2.0 Synopsis

AbbVie	**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, Open-label Study of the Human Anti-TNF Monoclonal Antibody Adalimumab to Evaluate the Efficacy and the Long-term Safety and Tolerability of Repeated Administration of Adalimumab in Pediatric Subjects with Crohn's Disease Who Have Demonstrated a Clinical Response in the M06-806 Study

Investigator: [redacted]

Study Sites: 31 sites in the US, Canada, and Europe

Publications: 1 manuscript, 6 abstracts

Studied Period (Years):	**Phase of Development:** 3
First Subject First Visit: 01 May 2008 Last Subject Last Visit: 07 February 2017	

Objective:

The objective of the study was to evaluate the long-term maintenance of clinical response, safety, and tolerability of repeated administration of adalimumab in pediatric subjects with Crohn's disease (CD) who participated in, and successfully completed, Study M06-806 through Week 52 and who met all of the inclusion and none of the exclusion criteria of this study.

Methodology:

This study was a multi-center, open-label (OL) study of the human anti-TNF monoclonal antibody adalimumab. Thirty-one sites that enrolled subjects in Study M06-806 participated in this study. Approximately 130 pediatric subjects were expected to enroll in this study and 100 subjects were enrolled. The Week 52 visit from Study M06-806 was the Baseline Visit for subjects entering Study M06-807. [redacted] Subjects were allowed to enroll in Study M06-807 if they participated in and successfully completed Study M06-806 through Week 52.

All subjects were on OL maintenance therapy during this study. Subjects who enrolled from blinded therapy in Study M06-806 received OL therapy at a dose dependent on their body weight as assessed at Baseline of this study. Subjects who weighed ≥ 40 kg at Baseline received adalimumab 40 mg every other week (eow), while subjects who weighed < 40 kg at Baseline received adalimumab 20 mg eow. Beginning at Week 8, subjects who had a disease flare may have been switched to every week (ew) treatment at the same dose of adalimumab received while on eow treatment. A disease flare was defined as an increase in the Pediatric Crohn's Disease Activity Index (PCDAI) of ≥ 15 points when compared to the PCDAI score obtained at the previous visit. The higher dose of 40 mg (given eow) was used to maintain blinding in Study M06-806.

Methodology (Continued):

Beginning at Week 8, subjects who developed a flare while receiving ew therapy or had a PCDAI ≥ 15 points higher than Baseline at any time during this study may have been discontinued from the study at the discretion of the investigator. In addition, the dose of adalimumab may have been increased to 40 mg, at the discretion of the investigator, for subjects whose body weight increased from < 40 kg to ≥ 40 kg from the Baseline Visit. Treatment may have been switched to the next lower treatment level for subjects who responded to their current treatment (improvement [≥ 15 point decrease] in PCDAI compared to the last observation prior to dose escalation in subjects who dose-escalated during Study M06-807 or compared to Study M06-806 Baseline in subjects who dose-escalated during Study M06 806 and entered Study M06-807 on open-label ew dosing). At least 8 weeks after dose frequency decrease, subjects with response may have had their dosage decreased.

Reductions in concomitant therapy were allowed for CD treatment-related toxicities (e.g., leukopenia, anemia, neuropathy) of Grade 3 or higher. Subjects were allowed to decrease prednisone (or equivalent) and budesonide if qualifications were met.

The duration of the study could have lasted up to 408 weeks (over 8 years). Subjects who completed, or who early terminated from the study were to be contacted 70 days after their last dose of study drug to obtain information on any ongoing and new adverse events (AEs).

This study was planned to conclude approximately 12 weeks after the following criteria had been satisfied:

- Study drug received country and local (if applicable) regulatory approval for pediatric Crohn's disease.
- All applicable local reimbursement procedures were completed.

Sites were to be notified once these criteria were met.

Following country and local (if applicable) regulatory approval and applicable local reimbursement approval of the study drug in a country, subjects were to attend their next scheduled study visit as specified in the protocol. The termination visit was to be conducted in place of subjects' regular scheduled study visit. These subjects were to be considered as having completed the study.

Number of Subjects (Planned and Analyzed):

Planned: 130 subjects

Analyzed: 100 subjects were analyzed for safety (Safety Population/Analysis Set); 100 subjects were analyzed for efficacy (intent-to-treat [ITT] Population/Analysis Set)

Diagnosis and Main Criteria for Inclusion:

- Subject must have had successfully enrolled in and completed Study M06-806 through Week 52.
- Subject must have been a responder at any time point during Study M06-806 (defined as having achieved at least a 15-point reduction in PCDAI from Baseline).

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

Adalimumab via subcutaneous (SC) injection

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

Bulk Product Lot Numbers: 06-007008, 07-011702, 07-014216, 08-015214, 08-019941, 09-021496, 09-022455, 10-001960, 10-003496, 10-005762, 11-005297, 11-005882, 13-000648, 13-003065, 13-005618, 14-004530, 15-000609

Duration of Treatment: over 8 years (including exposure in Study M06-806)
Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number: None.
Criteria for Evaluation **Efficacy:** For this final analysis of the study, efficacy was evaluated by the proportion of subjects with clinical remission, response, concomitant immunomodulator (IMM)-free remission, corticosteroid-free (for ≥ 90 days) remission per PCDAI and CDAI, and summary of CDAI and PCDAI over time. **Pharmacokinetic:** Serum concentrations of adalimumab and anti-adalimumab antibodies were determined from the samples collected. **Safety:** AEs, physical examination, vital signs, and laboratory data were assessed throughout the study.
Statistical Methods **Efficacy:** Efficacy analyses were conducted on the ITT Population, which was defined as all subjects who received at least 1 dose of adalimumab in Study M06-807 and also had at least one non-missing efficacy measurement during the study. For this final analysis, efficacy was evaluated by number and percent of subjects with clinical remission, response, corticosteroid-free remission, and IMM-free remission per PCDAI, and summary of PCDAI over time. These efficacy endpoints were also evaluated per CDAI among subjects who were at least 13 years old at Study M06-806 Baseline. Descriptive summary statistics were provided for each visit based on observed data. The baseline value was defined as the last non-missing value on or before the date of the first dose of study drug in Study M06-806. Subgroup analyses were performed for the number and percentage of subjects in PCDAI remission/response over time by age, Baseline weight, prior infliximab use, Baseline corticosteroid use, and Baseline IMM use. **Pharmacokinetic:** Not applicable.

Statistical Methods (Continued)

Safety:

Safety analyses were based on the safety population/analysis set, which was defined as all subjects who received at least 1 dose of adalimumab in Study M06-807. Adverse events were summarized by preferred term and system organ class (Medical Dictionary for Regulatory Activities [MedDRA®] version 20.0). Treatment-emergent AEs were defined as new events that began either on or after the first dose of the study drug in Study M06-806 and within 70 days after the last dose of the study drug in Study M06-807; however, AEs with an onset date more than 70 days during the gap between Study M06-806 and Study M06-807 were excluded.

The rate per patient years (PY) for AEs and for AEs of special interest, which were specifically examined using standardized MedDRA (version 20.0) queries (SMQs) or company MedDRA queries (CMQs), was provided. Subgroup analyses were performed by concomitant IMM with or without corticosteroid use at Baseline of Study M06-806 for the incidence of serious infections.

For laboratory parameters, the normal range of the analyzing laboratory was used and all values outside the normal range were flagged and listed. Additionally, descriptive statistics for the mean change from Baseline to minimum (smallest) value, maximum (largest) value, and final value during the study were calculated for the continuous clinical laboratory parameters. Shift tables were provided to cross-classify and tabulate subjects' value from Baseline to final value by the presence of clinically significant laboratory results. Each subject's Baseline value and final value were flagged in reference to the normal range (low, normal, high) and also categorized as clinically non-significant (Common Toxicity Criteria [CTC] grade < 3) or clinically significant (CTC grade ≥ 3).

Summary/Conclusions

Efficacy Results:

The final results through 04 April 2017 (last 70-day follow-up) demonstrated that long-term adalimumab treatment is effective to achieve and sustain remission and response in pediatric subjects (ages 6 to 17) with moderately to severely active CD who had failed conventional therapy for CD, including subjects who had previously received infliximab and lost response or had intolerance to infliximab.

The long-term efficacy of adalimumab in this pediatric population was demonstrated by the high proportion of subjects achieving response and remission as per PCDAI and CDAI over time as well as a sustained reduction in PCDAI and CDAI over time.

Rates of PCDAI remission and response remained stable over time. Approximately two-thirds or more of subjects were in PCDAI clinical remission (PCDAI ≤ 10) at each visit in Study M06-807. Approximately 90% or more of subjects achieved PCDAI clinical response (PCDAI decrease ≥ 15 points from Study M06-806 Baseline) at each visit.

Analyses by age group (< 13 versus ≥ 13 years), body weight group (< 40 versus ≥ 40 kg), prior infliximab use, Baseline corticosteroid use, and Baseline IMM use showed high rates of PCDAI remission and response for adalimumab across all subgroups.

Among subjects who were at least 13 years old at Study M06-806 Baseline, rates of CDAI remission and response were stable over time. Approximately 90% of subjects ≥ 13 years of age were in CDAI clinical remission (CDAI < 150) or response (CDAI decrease ≥ 70 points from Study M06-806 Baseline) at each visit.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

Rates of steroid-free remission remained stable over time. At entry into Study M06-807, approximately two-thirds of subjects who had been receiving systemic corticosteroids at the baseline of Study M06-806 were in steroid-free (for ≥ 90 days) PCDAI remission, and over three-quarters of subjects who were at least 13 years old at Study M06-806 Baseline were in steroid-free (for ≥ 90 days) CDAI remission at entry into Study M06-807. These rates were sustained throughout Study M06-807. Rates of IMM-free PCDAI and CDAI remission among subjects who had been receiving IMMs at Baseline of Study M06-806 increased over time.

Pharmacokinetic Results:

Results of pharmacokinetic analyses will be presented in a separate report.

Safety Results:

The results of this final analysis of Study M06-807, which includes 52-week Study M06-806, did not indicate any safety concerns with long-term adalimumab treatment in pediatric subjects with CD.

No deaths were reported. Approximately half of all subjects (48.0%) reported serious AEs (SAEs); 20 subjects (20.0%) discontinued study drug due to AEs. Most SAEs and events leading to discontinuation were attributable to a worsening or complication of the underlying CD. Most subjects (95.0%) reported at least one infection (126.4 events/100 PYs), including serious infections in 18 subjects (5.5 events/100 PYs). One subject discontinued study drug as a result of a serious infection (subcutaneous abscess). A greater proportion of subjects using concomitant IMMs reported serious infections compared with subjects not using concomitant IMMs (21.9% versus 7.4%). The highest incidence rates of serious infections occurred in subjects using both concomitant IMMs and CSs (36.4%, 10.7 events/100 PYs).

Among AEs of special interest (AESIs), infections (including 26 serious infections) accounted for approximately one-fourth of all reported AESIs (595/2316 events). Injection site reactions accounted for approximately 3% of all AESIs reported; other AESI categories each accounted for 1% or less of the AESI total. No malignancies (including lymphoma, nonmelanoma skin cancer, hepatosplenic T-cell lymphoma, melanoma, and leukemia), opportunistic infections excluding oral candidiasis; active tuberculosis, legionella infections, demyelinating disorders, vasculitis, Stevens-Johnson syndrome, sarcoidosis, myocardial infarction, cerebrovascular accident, congestive heart failure, pulmonary embolism, interstitial lung disease, diverticulitis, erythema multiforme, amyotrophic lateral sclerosis, progressive multifocal leukoencephalopathy, reversible posterior leukoencephalopathy syndrome, reactivation of hepatitis B, autoimmune hepatitis, or Humira® administration-related medication errors were reported.

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

Conclusions:

The final efficacy results from open-label Study M06-807 demonstrated that adalimumab treatment, after 52 weeks of treatment in Study M06-806, was effective in achieving long-term maintenance of remission and response in pediatric subjects (aged 6 to 17 years) with moderately to severely active CD who had failed conventional therapy for CD, including subjects who had previously received infliximab and lost response or had intolerance to infliximab. The long-term safety profile of adalimumab in pediatric subjects with CD, including data from both Study M06-806 and Study M06-807, was generally consistent with the safety profile observed in the 52-week Study M06-806; no new safety signals were identified.