were to receive either 20 mg adalimumab SC eow (if Week 4 BW ≥ 40 kg) or 10 mg adalimumab SC eow (if Week 4 BW < 40 kg). Subject BW taken at Week 26 was to be used to readjust the maintenance dosing regimen for subjects whose BW had increased from < 40 kg to ≥ 40 kg during the study.

Subjects were expected to remain on blinded eow therapy throughout the 48-week study DB Maintenance period. However, starting at the Week 12 study visit, subjects who experienced a disease flare (increase in the PCDAI of ≥ 15 points when compared to Week 4 and an absolute PCDAI above 30) or were non-responders (not achieving a decrease in the PCDAI score of at least 15 points when compared to the Baseline score for 2 consecutive visits at least 2 weeks apart) could be switched from blinded eow dosing to blinded ew dosing, continuing with the same blinded dose. During blinded ew treatment, if a subject continued to experience a flare or met the definition of non-response following an 8 week course of DB ew therapy, they were to be switched to OL ew therapy. The dosage of the OL ew therapy was 20 mg for subjects < 40 kg and 40 mg for subjects ≥ 40 kg.

The duration of the study was to be up to 65 weeks, which included a 1-week to 3-week Screening period, an OL Induction period, a Maintenance period, and a 70-day follow-up phone call for all subjects who either terminated early from the study or did not rollover into the extension study (Study M06-807).

In addition to the PCDAI, the Crohn's Disease Activity Index (CDAI) was applied to subjects ≥ 13 years of age. Additional efficacy assessments, as well as safety and PK measurements were performed throughout the study.

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

Planned: 186 subjects

Analyzed: 192 subjects were analyzed for safety; 188 subjects were analyzed for efficacy (intent-to-treat [ITT] Analysis Set)

**Diagnosis and Main Criteria for Inclusion:**

- Males and females between the ages of 6 and 17, inclusive, prior to Baseline dosing.
- Subjects with a diagnosis of CD for greater than 12 weeks prior to Screening, confirmed by endoscopy or radiologic evaluation.
- PCDAI > 30 despite concurrent treatment with an oral corticosteroid, and/or azathioprine (AZA) or 6-mercaptopurine (6-MP), or methotrexate (MTX).
- For subjects who had previously received infliximab, must have had an initial response and then discontinued use due to a loss of response or must have discontinued use due to intolerance to the medication.

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

Adalimumab via subcutaneous (SC) injection

Vials: Adalimumab 40 mg/0.8 mL, 20 mg/0.8 mL

Bulk Product Lot Numbers: 07-011601, 07-011602, 05-001943, 06-007907

Pre-filled syringes: Adalimumab 40 mg/0.8 mL, 20 mg/0.4 mL

Bulk Product Lot Numbers: 08-019941, 07-011196, 06-007039, 06-007008, 08-015241

**Duration of Treatment:** 52 weeks

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

None

**Criteria for Evaluation**

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**Efficacy:**

The primary efficacy endpoint [redacted] was to be the PCDAI clinical remission at Week 26 in the ITT population. [redacted] The internal primary analysis was to be the comparison of High-Dose versus Low-Dose with respect to the primary efficacy endpoint for internal comparison.

Major secondary efficacy endpoints (ranked) were:

- Proportion of subjects in PCDAI clinical remission at Week 52
- Proportion of subjects in PCDAI clinical response at Week 26
- Proportion of subjects in PCDAI clinical response at Week 52
- Proportion of subjects in PCDAI clinical remission at Week 26 who were Week 4 responders
- PCDAI clinical remission at Week 4
- Proportion of subjects receiving corticosteroids at Baseline who had discontinued corticosteroids for at least 90 consecutive days prior to Week 26 and were in PCDAI clinical remission at Week 26
- Change from Baseline in z-score for height velocity at Week 26
- Change from Baseline in total IMPACT III scores at Week 26

**Criteria for Evaluation (Continued):**

Non-ranked secondary efficacy variables assessed were:

- Proportion of subjects in PCDAI clinical remission over time
- Proportion of subjects in PCDAI clinical remission at Week 26 who were also in PCDAI clinical remission at Week 52 (and never had a flare between Week 26 and Week 52)
- Time in PCDAI clinical remission while on DB eow treatment
- Time to PCDAI clinical remission while on DB eow treatment
- Time to steroid-free PCDAI clinical remission while on DB eow treatment
- Proportion of subjects in PCDAI clinical response over time
- Proportion of subjects receiving corticosteroids at Baseline who had discontinued corticosteroids and were in PCDAI clinical remission at Weeks 12, 26, and 52
- Proportion of subjects receiving corticosteroids at Baseline who had discontinued corticosteroids and were in PCDAI clinical remission at Week 26 and who remained off corticosteroids and were in clinical remission at Week 52
- Proportion of subjects receiving corticosteroids at Baseline who had discontinued corticosteroids for at least 90 consecutive days prior to Week 52 and were in PCDAI clinical remission at Week 52
- Change from Baseline in serological markers of bone metabolism, osteocalcin, BSAP, and NTx at Week 26 and Week 52
- Change from Baseline in total IMPACT III scores at Week 12 and Week 52
- Change in WPAI Questionnaire scores (absenteeism, presenteeism, total work impairment, and activity impairment) over time
- Cumulative number of unscheduled outpatient visits (physician visits, emergency room visits, hospital admissions, and days of hospitalization) up to Week 52
- Change from Baseline in BMI at Week 26 and Week 52
- Change from Screening in Bone age at Week 52
- Change from Baseline in z–score for height velocity at Week 52
- Change from Baseline in corticosteroid dose at Week 26 and Week 52 (only for subjects who have not discontinued steroids at these time points)
- Proportion of subjects with fistula remission (defined as the closure of all fistulas that were draining at Baseline for at least 2 consecutive visits) while receiving DB eow treatment
- Proportion of subjects with improvement in the number of draining fistulas (defined as a decrease from Baseline in the number of draining fistulas ≥ 50% for at least 2 consecutive visits) while receiving DB eow treatment

**Criteria for Evaluation (Continued):**

- Proportion of subjects who dose-escalated in the DB period from eow to ew. Dose readjustment at Week 26 based on the Week 26 BW was not considered a dose-escalation.
- Proportion of subjects in PCDAI clinical remission at Week 52 after dose escalation for:
  - Subjects who had not achieved PCDAI clinical response prior to dose escalation and
  - Subjects who had achieved PCDAI clinical response but lost response prior to dose escalation
- Proportion of subjects who switched to OL dosing and were in PCDAI clinical remission at Week 52 for:
  - Subjects who had not achieved PCDAI clinical response prior to OL dosing and
  - Subjects who had achieved PCDAI clinical response but lost response prior to OL dosing
- Proportion of subjects receiving IMM at Baseline who had discontinued IMM and were in PCDAI clinical remission at Week 52
- Change from Baseline in CRP levels at Weeks 4, 26, and 52

**Pharmacokinetic:**

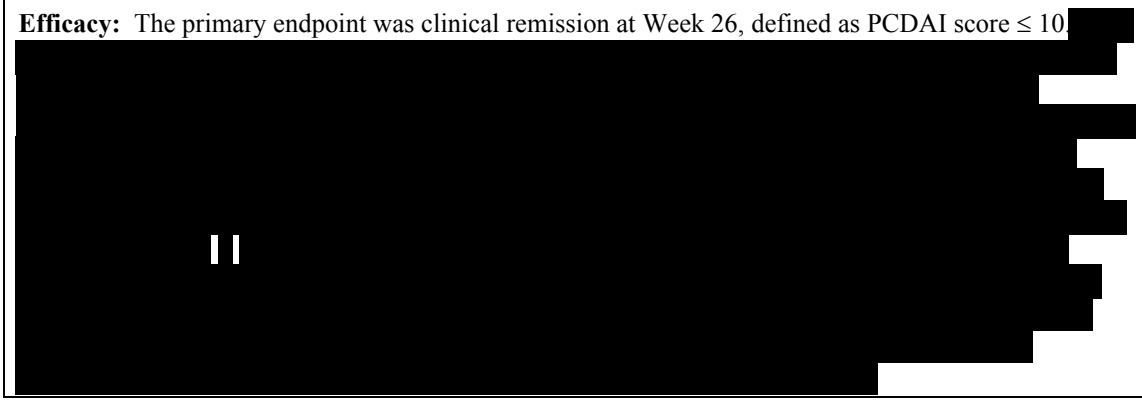
Blood samples were to be obtained for the measurement of adalimumab concentrations and anti-adalimumab antibodies (AAA) at Baseline and other specified time points during the study. Blood samples were to be obtained for the measurement of human anti-chimeric antibodies (HACA) to infliximab, and infliximab drug levels at Baseline.

**Safety:**

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

**Statistical Methods**

**Efficacy:** The primary endpoint was clinical remission at Week 26, defined as PCDAI score ≤ 10



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**Statistical Methods (Continued):**

The primary internal efficacy comparison was to be the comparison of High-Dose versus Low-Dose adalimumab with respect to the primary efficacy endpoint, proportion of subjects in clinical remission at Week 26. The extended Cochran-Mantel-Haenszel (CMH) test was to be used in the primary internal analysis, adjusting for strata (Week 4 response status [No, Yes] and prior infliximab experience [No, Yes]). The treatment–by-strata interaction was to be tested using Breslow-Day test at 10% significance level. The point estimates for the proportion of subjects who achieved PCDAI clinical remission in each treatment group and the difference in proportions between the groups were to be provided. The *P* value and 95% CIs for the difference were to be provided. This primary analysis was to be performed for the ITT and PP analysis sets using both the LOCF and NRI. The primary inference was to be based on the analysis of the ITT subjects via NRI. Fisher's exact test was to be used as an alternative method if the CMH test failed.

[redacted]

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Eight major secondary analyses were performed:

1. Proportion of subjects in PCDAI clinical remission at Week 52.
2. Proportion of subjects in PCDAI clinical response at Week 26.
3. Proportion of subjects in PCDAI clinical response at Week 52.
4. Proportion of subjects in PCDAI clinical remission at Week 26 who were Week 4 responders.
5. PCDAI clinical remission at Week 4.
6. Proportion of subjects receiving corticosteroids at Baseline who had discontinued corticosteroids for at least 90 consecutive days prior to Week 26 and were in PCDAI clinical remission at Week 26.
7. Change from Baseline in z-score for height velocity at Week 26.
8. Change from Baseline in total IMPACT III scores at Week 26.

[redacted] A hierarchical stepwise closed testing procedure with the above sort order was to be used to control the overall significance level at 0.05. This hierarchical testing procedure was to be implemented in the ITT population. Based on the closed testing procedure, a significance test for any individual major secondary efficacy endpoint in the hierarchy was to be inferential only if the hypothesis tests of all preceding major secondary efficacy endpoints were statistically significant at 0.05. Because hierarchical stepwise testing scheme was to be used, statistical testing was to be performed at alpha = 0.05 at each stage without any adjustment for alpha level.

**Statistical Methods (Continued):** Redacted information - 14May2013

The major secondary endpoints that were of the binary type were to be analyzed in a similar manner as the primary analysis described above using the CMH test for internal comparisons. [redacted]

Major secondary endpoints that were of the continuous type were to be analyzed as change from Baseline, and compared between the 2 treatment groups via analysis of covariance (ANCOVA), with treatment group as a factor and the Baseline of the corresponding endpoint (prior infliximab use and Week 4 response status as covariates). The estimated treatment mean difference, *P* values, and 95% CI for the treatment difference were to be provided. [redacted]

Additional analyses conducted after the blind break were:

- The subgroup analysis to compare the High-Dose group to the Low-Dose group based on prior infliximab use for the primary, major secondary variables, and PCDAI clinical remission/clinical response (at Week 26 and Week 52) for subjects who were responders at Week 4.
- The subgroup analysis to compare the High-Dose group to the Low-Dose group based on the body weight at Week 4 (weight < 30 kg or ≥ 30 kg) for both primary and major secondary categorical variables.
- The subgroup analysis to compare the High-Dose group to the Low-Dose group based on body weight at Week 4 (weight < 40 kg or ≥ 40 kg) for both primary and major secondary variables.
- The subgroup analysis for the primary variable, major secondary categorical variables, and PCDAI clinical remission/clinical response (at Week 26 and Week 52) for subjects who were responders at Week 4 by Week 4 weight group in 5 kg intervals and 10 kg intervals.
- The analyses of change from Baseline to each visit in PCDAI and CDAI total scores during eow DB period.

The following additional analyses have been conducted for the revision of the study report:

- The analyses of change from Baseline to each visit in PCDAI and CDAI total scores during the blinded maintenance period (eow and ew)
- The analyses of change from the last evaluation during eow period to Week 52 in PCDAI and CDAI total scores during ew blinded period
- The analyses to compare the proportion of subjects in PCDAI clinical remission/clinical response (at Week 26 and Week 52) during the eow and ew double-blind maintenance phase

In order to describe the total clinical response (or remission) at Week 52 including the dose escalation portion of the study, a modified NRI (mNRI) imputation method was utilized in a post hoc analysis: the mNRI imputation method considered all missing response (or remission) values as non-response (or non-remission). Subjects who dose escalated to adalimumab 40 mg weekly were considered as responders (or remitters) or non-responders (or non-remitters) according to their observed response (or remission) status after the dose escalation during the DB ew period.

**Statistical Methods (Continued):**

Similarly, mean change in PCDAI was assessed using a modified LOCF (mLOCF) method, whereby PCDAI values for subjects who dose escalated to DB adalimumab ew were not considered to be missing. Using the mLOCF method, subjects who switched to OL adalimumab 40 mg ew were considered to be missing from the time of the switch to OL.

**Pharmacokinetic:**

Adalimumab trough serum concentration were to be summarized by treatment group at each time point using descriptive statistics. Mean concentration versus time plots by treatment group were to be provided.

Serum concentrations of infliximab were to be summarized by treatment group using descriptive statistics.

Serum concentrations of AAA were to be listed by treatment group at each collection time.

**Safety:**

Adverse events, laboratory data, and vital signs were to be the primary safety parameters in this study. All safety comparisons were to be performed within the safety population (or the Safety analysis set). An overview of treatment-emergent AEs (TEAEs) was to be provided by n (%) of subjects, including AEs of special interest, AEs leading to death, and AEs leading to premature discontinuation, AEs by preferred term (PT) and system organ class (SOC), AEs by maximum relationship to adalimumab, and AEs by maximum severity. The most current implemented Medical Dictionary for Regulatory Activities (MedDRA®) was to be used. TEAEs were to be defined as new events that began either on or after the first dose of the study medication and within 70 days after the last dose of the study medication.

TEAEs were to be summarized separately for the OL induction (Week 0 – Week 4), DB eow dosing period (Week 4 – Last date before switching to DB ew dosing), and Study M06-806 (Week 0 – 70 days after the last dose of the study). Period-emergent AEs are AEs that either began or worsened in severity during the relevant reporting period.

Between treatment comparisons were to be performed only for the TEAEs and SAEs during the DB eow period, using Fisher's exact test.

Pre-treatment SAEs (i.e., SAEs with start date prior to the date of the first adalimumab injection) were also to be listed.

Other safety variables, such as laboratory data and vital signs, were to be described by statistical characteristics. Shift tables from Baseline to DB period also were to be provided to cross-classify subjects from Baseline to DB period in each treatment group by the presence of clinically significant laboratory test values.

**Statistical Methods (Continued)**

Additional analyses conducted after the blind break were:

TEAEs were also to be summarized by body weight at baseline and Week 4. Overviews of TEAEs were to be generated based on prior infliximab use for the induction period and DB eow period, eow dosing period for subjects who completed study on eow dosing and for subjects who switched to ew blinded dosing, and for the ew blinded period and ew period (ew blinded and OL). The number of SAEs per 100 patient years (PYs) tables were to be generated for the eow dosing period for subjects who completed study on eow dosing and for ew blinded dosing period for subjects who switched to ew blinded dosing. The subgroup analysis for mean change from Baseline to final value for hematology, chemistry, and vital signs results by dose-escalation status and summary of body weight at Week 4 for subjects who received at least one DB dose (< 13 years old at Baseline, ≥ 13 years old at Baseline).

In addition, the following additional analyses have been conducted for the revision of the study report:

TEAE overview tables were generated by prior infliximab use for the induction period and the DB eow period. TEAE overview tables were generated for the eow dosing period for subjects who completed study on eow dosing and for subjects who switched to ew blinded dosing. TEAE overview tables were generated for the ew blinded period and for ew period (ew blinded and OL). Analyses of SAEs (n [%] of subjects and E/100 PYs) were generated for the eow dosing period for subjects who completed study on eow dosing and for ew blinded dosing period for subjects who switched to ew blinded dosing . Analyses of severe events (n [%] of subjects and E/100 PYs) were generated for the DB ew + OL ew dosing period

**Summary/Conclusions**

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**Efficacy Results:**

[redacted]

The primary internal comparison between Low-Dose and High-Dose adalimumab treatment found that the High-Dose treatment had a higher PCDAI clinical remission rate (38.7%) at Week 26 than the Low-Dose treatment (28.4%), although the difference did not achieve statistical significance ($P = 0.075$). Comparing the treatment groups by prior infliximab use, however, yielded a statistically significant difference between the treatment groups ($P = 0.026$), in favor of the High-Dose treatment, in clinical remission rates at Week 26 (56.9% in High-Dose treatment group versus 35.2% in Low-Dose treatment group) for subjects without prior infliximab use.

[redacted]

**Efficacy Results (Continued):**

Differences between Low-Dose and High-Dose treatment groups in PCDAI clinical remission rates at Week 52 (ranked secondary endpoint number 1) were similar to the findings at Week 26: the High-Dose treatment group had a higher clinical remission rate (33.3%) compared to the Low-Dose treatment group (23.2%); however, the difference between treatment groups was not statistically significant.

There was no statistically significant difference in PCDAI clinical response rates at Week 26 (ranked secondary analysis No. 2) between the Low-Dose treatment and High-Dose treatment groups (48.4% versus 59.1%, respectively; $P = 0.073$).

The difference between dose groups in PCDAI clinical response rates at Week 52 (ranked secondary endpoint number 3) was statistically significant in favor of the High-Dose treatment group (41.9%) versus the PCDAI clinical response rate in the Low-Dose treatment group (28.4%). In addition, a greater proportion of subjects without prior infliximab use (43.8%) were in PCDAI clinical response at Week 52 compared to subjects with prior infliximab use (24.1%).

Results for other major secondary ranked endpoints were:

- A greater proportion of subjects in the High-Dose treatment group (59.1%) achieved PCDAI clinical response at Week 26 than did subjects in the Low-Dose treatment group (48.4%); however, this result did not reach statistical significance ($P = 0.073$) (ranked secondary analysis number 2).
- No statistically significant difference was observed between the Low-Dose and High-Dose treatment groups in the proportion of subjects who were in PCDAI clinical remission at Week 26 and who discontinued systemic corticosteroids at least 90 consecutive days prior to Week 26 (23.7% versus 30.3%, respectively; $P = 0.329$) (ranked secondary analysis number 6).
- No statistically significant difference was observed between the Low-Dose and High-Dose treatment groups in change from Baseline to Week 26 in z-scores for height velocity (ranked secondary analysis number 7).
- No statistically significant difference was observed between the Low-Dose and High-Dose treatment groups in change from Baseline to Week 26 in total IMPACT III score (ranked secondary analysis number 8).

The effect of dose escalation to ew dosing was assessed using a post hoc mNRI method whereby dose escalators were not considered to be non-responders during the DB period. The PCDAI clinical remission rate calculated using this method (i.e., including eow + ew dosing) was higher than the results observed using the prespecified NRI analysis (i.e., ew only) at Week 26 and Week 52.

Using the mNRI method, the PCDAI clinical remission rate at Week 26 was numerically higher in the High-Dose treatment group than the Low-Dose treatment group and was significantly higher at Week 52. Similarly, there was statistically significant difference between the proportions of subjects who achieved PCDAI clinical remission at Week 52 in those with no prior history of infliximab in favor of the High-Dose treatment group versus the Low-Dose treatment group. Mean change from Baseline in PCDAI, assessed using a similarly modified LOCF method whereby dose escalators receiving DB ew therapy were not considered to have missing values, was statistically significantly greater in the High-Dose treatment group than in the Low-Dose treatment group at all visits between Week 32 and Week 52.

**Pharmacokinetic Results:** Pharmacokinetic results and conclusions are presented in a separate PK report (R&D/10/977).

**Safety Results:**

**Induction Period:**

No deaths were reported during the OL Induction period. One or more TEAEs were reported by 52.6% of subjects. The majority of subjects reported TEAEs that were not related or probably not related to study drug and almost all subjects had events that were mild or moderate in severity. Six (3.1%) subjects reported at least 1 serious TEAE during the OL Induction period; none were considered by the Investigator to be related to study drug. One subject prematurely discontinued due to a TEAE.

Twenty-seven subjects (14.1%) reported an infection during the Induction period. Two subjects reported serious infections, but no subjects reported an opportunistic infection or tuberculosis (TB). Twenty-two subjects (11.5%) reported an injection site reaction. No subject reported a malignancy, congestive heart failure, demyelinating disease, hepatic-related TEAE, allergic reaction, or lupus-like syndrome during the Induction period.

**DB Maintenance Period:**

No deaths were reported during the eow DB Maintenance period (subjects who received ≥ 1 DB dose, prior to ew DB dosing). A greater proportion of subjects in the High-Dose treatment group (92.5%) reported at least 1 treatment-emergent adverse event (TEAE) compared to the Low-Dose treatment group (85.3%); however, the High-Dose treatment group had a lower rate of TEAEs (937.2 E/100 patient-year [PY]) compared to the Low-Dose Treatment group (976.8 E/100 PY) as well as a lower rate of infections (181.1 E/100 PY for the High-Dose treatment group versus 212.6 E/100 PY for the Low-Dose treatment group). Approximately 60% of subjects in both treatment groups reported TEAEs that were considered by the Investigator as not related or probably not related to study drug. By events per 100 analysis, the Low-Dose treatment group had a slightly higher rate of TEAEs that were possibly or probably related to study drug compared to the High-Dose treatment group (231.6/100 PYs versus 205.2/100 PYs, respectively). A greater proportion of subjects in the High-Dose treatment group had at least 1 severe TEAE compared with subjects in the Low-Dose treatment group (20.4% versus 11.6%, respectively). By events per 100 PY analysis, the trend was similar. Approximately 20% of subjects in each treatment group reported at least 1 SAE during the eow DB Maintenance period. Almost all were considered not related or probably not related to study drug per the Investigator.

Twelve (12.6%) and 15 (16.1%) subjects from the Low- and High-Dose treatment groups, respectively, prematurely discontinued from the study due to a TEAE; the same trend is seen in the E/100 PY analysis.

**Safety Results (Continued):** Redacted information - 14May2013

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Eight subjects reported serious infections (3 subjects in the Low-Dose treatment group and 5 subjects in the High-Dose treatment group). One subject in each treatment group reported an opportunistic infection (excluding TB). No subject reported TB, malignancy, lymphoma, non-melanoma skin cancer, congestive heart failure, demyelinating disease, or lupus-like syndrome during the eow DB Maintenance period. The proportion of subjects, approximately 10%, who reported an injection site reaction was similar between treatment groups. Hepatic-related TEAEs and hematologic-related TEAEs were infrequent, with similar proportions of subjects reporting these events in each treatment group.

**Any Adalimumab Exposure:**

Of subjects who received at least 1 dose of adalimumab at any time during the study (OL Induction eow DB Maintenance, ew DB, and OL), 95.8% reported at least 1 TEAE. TEAEs that were assessed by the Investigator as possibly or probably related to study drug were reported by 50% of subjects. Severe AEs were reported by 27.1% of subjects, and SAEs were reported by 32.8%. Approximately 20% of subjects prematurely discontinued due to a TEAE. Infections were reported by 67.2% of subjects, with 6.3% of subjects reporting a serious infection. Two subjects reported an opportunistic infection excluding TB; no cases of TB were reported. No subject who received at least 1 dose of adalimumab reported malignancy, lymphoma, or non-melanoma skin cancer. Approximately 20% of subjects reported an injection site reaction. No subject who had at least 1 dose of adalimumab at any time during the study reported congestive heart failure, demyelinating disease, or lupus-like syndrome. Hepatic-related TEAEs, allergic reactions, and hematologic-related TEAEs were reported infrequently (< 6%).

[redacted]

In a post hoc analysis of subjects who had escalation from adalimumab eow to ew during the DB period, the proportion of subjects reporting TEAEs, at least possibly related TEAEs or AEs leading to discontinuation of study drug and the number of events/100 PYs was similar regardless of frequency of dosing (ew or eow). An increased number of serious events/100 PYs in those receiving adalimumab DB ew versus eow in both treatment groups was mainly due to a higher number of CD (flare or worsening) events reported as an SAE in both the Low-Dose and High-Dose treatment groups.

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

**Conclusions:**

In Study M06-806, the OL adalimumab induction doses (160/80 mg for subjects ≥ 40 kg, 80/40 mg for subjects < 40 kg) and both the Low-Dose (10 mg, BW < 40 kg, or 20 mg, BW ≥ 40 kg) and High-Dose (20 mg, BW < 40 kg, or 40 mg, BW ≥ 40 kg) maintenance regimens were efficacious for inducing and maintaining clinical remission in pediatric subjects aged 6 to 17 years who were diagnosed with moderate to severe CD and had failed conventional therapy for CD or previously received infliximab and lost response or had intolerance to infliximab. The High-Dose maintenance regimen produced numerically higher rates of clinical remission, but was not statistically significantly different from the Low-Dose maintenance regimen. The rate of clinical remission (irrespective of treatment regimen) was higher among subjects who had no prior exposure to infliximab. Dose escalation to weekly dosing resulted in a higher rate of clinical remission as well as improved PCDAI scores.

The safety profile observed throughout this study was consistent with the established safety profile of adalimumab, and no new safety signals were observed. The safety profile with weekly dosing was similar to that observed with dosing every other week.

**Date of the Report:** 21Apr2011